ORAL PRESENTATIONS

Basic Kidney Ischemia-reperfusion and preservation

OS001 LIPID CATABOLISM PROVIDES ALTERNATIVE ENERGY SOURCE AND COMPENSATES FOR MITOCHONDRIAL DYSFUNCTION IN REPERFUSED KIDNEYS AFTER WARM ISCHAEMIA

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Background: Ischaemia and reperfusion injury (IRI) is the leading cause of acute kidney injury (AKI), which contributes to high morbidity and mortality rates in a wide range of injuries as well as the development of chronic kidney disease. The cellular and molecular responses of the kidney to IRI are complex and not fully understood.
Methods/Materials: Here, an integrated proteomic and metabolomic approach was used to investigate the effects of ischaemia reperfusion injury (IRI) on protein expression and metabolite levels. Rat kidneys were subjected to 45 min of warm ischaemia followed by 4 h and 24 h reperfusion, with contralateral and healthy kidneys serving as controls.
Results: Kidney tissue proteomics after IRI revealed elevated proteins belonging to the acute phase response, coagulation and complement pathways, and fatty acid (FA) signalling. Metabolic changes were already evident after 4 h reperfusion and showed increased level of lipids and FAs, whilst mitochondrial function and ATP production was impaired after 24 h.
Conclusions: Our data also indicated elevated levels of enzymes involved in FA consumption at 4 h post IRI. Such a 'metabolic switch' could represent a compensatory mechanism for the developing energy deficit and reduced mitochondrial function. Novel strategies to target these early metabolic changes could reduce IRI, accelerate repair and minimize chronic kidney disease progression.

OS002 RENAL ISCHEMIA REPERFUSION INJURY IS ATTENUATED IN C5AR2 DEFICIENT MICE VIA FGF1 AND AKT DEPENDENT SIGNALLING PATHWAYS

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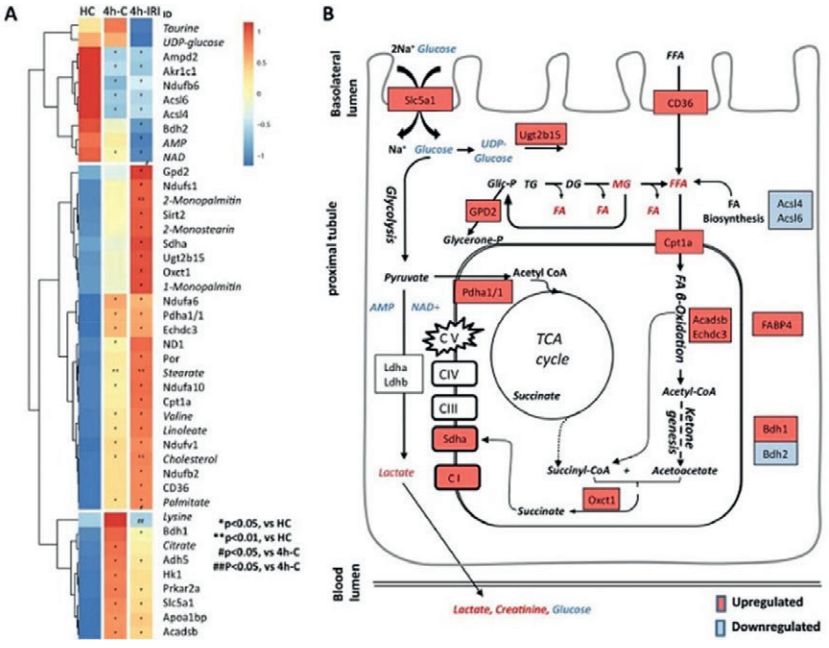
Background: Ischemia reperfusion injury (IRI) contributes to acute kidney injury (AKI) and to delayed graft function which can be up to 50% due to prolonged cold ischemia time kidney transplantation. A hallmark of IRI is activation of the complement system but so far, there is little known about the different roles of the two C5a receptors (C5aR1 vs. C5aR2). In this study C5aR1 and C5aR2 deficient mice were investigated used in the renal IRI model and different pathological responses were by longitudinal monitoring.
Methods: Unilateral IRI of 45 min was done in C5aR1, C5aR2 -/- and wild type mice (WT). Renal morphology, inflammation, regeneration and renal fibrosis were investigated by immunohistochemistry and qPCR. To measure renal perfusion functional magnetic resonance imaging (MRI) was done at day 1, 7 and 21. Renal tissue was processed for high content antibody microarrays and differential total protein and phospho protein expression was analyzed. Based on the proteomics results AKT and p-AKT protein expression in the tissue was investigated by Western blotting.
Results: Extensive renal fibrosis was detected in WT mice within 3 weeks after IRI whereas C5aR deficient mice showed partial protection. Especially, C5aR2 deficient mice showed enhanced tubular proliferation measured by Ki-67 expression and improved renal perfusion over time.

Macrophage infiltration was attenuated in C5aR2 -/- mice and the transcript of the anti-inflammatory cytokine IL-10 was significantly up-regulated. Moreover, proteomics revealed significantly enhanced phosphorylation of the pro-angiogenic FGF1 in C5aR2-/- IRI kidneys at d1. In addition, total AKT protein and consecutively also phospho-AKT was significantly higher in C5aR2-/- compared to the other mouse strains.
Conclusion: C5aR2 deficient mice have enhanced p-FGF and p-AKT levels after IRI which might have contributed to improved regeneration of peritubular capillaries, tubular epithelial cells and better renal.



OS003 IPC REDUCES IRI IN THE RAT KIDNEY BY REPRESSING ITS UNIQUE MICRORNA EXPRESSION PROFILE

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Background: MicroRNAs are important post-transcriptional regulators of gene expression, implicated in many physiological and pathophysiological processes, including kidney disease. Ischaemia reperfusion injury (IRI) is an inevitable consequence of transplantation and results in delayed graft function and primary non-function. The aim of this research was to characterise the role of microRNAs in kidney IRI and their response to the therapeutic strategy of Ischaemic Preconditioning (IPC).
Methods: An *in vivo* model of IRI and IPC was utilised, in which adult male lewis rats underwent surgery and were divided into 3 groups: sham; IRI (45 min bilateral renal pedicle cross-clamping); and IPC+IRI (3 cycles of 2 min ischaemia and 5 min reperfusion, prior to 45 min of IRI). Kidney tissue was retrieved at 48 h and blood samples taken at 0 h and 48 h. Histological, biochemical and mRNA AKI marker analysis was undertaken. MicroRNAs were profiled using Next Generation Sequencing (NGS) and hybridisation arrays, and changes in selected microRNAs confirmed by RT-qPCR.
Results: IRI was characterised by: marked histological damage including acute tubular necrosis and endothelial cell loss; increased serum creatinine; and increased NGAL and KIM-1 expression. In contrast IPC reduced the histology scores, serum creatinine and NGAL and KIM-1 expression. NGS and Microarray analyses identified 18 differentially expressed microRNAs in IRI, which were confirmed by RT-qPCR. This microRNA expression profile was attenuated by IPC, with particular changes noted in 4 microRNAs ((miR-21, -221, and -222, up-regulated in IRI and down-regulated by IPC) and (miR-375-3p, down-regulated in IRI and up-regulated by IPC)).
Conclusion: These data have identified a unique microRNA signature of IRI in the rat kidney, and have shown that pulsatile IPC improved injury by attenuating this microRNA signature. MicroRNAs thus show significant promise as biomarkers of injury and potential therapeutic targets in this context.

OS004 ADMINISTRATION OF MESENCHYMAL STROMAL CELLS BEFORE RENAL ISCHEMIA/REPERFUSION ATTENUATES KIDNEY INJURY AND MODULATES RENAL LIPID METABOLISM IN RATS

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Background: Mesenchymal stromal cells (MSC) have been demonstrated to attenuate renal ischemia/reperfusion (I/R) damage in rodents. The mechanisms of such nephroprotection remain unclear.
Materials and Methods: Male *Lewis* rats aged of 8–10 weeks received tail i.v injection of $1.5x10^6$ MSC in 1 mL saline (MSCD-7, $n = 11$) or saline alone (SD-7, $n = 6$) 7 days before renal I/R. Left renal ischemia (by clamping the renal pedicle) lasted 45 min. Right nephrectomy was simultaneously performed. Blood sample was collected from inferior vena cava 48 h post reperfusion. Renal function was assessed by measuring serum creatinine (SCr) levels. Expressions of inflammatory and apoptotic markers by real-time (RT)-qPCR were comparatively quantified. High-throughput RNA sequencing was applied to MSCD-7 vs. SD-7 non-ischemic right kidneys. Relevant pathways were detected using an Over-Representation Analysis with WebGestalt, and confirmed by RT-qPCR.
Results: Scr levels reached 1.4 ± 0.7 vs. 2.4 ± 0.8 mg/dL in MSCD-7 vs. SD-7 group ($p < 0.05$). MSC infusion significantly reduced mRNA expression of *Casp3, Hsp 70, Kim-1, Mcp-1* and *Il-6* and increased mRNA expression of *Bcl* compared to saline. Among 25 908 genes, 748 were identified as significantly differentially expressed (False Discovery Rate (FDR), <0.05) between MSCD-7 and SD-7 non-ischemic kidneys. Among the most affected metabolic pathways, renal lipid metabolism was significantly altered, with down-regulation of fatty acid biosynthesis and an up-regulation of PPARα pathway in MSCD-7 vs. SD-7 groups. By immunoblotting, PPARα and phosphorylated-PPARα were significantly increased in MSCD-7 vs. SD-7 kidneys, in both non-ischemic and ischemic conditions. Moreover, levels of malondialdehyde-derived lipid peroxidation products were decreased in MSCD-7 ischemic kidneys in comparison to SD-7 ischemic kidneys.
Conclusion: MSC infusion at day 7 prior injury critically impacts renal lipid metabolism, which may condition kidney parenchyma against I/R.

OS005 COLLECTIN-11 PROMOTES RENAL TUBULOINTERSTITIAL FIBROSIS FOLLOWING RENAL ISCHEMIA REPERFUSION

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Collectin-11 (CL-11) is a newly identified collectins of the innate immune system and recently has been suggested to play a pathogenic role in acute kidney injury induced by renal ischemia reperfusion (IR). However, the impact of CL-11 on the late phase of renal IR injury is unknown. In the present study, we investigated whether CL-11 is involved in the pathogenesis of renal tubulointerstitial fibrosis following renal IR and the underlying mechanisms.

We employed a murine model of renal IR injury and CL-11-/- mice to determine the roles of CL-11 in renal inflammation and tubulointerstitial fibrosis. To investigate cellular mechanisms that CL-11 contributes to renal inflammation and the development of tubulointerstitial fibrosis we performed a series of *in vitro* experiments using freshly prepared peritoneal neutrophils or mono/macrophages and primarily cultured renal fibroblasts.

We show that CL-11 deficiency protected mice from the development of tubulointerstitial fibrosis following renal IR. Compared to the wild littermates, CL-11-/- mice had significantly reduced renal fibrosis, as evidenced by reduced renal function impairment, tubular injury, renal leukocyte infiltration (i.e. CD45, neutrophils, macrophages), collagen deposition in the kidney as well as intrarenal gene expression of proinflammatory (TNF-alpha, IL-1beta, IL-6) and profibrotic (TGF-beta) molecules. *In vitro* study showed that CL-11 had potent effects in promoting leukocyte migration and stimulating renal fibroblast proliferation.

Therefore, our findings demonstrate a pathogenic role for CL-11, particularly locally produced, in renal tubulointerstitial fibrosis following renal IR and suggest a novel mechanism for CL-11 in promoting leukocyte chemotaxis and stimulating fibroblast proliferation in renal fibrosis. CL-11 may represent a novel therapeutic target in both the early and late phases of kidney IR injury.

Translational Kidney Ischemia-reperfusion and preservation

OS006 DIRECT COMPARISON OF HYPOTHERMIC AND NORMOTHERMIC MACHINE PERFUSION IN A PORCINE *EX-VIVO* KIDNEY MODEL

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Background: Hypothermic machine perfusion (HMP) is a well established method for deceased donor organ preservation, assessment and preconditioning. Translational studies have shown that normothermic perfusion (NMP) offers similar and perhaps greater advantages. However, data on a direct comparison of the two methods are scarce. Therefore, the aim of this study was to compare the two methods in an *ex-vivo* model using porcine kidneys.
Methods: 16 kidneys from 8 donor pigs retrieved at an abattoir after 25 min of warm ischaemia time were stored on ice for 24 h. They were then perfused hypothermically (4°C, $n = 7$) or normothermically (37°C, $n = 7$) for 4 h using an RM3 pulsatile perfusion machine or left on ice ($n = 2$). Kidneys were reperfused with whole blood for 2 h at 37°C. Physiological parameters e.g. perfusate flow rate, urinary output and oxygen consumption were compared. Levels of IL-1β and NGAL in perfusate samples were measured by ELISA and mRNA expression of TNFα, IL-1β, NGAL and EDN-1 were determined by RT-PCR. Statistical analysis was performed using ANOVA.
Results: Kidneys after HMP showed significantly higher urinary output (5.7 ± 2.26 ml/min vs. 2.15 ± 1.24 ml/min, $p = 0.0048$) as well as oxygen consumption ($p = 0.0032$) and perfusate flow rates ($p = 0.036$) at reperfusion than kidneys after NMP. At mRNA level, expressions of proinflammatory markers were higher for the HMP group, which reached significance for the expression of EDN-1 ($p = 0.03$). IL-1β levels in perfusate samples were similar between the two groups.
Conclusion: In direct comparison to normothermic machine perfusion, hypothermic machine perfusion of porcine kidneys resulted in improved physiological parameters and led to significantly increased urinary output rates despite showing a higher upregulation of inflammatory markers at mRNA level. Further investigations of the physiological and immunological parameters of both preservation methods are needed to optimise outcomes.

OS007 PRELIMINARY RESULTS ON IMPACT OF DIFFERENT MACHINE PERFUSION STRATEGIES ON EARLY RENAL FUNCTION IN A PORCINE DCD AUTO-TRANSPLANT MODEL

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Background: Hypothermic machine perfusion (HMP) and end ischemic *ex vivo* normothermic perfusion (EVNP) have demonstrated improved early graft function compared to static cold storage (SCS). The aim of our study was to evaluate the impact of several machine perfusion variables on early graft function.
Methods: A porcine auto-transplant model was used. The left kidney of female Landrace pig (35–40 kg) was exposed to 30 min of warm ischemia by vascular clamping and preserved by 1 of the 6 study groups: 1) 22 hrs SCS, 2) 22 hrs HMP, 3) 22 hrs oxygenated HMP, 4) 20 hrs HMP + 2 hrs EVNP, 5) 20 hrs SCS + 2 hrs oxygenated HMP, and 6) 20 hrs SCS + 2 hrs EVNP. The LifePort Kidney Transporter® (Organ Recovery Systems) was used for all machine perfusion strategies. The left kidney was auto-transplanted in a right orthotopic position. The primary endpoints were kidney function and graft survival at 2 weeks.
Results: 34 auto-transplants were performed (minimum 5 pigs per study group). Peak serum creatinine at day 3 after transplantation was significantly lower both in the 22 hrs oxygenated ($p = 0.0025$) and non-oxygenated HMP ($p = 0.0134$) group compared to the other study groups. There was no significant difference between 22 hrs oxygenated and non-oxygenated HMP groups ($p = 0.7480$). Use of delayed machine perfusion strategies, oxygenated HMP as well as EVNP, yielded higher serum creatinine peaks compared to continuous HMP strategies. Renal function at 1 week and 13 days was comparable between all groups. EVNP provided the highest renal blood flow compared to other machine perfusion groups. No difference was found in perfusate biomarkers (AST, LDH, glucose) between machine perfusion groups.
Conclusion: HMP strategies only when applied from time of kidney procurement until transplantation until transplantation and irrespective of supplemental oxygenation, led to a positive effect on early graft function. End ischemic EVNP contributed to higher renal blood flow, but did not affect early graft function.

OS008 *EX VIVO* NORMOTHERMIC RENAL HEMO-PERFUSION: A FUNCTIONAL EXPLORATION OF PERFUSION, FILTRATION, TRANSPORT AND RESPIRATORY PERFORMANCES OF PIG KIDNEYS AFTER SHORT-TERM COLD-STORAGE

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Background: To preserve or recondition lower quality organs, *ex vivo* normothermic perfusion (EVNP) gains interest, but mechanisms are unclear and experimentals show strong heterogeneity. We explore the functional status of cold-stored kidneys next submitted to 2 h-EVNP with Krebs-Henseleit (KH) vs. plain whole-blood (WB). To reduce the use of animals, we use Pig kidneys from transplantation studies and WB from end-protocol controls.
Methods/Material: Kidneys flushed and cold-stored (SCOT15®; 3 h); WB were cold-stored in CPDA-1 bags. The kidney was mounted for perfusion flow (PEF mL/(min/g)) and urine production (UP, μL/(min.g)) monitoring, at constant 80 mmHg pressure (PP); renal resistance RR = PP/PEF. Perfusion media were equilibrated with 95%O2/5%CO2 (KH, 60% BSA). Na fractional reabsorption (FRN) was calculated from glomerular filtration rate (GFR; μL/(min.g) = creatinine clearance), Na transport (μmol/(min.g)) and excretion (μmol/(min.g)); av-QO2 consumption (QO2, μmol/(min.g)) was calculated from PEF and arterial and venous O2 levels. Results given as mean ± SD(*n*).
Results: (Hep = Heparin): 1) KH-BSA yields the highest PEF and QO2, but low GFR and UP, and insignificant Na reabsorption and TNa/QO2 (a measure of transport efficiency). 2) When perfusing with WB-250 UI/l Hep, PEF decreases, but GFR, TNa, FRN and UP increase; conversely, QO2 is reduced (TNa/QO2 increased). 3) Increasing Hep to 5000 IU/l, PEF remains similar, but GFR, UP, TNa, FRN, and transport efficiency strongly increase (2–6 fold).
Conclusion: EVNP optimal conditions remain to be established. Using a Pig preclinical model of static cold storage, we show a strong decoupling between (high) perfusion (high) and function (very low) with KH-BSA, which thus appears unsuitable for renal function. Conversely, properly heparinized whole-blood yields better function, approaching "physiological" values, especially in terms of transport respiratory efficiency. On behalf of the COPE consortium.

	n	PEF	RR	GFR	UP	TNa	FRN	QO2	TNa/QO2
KH-BSA	6	2.9 ± 1.0	0.24 ± 0.10	3.5 ± 3.0	2.1 ± 2.0	0.0 ± 0.1	11 ± 8	1.5 ± 0.5	0.0 ± 0.1
WB-250	5	0.8 ± 0.6	1.70 ± 1.1	7.4 ± 6.8	5.3 ± 2.7	2.4 ± 1.0	64 ± 6	0.4 ± 0.4	4.3 ± 2.0
WB-5000	4	1.0 ± 0.3	0.67 ± 0.24	48.1 ± 26	11.1 ± 7.0	9.3 ± 4.6	80 ± 20	0.9 ± 0.2	10.1 ± 4.8

(units above).

Translational Kidney Immunology

OS009 GENERATION OF NATURAL ANTIBODIES POST TRANSPLANT AND ASSOCIATION WITH KIDNEY ALLOGRAFT LOSS

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The development of donor specific antibodies (DSA) reacting to mismatched donor class I and class II HLA is a prominent risk factor for kidney graft loss. Over the past few years our lab investigated the implications of a different type of antibodies referred to as natural antibodies (Nabs) in the outcome of kidney transplant alongside DSA. These antibodies are polyreactive IgG binding to multiple immunogenic determinants, including oxidized epitopes. Here, we assessed Nabs in 1462 serum specimens collected from 635 patients immediately pre-transplant and either at time of biopsy proven rejection within the first year post-transplant or at one year post-transplant in patients without immunological event. This large prospective observational cohort from Necker Hospital in Paris, France, includes patients transplanted between 2005 and 2010. All specimens were tested blindly from the patient clinical information. Nabs were assessed by ELISA through their reactivity to malondialdehyde (MDA). A univariate Cox regression model identified the development of Nabs

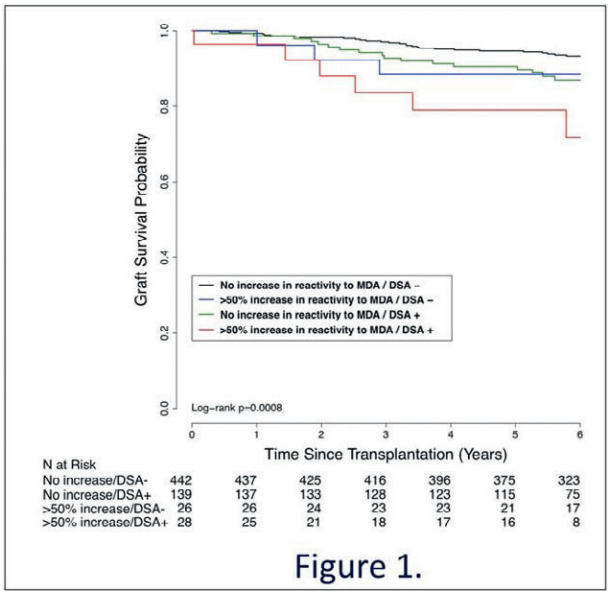

Figure 1.

post-transplant (>50% increase in reactivity to MDA) as a significant risk factor for graft loss ($p = 0.0078$; HR = 2.372). A multivariate Cox confirmed the development of Nabs as a risk factor independent from DSA. Furthermore, the development of Nabs synergized with DSA (Figure 1) resulting in increased risk of kidney graft loss. These findings support an association of Nabs with kidney transplant survival and suggest their potential implication in immune mechanisms of rejection

Basic Kidney Immunology

OS010 NATURAL KILLER CELLS ARE POTENT EFFECTORS OF THROMBOINFLAMMATORY ENDOTHELIAL DYSFUNCTION ASSOCIATED TO ANTIBODY-MEDIATED TRANSPLANT VASCULOPATHY

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Background: Specific alloantibodies (DSA) are involved in the progression of kidney allograft vascular lesions and transplant associated thrombotic microangiopathy (TA-TMA). This work aimed to investigate whether antibody-driven Natural Killer cell cytotoxic activation (NK-ADCC) can be identified as a mechanism promoting prothrombotic adverse effects of donor specific alloantibodies (DSA). Our working hypothesis was that CD16-dependent NK cell recognition of antibody coated cells may favour acquisition of a procoagulant endothelial phenotype.
Methods: A flow cytometry (FCM) Cellular Humoral Activation Test (NK-CHAT) was designed to evaluate CD16-dependent NK-cell activation towards allogeneic endothelial cells in response to DSA. Endothelial activation and TF-dependent microparticle release
was evaluated by FCM analysis of ICAM1/CD54 and Tissue factor (TF/CD142) cell surface expression endothelial activation markers. Evaluation of tissue factor dependent procoagulant activity of microparticles released in response to DSA-triggering of NK cell ADCC was evaluated by assay of FXa generation in presence of FX et FVII.
Results: NK-cell recognition of DSA-coated endothelial cells could be associated with up regulation of Tissue Factor transcripts, enhanced susceptibility of allogeneic glomerular cells to NK-cell mediated lysis and increased endothelial cell microvesicle release. Endothelial microparticles resulting from DSA-driven NK cell activation towards endothelial cells expressing cognate HLA alloantigens, exhibit enhanced TF dependent procoagulant activity *in vitro*.
Conclusions: Our data suggest that upon exposure of graft vasculature to DSA, NK-cell recognition may promote thrombotic and inflammatory activation associating to allograft vascular injury. Through indexing of complement independent mechanisms that control intensity of DSA cytotoxic effects, non-invasive NK-CHAT monitoring may allow to refine appraisal of humoral and thrombotic risk on an individual basis.

Basic Others Immunology

OS011 IMMUNOSUPPRESSIVE TREATMENT ALTERS GUT MICROBIOTA AND MODIFIED GUT MICROBIOTA AFFECTS IMMUNE STATUS

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Introduction: Immunosuppressive therapies in transplantation could change the host-microbial interactions, especially gut microbiota in transplant recipients, which is an important component in systemic immunity. We tried to investigate the immune function by fecal microbiota transplantation in mice models.
Materials and Methods: Mice models were established using C57BL6 mice, male, 6–8 weeks. Tacrolimus group (T group) ($n = 8$) were given 10 mg/kg tacrolimus by gavage each day; fecal microbiota transplantation group (F group) ($n = 8$) took fresh feces from T group (No tacrolimus left tested by ELISA); control group (C group) ($n = 5$) transplant fresh feces from blank mice. Flow cytometry has been used to characterize peripheral blood lymphocytes and gut microbiota was analyzed by 16S rRNA gene sequencing. Skin transplantation acute rejection model is established by Babl/C mice to C57BL6 mice.
Results: Phylogenetic classification of 16S rDNA frequencies in the fecal from samples collected from control group, tacrolimus group on 14 days, or FMT group on 14 days. Erysipelotrichales at the order level shows the most significant differences.($p < 0.001$, ANOVA test) (Figure 1). Comparing with T group, F group shows the similar tendency on gut microbiota after 7 days. The percentage of Treg cell was significantly increased in both groups, T group has higher percentage and earlier increase than F group. Both group has lower IL-2 expression in many type of T cell (CD3 +, CD4 +, CD8 +, Treg cell) (Figure 2). Allograft skin in mice showed striking differences after day 5. Survival analysis showed that FMT and Mixture group prolonged the survival time of allograft skin, which is significantly different to Saline group ($p < 0.01$) (Figure 2).
Conclusion: Based on these findings, the gut microbiota could be changed by systemic immune status, such as immunosuppressive therapies, and modifications of gut microbiota are considered to affect the immune status.

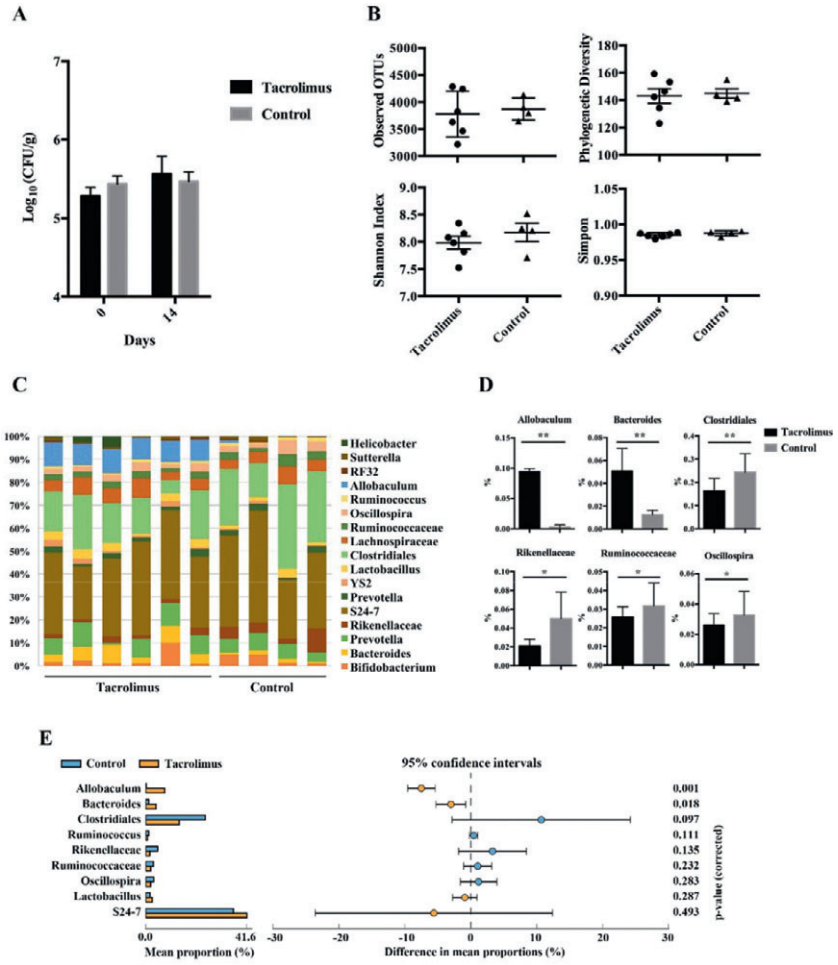
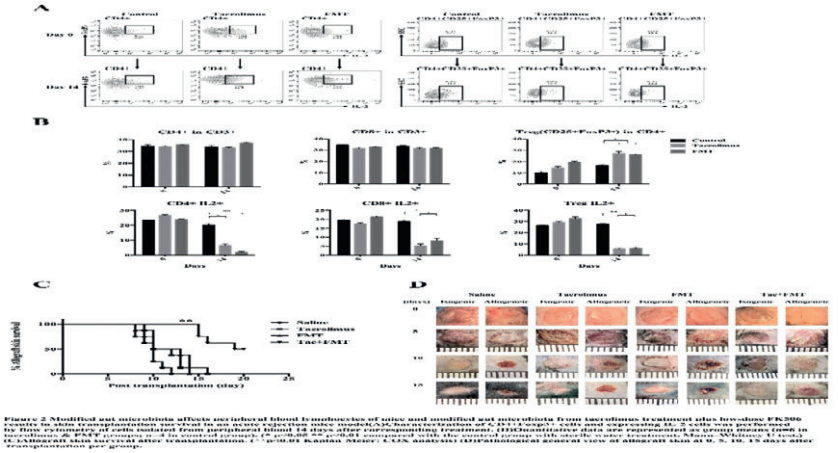


Figure 1 Effect of tacrolimus on microbiota in fecal samples. Mice received an oral gavage daily dose of tacrolimus 10mg/kg or sterile water. (A)Fecal sample's CFU (colony-forming unit) shows no difference at day 14 between tacrolimus and control groups. (B)The comparison of community diversity indices as group means on 16S rRNA gene sequences shows no difference between these groups at day14. (C)Phylogenetic classification of taxonomy (genus level) in the fecal samples from each groups at day 14. Each bar represents the microbiota of an individual mouse. (D)(E)Relative abundance at the genus level in fecal samples from each group. Allobaculum shows the most significant increase in tacrolimus group, and other changes were also seen in fecal samples from mice treated with tacrolimus. (n=6 in tacrolimus group; n=4 in control group)(* p<0.05 ** p<0.01 two-sided Welch's t-test)



Basic Heart Immunology

OS012 TOLL-LIKE RECEPTOR (TLR)-3 - A NOVEL TARGET FOR THE PREVENTION OF ISCHEMIA-REPERFUSION INJURY IN CARDIAC TRANSPLANTATION

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Background: Toll-like receptor (TLR)-3 represents a pattern recognition receptor involved in the innate immune response. Recently it has been proposed as a candidate molecule for the modulation of cardiac ischemia reperfusion (IRI) *in vitro*.
Methods: In order to investigate the detailed effects of TLR3 on cardiac IRI *in vivo*, syngeneic heart transplantation was performed in either C57BL/6 wild type (WT) or TLR3 knockout ($TLR3^{-/-}$) mice following 9 h of cold ischemia.
Results: TLR3 knockout significantly diminished IRI-related injury 48 h after reperfusion as demonstrated by a cumulative histological damage score ($TLR3^{-/-}$: 5.8 $\pm$ 0.8 vs. WT: 8.8 $\pm$ 0.3; $p = 0.006$). In particular, epicardial and myocardial damage was alleviated ($p < 0.05$, respectively). Furthermore, the presence of infiltrating lymphocytes significantly decreased ($p = 0.0009$). This was accompanied by reduced intragraft (CCL3, CCL4) and splenic mRNA expression of pro-inflammatory cytokines (TNFα, IL1b, CCL4, CXCL10; all $p < 0.05$). Whereas elevated levels of anti-inflammatory factors (TGFβ) were observed, those indicating hypoxia (HIF1α) significantly declined ($p < 0.05$, respectively). Importantly, in contrast to the depletion of TLR3 expression in $TLR3^{-/-}$ recipient grafts and spleens, other toll-like receptors (TLR2, TLR4) remained unaffected, indicating that the observed protective effects were solely due to TLR3 deletion.
Conclusion: This study outlines for first time the detrimental influence of TLR3 signaling on the development of IRI after cardiac transplantation. Our data indicate that TLR3 represents a possible novel target for future pharmacologic therapies in solid organ transplantation.

Basic Cell Other

OS013 IMPACT OF CULTURE EXPANSION AND INFLAMMATORY CYTOKINE CHALLENGE ON DNA METHYLATION PROFILES IN MSC

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Mesenchymal stromal cells (MSC) are studied as possible immunotherapy after solid organ transplantation. To obtain sufficient numbers, cells need to be expanded in culture. Also, MSC may be challenged with inflammatory cytokines to optimise their immunomodulatory properties. It is unknown whether culture expansion and inflammatory challenge induce epigenetic changes in MSC that could affect their function by gene expression changes. In this study, changes in DNA methylation patterns in MSC after cytokine stimulation and culture expansion were examined.

Human umbilical cord derived MSC were cultured for 3 days with IFNγ, TGFβ or a combination of cytokines (MC), which consists of combined stimulation with IFNγ, TGFβ and retinoic acid). Next, cytokines were removed and MSC were cultured for another 14 days. Genome-wide DNA methylation was measured (single CpG site, gene ontology and regions) directly after stimulation (day3) and after long term removal of cytokines (day17) with Infinium MethylationEPIC Beadchip and analysed with R.

At day3, CpG site located on chromosome 2 (Cg00221794), within active enhancer regions, was significantly hypermethylated in MSC(IFNγ) and MSC (MC), compared to MSC(-). At day17, this site remained hypermethylated, with an additional 5 and 16 differently methylated CpG sites (DMS), respectively. TGFβ stimulation did not affect DNA methylation. Comparison of MSC(-) at day3 and day17 resulted in >4000 significantly DMS and >100 significantly differentially methylated regions, corresponding to cytoskeleton, mitochondria, apoptosis and immune related genes.

DNA methylation patterns of MSC are altered by various cytokines, some of which persist after removal of cytokines, indicating imprinting. Interestingly, we observed a large impact of *in vitro* culturing on the DNA methylation patterns of MSC. These findings impact the way we currently look at and implement MSC stimulation, as well as the manner of culturing of MSC, which greatly influence them.

OS014 TRACKING AND FATE OF UMBILICAL CORD DERIVED MSC AFTER INTRAVENOUS INFUSION IN MICE

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Mesenchymal stromal cells (MSC) are under investigation as an experimental immunotherapy after solid organ transplantation. Their administration is commonly by intravenous (IV) infusion, although previous studies have reported that MSC infused by this method are trapped in the lungs and mostly disappear within a day. It is unclear what happens to MSC after their disappearance from the lungs. In this study we examine the fate of IV infused MSC after their disappearance from the lungs and the role of the innate immune system in the shortevity of MSC.

Human umbilical cord derived MSC were double-labelled with Qdots, which are contained in live cells, and Hoechst, which is a DNA stain visible in live and dead cells. 150 000 labelled MSC were infused IV into C57Bl/6 mice. To analyse the biodistribution of live and dead cells, whole body imaging was performed at 5 min and 24 h via 3D imaging using CryoViz. Additionally, immune cells were co-cultured together with PKH26 labelled MSC for 1, 4 and 24 h, next phagocytosis of MSC by these cells and monocyte phenotype were analysed using flow cytometry and confocal microscopy.

Directly after administration, the majority of MSC were alive and located in the lungs (70 ± 16.10^3). After 24 h a significant decrease in the numbers of live MSC in the lungs (14 ± 7.10^3) was observed, whereas an accumulation of dead cells was observed in the liver (32 ± 11.10^3). *In vitro*, a significant increase over time of PKH26 positive neutrophils (22 ± 8 *p*) and monocytes (91 ± 3 *p*) was observed after 24 h. Also, MSC induced monocytes towards a $CD14^{++}CD16^{+}$ and $CD14^{+}CD16^{++}$ phenotype.

From these data we can conclude that after getting trapped in the lungs, MSC are relocated to the liver, where at this stage most MSC are dead. Meanwhile, monocytes are activated and rapidly start to phagocytose MSC, affecting their polarization. These findings help us elucidate the fate of MSC after intravenous infusion, which enables further understanding of the mechanism of MSC immunotherapy.

Basic Others Other

OS016 NK CELLS PREFERENTIALLY TARGET MATURE LYMPHOCYTES UNDER INFLAMMATORY CONDITIONS BY MISSING-SELF RECOGNITION

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Background: The classical hybrid resistance model allowed to investigate the basic principles of natural killer (NK) cell mediated bone marrow (BM) rejection including missing-self recognition. In this model F1 (BL6 $\times$ BALB/c) recipients are lethally irradiated and NK cells are pre-activated to reject parental BM. The establishment of irradiation free regimens inducing mixed chimerism to achieve transplantation tolerance now demands to reconsider the circumstances under which NK cells reject allogeneic BM.
Methods: To assess successful engraftment and chimerism, we bred F1 mice whose leukocytes concomitantly express both CD45.1 and CD45.2. Irradiated or non-irradiated F1 recipient mice received varying doses (20–5 $\times$ 106) of unseparated parental BALB/c (CD45.2) or syngeneic CB6F1F1 (CD45.2) BM cells. Selected mice received total body irradiation (d-1), α-NK1.1 (d-1,d2,d5, d8) or poly (I:C) (d-1).
Results: 20 $\times$ 106 BALB/c BM cells readily engrafted in F1 mice receiving 3 Gy total body irradiation. Gradually decreasing irradiation intensity revealed that non-irradiated F1 mice were not able to reject parental BALB/c BM even at low doses (5 $\times$ 106). However, the effect of hybrid resistance became noticeable by lower chimerism levels of BALB/c donors compared to syngeneic F1 donors (1.4 ± 0.08 *p* vs. 2.8 ± 0.17 *p*, $p = 0.0003$). Chimerism persisted

for 150 days and recipient NK cells re-shaped their receptor repertoire in favor of donor cells. Pre-activating NK cells with the TLR-3 agonist poly (I:C) significantly reduced parental chimerism but could not completely abolish it. In contrast, poly (I:C) treated mice were able to completely reject equal numbers of BALB/c lymph node cells.
Conclusion: Therefore we conclude that NK cell mediated BM rejection in non-irradiated recipients is markedly enhanced in the course of inflammation and preferentially targeted against mature lymphocytes while NK cells preferably adapted to allogeneic cells under non-inflammatory conditions.

Clinical Liver Donation and donor types

OS017 INFLUENCE OF TYPE II DONATION AFTER CARDIAC DEATH IN HEPATOCELLULAR CARCINOMA RECIPIENTS

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Background: Liver transplantation (LT) is limited by the availability of liver grafts, despite the use of extended criteria donors to increase the donor pool. Type II donation after cardiac death (DCD) is accepted as a source of grafts in order to increase the ratio of donors to recipients. Hepatocellular carcinoma (HCC) is an extended and established oncological indication for LT. The aim of this study is to determine how grafts obtained from DCD type II influence in the survival in HCC patients, comparing with those obtained from a donation after brain death (DBD).
Methods/Materials: A retrospective study on data extracted from a single institute was performed. During the period between January 2006 and December 2015, 711 LT were performed. Excluding HIV positive recipients, split grafts and simultaneous kidney and liver transplantation, we analyzed 404 patients. There were 146 recipients listed for HCC, 37 of which received a DCD type II LT (group A) and 109 received a DBD LT (group B). A comparison was made between groups A and B.
Results: The mean age in group A was 61 $\pm$ 7 and in group B 57 $\pm$ 8 ($p = 0.03$). Average MELD was 13 $\pm$ 5 in group A and 11 $\pm$ 6 in group B; MELDNa value was 15 $\pm$ 6 vs. 11 $\pm$ 5 in group B ($p < 0.05$). McCluskey index (group A 3 vs. group B 2) and ICU stay (group A 6.3 days vs. group B 6.5 days) were similar. The rates of HCV in groups A and B were 57% and 75% respectively. Average donor age was similar in both groups. DCD type II and DBD had equivalent 1.3 and 5 year overall survival in patients with HCC (88%, 73% and 73% in group A vs. 87%, 83% and 80% in group B; $p = 0.4$). For both DBD and DCD grafts main cause of death was HCV recurrence, stroke being the second one in DBD grafts and sepsis in DCD grafts.
Conclusions: Despite these results, we need a larger sample size and a longer term follow-up. DCD type II has no influence on the OS in the first year after LT in HCC recipients. Recipients with DCD type II do no worse in terms of OS at 3 and 5 years than those with DBD.

OS018 PREVENTION OF ISCHEMIC CHOLANGIOPATHY AFTER DCD LIVER TRANSPLANTATION: ROLE OF THROMBOLYTIC DONOR FLUSH AND SHORT COLD ISCHEMIA TIME

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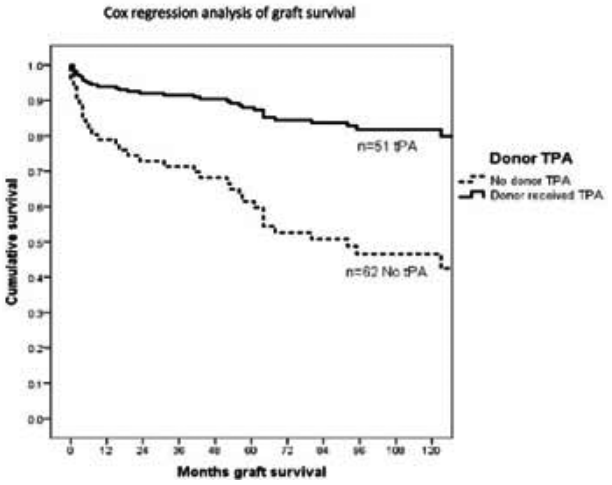
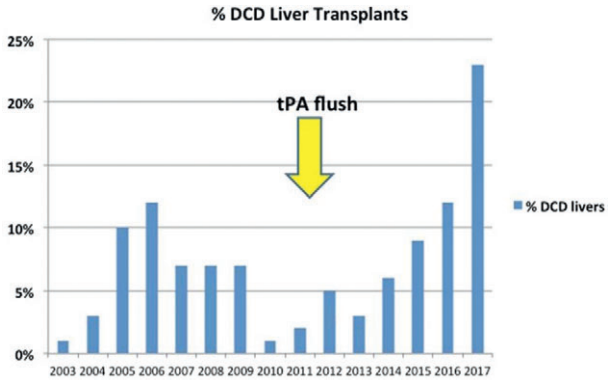
Background: Donation after cardiac death (DCD) donor pool remains underutilized for liver transplantation (LT). Ischemic cholangiopathy is a major complication associated with DCD LT, often leading to graft loss. To prevent IC, we introduced thrombolytic flush along with measures to shorten ischemic times.
Methods: Outcomes of DCD LT performed at our center from 2004 to 2016 were reviewed retrospectively. In July 2011, to improve outcomes, measures were taken to minimize CIT, operative time and recipient WIT along with the use of tissue plasminogen activator (tPA) flush during DCD procurements. During DCD procurements 100 mg tPA in 1L normal saline at room temperature was flushed through aortic cannula prior to cold preservation. Once the liver was deemed suitable for transplant, the recipient preparation and surgery was started by another surgeon to minimize CIT. Fifty-one such consecutive DCD LTs were performed prospectively (tPA group). Outcomes were compared with 62 historic controls (control group).
Results: With the introduction of optimization maneuvers (tPA group), the median CIT, hepatectomy time, and recipient WIT were significantly shorter [Table 1]. In the tPA group there were fewer overall biliary complications and none developed IC (0% vs. 18%; $p = 0.001$). One-year graft survival was better in tPA group (94% vs. 79%; $p = 0.02$) [Figure 1]. With this approach percentage of DCD liver transplants has increased to 23% at our program [Figure 2].
Conclusions: Optimizing peritransplant conditions, such as shortening ischemic times with the use of thrombolytic donor flush, may prevent IC after DCD LT. With this approach, the DCD donor pool may be expanded.

Table 1

	Donor tPA Flush ($n = 51$)	No Donor tPA Flush ($n = 62$)	p
Recipient laboratory values*			
Peak ALT	1196	805	0.83
Peak Total Bilirubin	7.6	6.4	0.61
Overall biliary complications			
Anastomotic stricture	27%	45%	0.04
Ischemic cholangiopathy	0%	18%	0.001
Early allograft dysfunction**	57%	47%	0.34
Survival outcomes			
7-day graft survival	100%	95%	0.25
30-day graft survival	100%	95%	0.25
1-year graft survival	94%	79%	0.02





OS019 NORMOTHERMIC REGIONAL PERFUSION OF DONORS FOLLOWING CIRCULATORY DEATH IS ASSOCIATED WITH IMPROVED OUTCOMES AND NO CHOLANGIOPATHY

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Introduction: Donation after Circulatory Death (DCD) provides 23% of UK livers for transplantation, but such transplants are associated with primary non function and early graft loss, particularly from ischaemic cholangiopathy, as well as acute kidney injury. Normothermic regional perfusion (NRP), where a circulation is restored to the abdominal organs after circulatory arrest but before retrieval, has been suggested to improve outcomes. Here we review our experience of NRP.
Methods: Data on all patients who had undergone NRP either by ourselves or Papworth hospital were reviewed, and compared to a comparator group of twice the number of patients transplanted before and after each NRP case. Livers that underwent normothermic preservation were excluded.
Results: 22 NRP liver transplants were compared to 44 contemporaneous "controls". The NRP donors were younger (median 37y vs. 50 years) with more head injury donors (36.4% vs. 11.4%), and a shorter cold ischaemic time (medians 355 vs. 429 min). The duration of the withdrawal period to circulatory arrest, and arrest to *in situ* perfusion was the same in both groups. There was one primary non function, 3 hepatic artery thromboses and one re-transplant for cholangiopathy in the non-NRP arm; there were no grafts lost in the NRP arm.

	NRP livers (N = 22)	Comparator cohort (n = 44)
1y actuarial graft survival (censored for death)	100%	88.2%
1 year actuarial patient survival	94.9%	93.8%
1y actuarial graft survival (not death censored)	94.9%	83.4%
Peak ALT (iu/l) in week one (median (IQR))	506 (294–850)	783 (478–1378)
Biliary anastomotic leaks	2 (9%)	5 (11.3%)
Biliary anastomotic strictures	2 (9%)	4 (9.1%)
Ischaemic type biliary strictures	0	9 (20.4%)
Median fall in CKD-Epi GFR at 12 months	19 ml/min	32 ml/min

Discussion: NRP is associated with less early graft damage (ALT rise), better graft survival and less renal impairment compared to contemporaneous DCD liver transplants without NRP. Moreover no ischaemic cholangiopathy was seen post NRP, compared to a 20% incidence in "controls".

OS020 THE OUTCOMES OF DCD TYPE 3 LIVER TRANSPLANTATION IN THREE WELL-ESTABLISHED TRANSPLANT CENTERS

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Background: Over the last 10 years, Belgium, the United Kingdom and the Netherlands had the highest increase in donors after circulatory death (DCD) rate. Each of these countries has a different protocol considering the procurement of DCD grafts that might influence the outcome of transplantation. The aim of this study is to compare the outcomes of DCD type 3 liver transplantation (LT) from three European centers.
Methods: All adult DCD type 3 LT performed in the University Hospital of Leuven, the University Hospital of Birmingham and the Erasmus University Medical Center Rotterdam between January 2009 and August 2016 were included.
Results: A total of 494 DCD type 3 LT were performed. The 1-, 3- and 5-year patient and graft survival for the complete cohort were 89%, 81% and 76% and 84%, 75% and 68% respectively. Patient and graft survival did not differ significantly between the centers. However, the retransplantation rate was substantially higher in Rotterdam (16% compared to 4% in Leuven and 6% in Birmingham, $p = 0.006$). Cold Ischemia Time was the shortest in Leuven (mean 325 min, $p < 0.001$), whereas Total Warm Ischemia Time was the shortest in Rotterdam (mean 44 min $p < 0.001$). Based on a Cox regression on the preliminary data, only recipient age and length of hospital stay had an influence on the patient survival. The incidence of primary non-function, hepatic artery thrombosis and biliary complications, including Non-Anastomotic Strictures, did not significantly differ among the three centers
Conclusion: Based on this study, the survival after DCD type 3 LT is not different among three well-established transplant centers. Furthermore, the incidence of most postoperative complications was similar in the three centers. Surprisingly, the ischemia times and MELD score appear not to be of influence on the patient survival in this cohort. A propensity matched analysis of the data is currently under investigation.

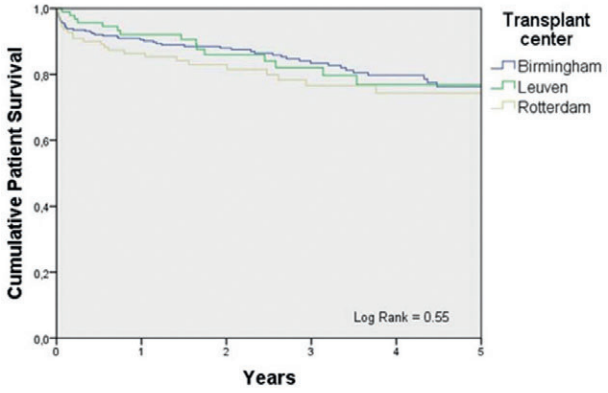

Figure 1: Patient survival

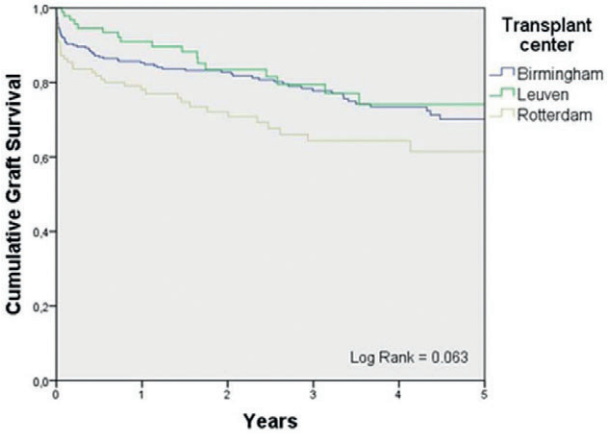

Figure 2: Graft survival (i.e. death or retransplantation)

OS021 FACING PROLONGED WARM ISCHEMIA TIME IN DONATION AFTER CARDIAC DEATH LIVER TRANSPLANTATION: RESULTS OF THE FIRST ITALIAN SERIES

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Background: Donation after cardiac death (DCD) liver transplantation has long been considered impractical in Italy due to the legally obliged no-touch period of 20 min. The application of new technologies such as normothermic regional perfusion (NRP) and hypothermic machine perfusion (HMP) has recently changed this scenario.
Methods: We analyzed the first 10 DCD liver transplants performed at our institution. In all donors (8 uncontrolled and 2 controlled) NRP was established to restore blood flow after death declaration. Acceptance of the grafts was based on the trend of serum transaminase and lactate during NRP, the macroscopic appearance, and the liver biopsy. HMP was associated in 7 cases to improve cold storage before implantation. The 10 DCD liver transplants were

matched to 20 transplants from donation after brain death (DBD) and compared for overall survival, graft survival, and biliary complications. Matching criteria included donor and recipient age and sex, total cold ischemia time, and recipient Model for End-stage Liver Disease score.
Results: Among the DCD group, transplant-related mortality was 0% and one patient was retransplanted due to surgical-related complication. One-year overall and graft survival were both 90% for the DCD group vs. 85% and 90%, respectively, for the matched DBD group ($p = 0.876$ and $p = 0.914$). No cases of ischemic cholangiopathies were observed in the DCD group after a median follow-up of 12 months, and 2 patients developed anastomotic strictures, which resolved after endoscopic stenting. Overall biliary complication rate was not significantly different in the DCD group compared to the DBD group (20% vs. 15%, $p = 0.551$).
Conclusion: DCD liver transplantation is possible in Italy with good results, despite the exceptionally prolonged warm ischemia time. Long-term results and the real impact of this resource are still to be further investigated.

Clinical Others Donation and donor types

OS022 THE FIRST PROTOCOL IN SCANDINAVIA FOR CONTROLLED DONATION AFTER CIRCULATORY DEATH USING NORMO-THERMIC REGIONAL PERFUSION

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Background: Donation after circulatory death (DCD) will increase the number of organs for transplantation and provides the "opportunity" for organ donation as end of life care. We hereby present a study protocol including controlled DCD technique and our preliminary results.
Methods: Data from 8 cDCD using norm-thermic regional perfusion (NRP) and transplantation results were analyzed. The expectations, attitudes and experience of the deceased next of kin were also evaluated in a qualitative investigation.
Results: Patients with unrecoverable brain injury were enrolled in the protocol from 2014 to -15. Life-sustaining treatment was withdrawn in acceptance with the next of kin whom supported organ donation. Cardiac arrest occurred shortly (mean = 14 min, range 6–24) after withdrawal. After 5 min "no-touch" period, the NRP cannulas were inserted after heparinization using Seldinger's technique trough a Secalone T placed premortally in the femoral vein and artery. An aortic occlusion catheter was placed in the descending aorta enabling NRP of abdominal organs only. Mean functional warm ischemic time and NRP time was 32 (range 20–49) and 90 (range 54–106) minutes, respectively. 14 kidneys and 2 livers were retrieved and subsequently transplanted. Due to misplacement of the aortaballon catheter, organs from one donor were not transplanted.

One kidney recipient had delayed graft function and developed graft loss. The other 15 recipients had clinical 1 year outcome after transplantation in line with our results from DBD transplantation. Measured GFR for the kidney patients was 67 ml/min/1.73 m.

No signs of biliary complications have been seen in the 2 liver grafts.
Conclusion: cDCD with NRP helps increase the number of good quality organs for transplantation. Acceptance for cDCD has created challenges for the medical, ethical and transplant community, but excellent transplant outcomes and satisfied next of kin has encouraged us to continue our work.

OS023 THE INTRODUCTION OF A DCD DONOR ASSESSMENT PATHWAY HAS INCREASED DCD REFERRALS, PROCEEDING DCD DONORS AND DECREASED THE RATE OF UNNECESSARY FAMILY APPROACHES FOR CONSENT

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Background: In the UK in 2014/15, 5157 patients in whom imminent death was anticipated were referred to a specialist nurse – organ donation. The approach for consent rate was 47.1%, resulting in 493 DCD donors, with a conversion rate of 9.5%.

The rate of non-proceeding DCD donations was having a negative impact on the families involved, morale, staffing resources within NHSBT and the appetite of healthcare colleagues to make donor referrals.
Methods: A 4 month data collection exercise took place in 2015 to review DCD donor referrals, develop a formal assessment pathway and identify DCD donor exclusion criteria.

Donor characteristics and outcomes from both the exercise and routine audit were collated and analysed. DCD Donor Exclusions were agreed with the clinical community and developed in to a DCD Donor Assessment and Kidney Screening Tool. This was launched throughout the UK for clinical use in December 2015.

The tool has been widely welcomed by referring centres as improving the referral process.
Results: In the 12 months since introduction of the tool there has been 6182 patients referred for assessment as a potential DCD donor

25% were excluded through the systematic application of DCD exclusion criteria

This has resulted in

- Rapid application of Absolute Contraindications and DCD exclusions providing timely updates to referring centres regarding suitability for approach for consent
- Improved engagement and reputation with referring hospitals
- A reduction in inappropriate approaches for consent
- An increase in DCD donor referrals and an associated 20% increase in DCD donors

Conclusion: The implementation of the assessment pathway has improved the reputation of the organisation with a resulting increase in donor referrals.

DCD donor referrals are managed efficiently and effectively with a resulting increase in proceeding DCD donors and a reduction in the number of unnecessary family approaches for consent

OS024 IMPROVING THE OUTCOMES OF ORGANS OBTAINED FROM CONTROLLED DONATION AFTER CIRCULATORY DEATH DONORS USING ABDOMINAL NORMOTHERMIC REGIONAL PERFUSION

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Background: Donation after circulatory death (DCD) has experienced a significant expansion over the last decade. However, warm ischemia results in a greater risk for transplantation. Indeed, controlled DCD (cDCD) was associated with inferior outcomes compared to donation after brain death. The use of abdominal normothermic regional perfusion (nRP) to restore blood flow prior to organ recovery in cDCD has been proposed as a better alternative than rapid recovery to reverse the effect of ischemia and improve recipients' outcome.
Methods: The first Spanish series using abdominal nRP as *in situ* conditioning method is reported. A specific methodology to avoid restoring circulation to the brain after death determination is described.
Results: Twenty-seven cDCD donors underwent abdominal nRP during at least 60 min (September 2014–2016). Donors in our series were much older (median age 58 years) compared to previous studies. Thirty-seven kidneys, 11 livers, 6 bilateral lungs and 1 pancreas were transplanted. All transplant recipients had a minimum 3-month follow-up. The median follow-up of recipients was 17 months (IQR 7–22 months). One year death-censored kidney survival was 91% and delayed graft function was 27%. One year liver survival was 90.1% with no case of ischemic cholangiopathy. Lungs and pancreas transplants performed exhibited primary function.
Conclusions: The use of nRP may represent an advance to increase the number and quality of grafts in cDCD. Poor results in cDCD livers could be reversed with nRP. Abdominal nRP combined with RR of the lungs is safe for both abdominal and thoracic grafts. Concerns about restoring brain circulation after death are easily solved. Further studies are needed to confirm our findings and to explore the impact of abdominal nRP on donor age, upper limit for functional warm ischemic time, ischemic injury modulation or duration of regional perfusion.

Translational Kidney Biomarkers and molecular changes

OS025 GLOBAL EXPRESSION PROFILES OF MIRNA IN ONE-HOUR BIOPSY SPECIMENS OF HUMAN KIDNEY TRANSPLANTATION FROM DONORS AFTER CARDIAC DEATH

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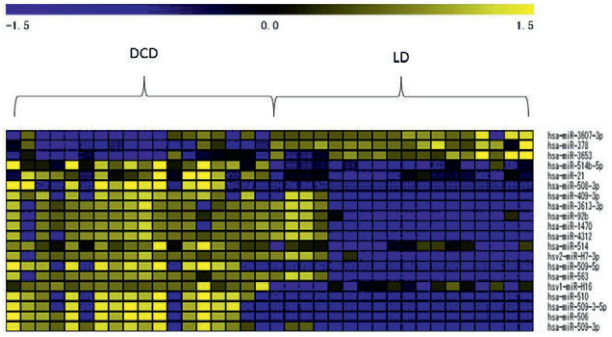
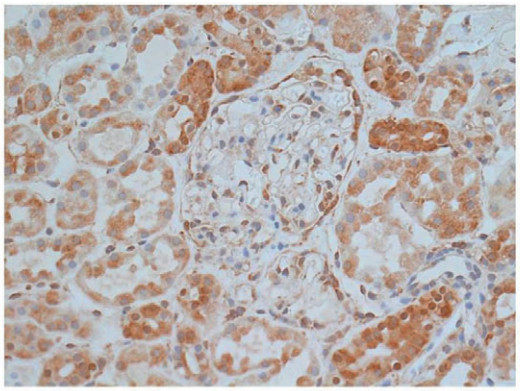
Because of the global shortage of renal grafts, kidney transplantation (KTx) from donors after cardiac death (DCDs) is an alternative way of obtaining KTx from brain-dead donors. Although the prognosis of DCD KTx is gradually improving, the graft often suffers from a delayed graft function (DGF); as such, managing DGF is essential for post-KTx patient care. In an attempt to characterize the etiology of DGF, genome-wide gene expression profiling of miRNA was performed using renal biopsy samples obtained at 1 h after KTx from DCDs ($n = 18$), and the data were compared with those of KTx from living donors (LDs) ($n = 18$). A SurePrintG3 Human miRNA Microarray kit (Release 16.0; Agilent Technologies) was used, and a total of 2549 miRNA genes were analyzed. After performing Z-scoring of the miRNA expression, a total of 20 genes showed significantly different expression profiles between the 2 groups ($p < 0.00001$ by Welch's t-test test).

The validation of the microarray experiments was performed by real-time polymerase chain reaction. The miR-21, miR-514 and miR-509-3p genes were up-regulated, and miR-378 was down-regulated significantly in the DCD group relative to the LD group ($p < 0.005$). We also performed *in situ* hybridization while focusing on the expression patterns and localization of the miR-21 gene. The miR-21 expression was much higher in the renal tubule cytoplasm, in addition to the nucleus of tubules and glomeruli in the DCD kidneys than in the LD kidneys.

miR-21 is a recently identified, typical miRNA that functions as a regulator and is known to be involved in apoptosis as well as the inflammatory and fibrotic signaling pathways in acute kidney injury. These data suggest good miRNA candidates for biomarkers that may be useful for controlling DGF.



A total of 20 genes were found to have significantly different expression profiles between the DCD and LD. Yellow indicates up-regulated genes, while blue shows down-regulated genes (p<0.00001 by Welch's *t*-test).



In situ hybridization of miR-21. The miR-21 expression was markedly elevated in renal tubule cytoplasm, in addition to the nucleus of tubules and glomeruli, in the DCD kidneys.

Basic Kidney Biomarkers and molecular changes

OS026 METALLOTHIONEINS 1 AND 3 DISCRIMINATE ACCOMMODATION AND ANTIBODY MEDIATED REJECTION IN KIDNEY TRANSPLANTATION

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Background: Accommodation has been defined as C4d positivity in ABOi kidney transplant protocol biopsies without rejection and graft dysfunction in the long term, however the involved mechanisms remain to be elucidated. Thus molecular processes involved in accommodation and antibody mediated rejection (AMR) were compared.
Methods: Transcriptome of 3-months protocol biopsies with C4d positivity in patients with normal kidney graft function was assessed in ABOi cohort with present hemagglutinins ($n = 11$) and in ABOc cohort with donor specific anti HLA antibodies (DSA) using Illumina Human HT-12 v4 Expression BeadChips. Both groups did not differ in Banff scores. Differentially expressed genes were defined as those with fold change ≥ 2 and $p < 0.05$. The enrichment of deregulated genes in biological processes was analyzed using DAVID database and results were validated using real-time qPCR at the independent cohort ($n = 24$).
Results: In AMR group the annotation enrichment analysis for upregulated genes revealed GO terms with the highest fold enrichment such as cadmium ion binding ($p = 6.9E-05$), anion antiporter activity ($p = 0.02$), anion transmembrane transporter activity ($p = 0.009$) and apical plasma membrane ($p = 0.02$). In ABOi group the most enriched GO terms were extracellular matrix part ($p = 0.044$) and proteinaceous extracellular matrix ($p = 0.007$). Majority of deregulated genes between both groups belongs to metallothioneins (MT) and solute carrier family (Slc) genes and two different clusters of Slc genes as well MT1 and MT3 discriminated AMR group from ABOi one.
Conclusion: While anti-HLA antibodies activate both MT1 and distinct Slc genes in AMR which suggest processes associated with enhanced CD4 + T activation, hemagglutinins trigger MT3 and different Slc gene expressions known to be associated with immune regulation and pathogen tolerance. Distinct zinc-signaling dependent pathways are involved in the accommodation phenomenon.

Translational Kidney Rejection

OS027 RENAL TRANSPLANT PATIENTS WITH DE NOVO DONOR-SPECIFIC HLA-ANTIBODIES HARBOUR AN INCREASED FRACTION OF ALLOSPECIFIC T-CELLS AND FOLLICULAR T-HELPER-CELLS

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Background: Renal transplant patients (RTX) rely on lifelong immunosuppression. However, some patients develop de novo donor-specific HLA-antibodies (DSA) thus being at risk for antibody-mediated rejection (AMR). Lately, follicular T-helper-cells (TFH) were found to play a key role in antibody formation. Hence, we studied TFH in RTX with DSA.
Methods: 76 RTX with stable renal allograft function for at least six months and 21 age-matched healthy controls (HC) were enrolled. 35 RTX patients had DSA and in 41 RTX patients DSA were not detectable. Peripheral blood mononuclear cells (PBMC) were isolated by ficoll gradient isolation and TFH were considered to be CXCR5 + , IL21 + , and/or Bcl-6 + . Allospecific T-cells

were detected by CFSE-based tracking of recipient T-cell proliferation upon donor-specific stimulation. Lastly, TFH were examined for phosphorylation status of p70S6 kinase (p70S6K) and expression of CD25.
Results: $IL21^+$TFH were increased in RTX with DSA as compared to HC (% $IL21^+$ of $CD3^{pos}CD8^{neg}$: 12.84 ± 6.3% vs. 9.5 ± 2.4%, $p = 0.04$). $IL21^+$TFH of RTX without DSA were not different compared to HC ($p = 0.4$). RTX with DSA had an enhanced allospecific proliferation of T-cells compared to RTX without DSA (%$CFSE^{low}$ of $CD3^{pos}CD8^{neg}$: 2.5 ± 0.6% vs. 0.67 ± 0.3%, $p = 0.0001$). Interestingly, TFH of RTX with DSA displayed a higher functional activity as compared to RTX without DSA. This was indicated by increased phosphorylation of p70S6K as well as increased expression of CD25 on TFH from RTX with DSA (%$CD25^+$ of $CD4^+Bcl\text{-}6^+$: 14.2 ± 9% vs. 7.9 ± 3.1%, $p = 0.01$).
Conclusion: An enhanced fraction of $IL21^+$TFH and increased allospecific T-cell reactivity was found in RTX with DSA compared to RTX without. Moreover, TFH of RTX with DSA displayed a higher functional activity, i.e. elevated levels of p70S6K and increased expression of CD25. TFH may thus elicit formation of DSA and could play a pivotal role in AMR.

Translational Kidney Biomarkers and molecular changes

OS028 THE ACTIVITY OF ANTIBODY-MEDIATED REJECTION IN KIDNEY TRANSPLANTATION IS REFLECTED BY ACTIVATED NATURAL KILLER CELL TRANSCRIPTS: THE BIOMARGIN STUDY

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Background: Antibody-mediated rejection (ABMR) is now recognized as a foremost cause of kidney graft failure. Identification of the best therapeutic target(s) for ABMR still remains largely elusive. We therefore aimed to elucidate the principal immune cell subtypes in ABMR.
Methods: We used unbiased microarray transcriptomic analyses in the BIOMARGIN case-control study ($n = 95$) and in three publicly available external datasets ($n = 985$) of kidney transplant biopsies (in total 1080 biopsies). Given the co-occurrence of ABMR and TCMR, we built an innovative bioinformatics pipeline to discriminate ABMR-specific mRNA markers.
Results: Our pipeline showed specific differential expression of 652 ABMR-specific transcripts (503 unique genes). Pathway analysis illustrated enrichment of immune pathways in ABMR, specifically NK cell pathways. Next, we used a recent deconvolution algorithm to estimate the relative fraction of major leukocytes subtypes based on the mRNA transcripts expression. This independent analysis further corroborated the prominent role of activated NK cell transcripts in ABMR in the BIOMARGIN dataset, which was validated in the external cohorts. No other cell type differentiated ABMR from TCMR. The estimated infiltration of activated NK cells specifically reflected histological lesions of ABMR disease activity (glomerulitis and peritubular capillaritis). Logistic regression analysis showed that activated NK cell infiltration, estimated from the micro-array gene expression data, was highly specific for ABMR vs. no rejection (AUC = 0.92), but also discriminated ABMR from TCMR (AUC = 0.77).
Conclusion: These thoroughly validated data in 1080 kidney allograft biopsies show that NK cell activation has great potential as therapeutic target in ABMR, and that intrarenal NK cell-specific gene sets could be used as biomarker for ABMR activity.

Basic Kidney Biomarkers and molecular changes

OS029 COMPLEMENT-MEDIATED ISCHEMIA REPERFUSION INJURY INDUCED KIDNEY SENESCENCE BY MODULATING DNA METHYLATION IN TUBULAR EPITHELIAL CELLS

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Renal senescence is characterized by a subclinical inflammatory state and by a diminished regenerative potential of tubular epithelial cells (TEC).Complement-mediated injury following I/R may lead to premature graft aging. TEC express the receptor of C5a, but little is known about the downstream effect of C5a-C5aR interaction.

Ten pigs underwent to 30 min of renal warm Ischemia, followed by 24 h of Reperfusion (T24 CTRL). Five pigs were treated with C1-Inhibitor (C1-Inh, 500U/Kg, 5 min before reperfusion) (T24 C1-INH). Biopsies were analyzed for markers of inflammaging (SA-βGal, p16INK4a, p21WAF1 and IL-6) by IHC. *In vitro*, TEC were exposed to C5a (3 h, 24 h) and analyzed for SA-βGal, p53, IL-6, MCP-1 and CTGF by WB and qPCR. Whole-genome DNA methylation profile was investigated by the Illumina Human Methylation 450 BeadChips.

I/R injury led to increased expression of inflammaging markers as SA-β Gal, p21, p16 and IL-6, indicating tubular senescence. C1-INH efficiently antagonized senescence by restoring p16, p21, IL-6 expression and SA-β Gal at basal level ($p < 0.05$). *In vitro*, short stimulation of TEC by C5a induced senescence by up-regulating SA-β Gal, IL-6, MCP-1, CTGF gene and p53 protein expression, as sign of stable cell cycle arrest. Next we studied changes in DNA methylation following C5a stimulation for 24 h. Interestingly, 144 sites were hypomethylated and 24 sites were hypermethylated by C5a. In accordance, the differentially methylated DNA regions included genes involved in DNA damage checkpoints, cell cycle and WNT pathways. The most representative protein classes were: nucleic acid binding proteins, enzyme modulators, transcription factors and cytoskeletal protein. RT-PCR analysis confirmed the correlation between gene expression and DNA methylation.

These results suggest a role of complement system in inducing cellular senescence in I/R injury. Targeting epigenetic mechanisms may represent a strategy to protect TEC from aging and promote kidney repair.

Translational Kidney Biomarkers and molecular changes

OS030 DELAYED GRAFT FUNCTION OUTCOME IS ASSOCIATED WITH SENESCENCE PROGRAMMES

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Ischaemia reperfusion injury (IRI) can lead to acute injury (AKI), and in 25%–50% of cases to delayed graft function (DGF), with higher incidence and longer recovery times in older and marginal donors. DGF is associated with increased allograft biological age (i.e. miles on the clock) and perturbation of metabolic pathways such as mTOR and IGF signalling, common to the regulation of ageing across taxa. Whether this association reflects pre-existing allostasis (i.e. burden of stress) in these organs, or is due to a lack of resilience to peri-transplant stresses remains to be determined.

Twenty four pairs of cortex biopsies representing extreme phenotypes of immediate and delayed graft function collected immediately before transplant (pre-perfused) and following anastomosis after 45 min reperfusion (post-perfused) underwent small RNAseq to identify microRNA signatures associated with DGF outcome in the context of perfusion driven responses.

Amongst 37 microRNAs associated with DGF; hsa-miR-125b previously described by our group DGF marker and microRNA linked with good allograft performance (hsa-miR-101-3p or hsa-miR-124a) were identified. Seven microRNAs were associated with DGF outcome in pre-perfusion biopsies; with 6 being common with DGF phenotype after adjustment for reperfusion injury. Further analysis has revealed that allografts displaying DGF responded differentially to reperfusion and this can be linked to the activation of common senescence pathways, genome stability, cellular homeostasis, telomere stability and mitochondrial functions.

This would suggest that allograft resilience is linked to ageing pathways and thus reflects its biological age, furthermore this links poorer age related function with negative outcomes post-transplant. These signatures drive molecular events leading to impaired graft function and represent potential nodes for therapeutic interventions targeting the micro-transcriptome.

OS031 AGING IS ASSOCIATED WITH EPIGENETIC CHANGES IN GENES INVOLVED IN RENAL FIBROSIS: AN EPIGENOME-WIDE ASSOCIATION STUDY

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Background: Advanced donor age is one of the key factors associated with allograft fibrosis and impaired outcome after kidney transplantation. Recently, it became clear that DNA methylation changes hallmark aging. In this study, we investigated aging-associated changes in DNA methylation in kidney transplants.
Methods: We profiled DNA methylation in two cohorts of kidney allograft biopsies: across >800 000 genome-wide CpG sites in 95 pre-implantation biopsies, and across >400 000 genome-wide CpG sites in a second cohort of 67 post-reperfusion biopsies. Donor age ranged from 16 to 79 years.

Results: Donor age associated significantly with methylation levels at 92 778 CpGs (12% of probes) in the pre-implantation cohort and at 64 336 CpGs (15% of probes) in the post-reperfusion cohort (FDR < 0.05), adjusted for donor gender, living vs. deceased donation, and cold ischaemia time. These sites corresponded to 10 285, respectively 6098 differentially methylated regions. The overlapping, validated differentially methylated regions spanned 9.4 mega base pairs of the renal genome. Almost all differentially methylated regions in gene promoters were hypermethylated upon aging, and preferentially occurred in genes involved in several relevant signaling pathways. Only 10 gene promoters entailed a differentially methylated region that became hypomethylated with aging, including WISP2, a gene involved in the Wnt signaling pathway that has been linked to renal aging, and BBC3, a gene with pro-apoptotic characteristics. We are currently evaluating the association of expression changes in these pathways and post-transplant fibrosis.
Conclusion: There is a strikingly pervasive association between age and DNA intrarenal methylation changes. These DNA methylation changes occur at genes involved in essential cellular functions, injury and fibrosis, suggesting a link between advanced donor age and chronic allograft dysfunction.

OS032

A STUDY OF EPIGENETIC DYNAMICS OF RENAL ALLOGRAFT: FROM ISCHEMIA/REPERFUSION INJURY TO LONG-TERM ALLOGRAFT FUNCTION

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[1]Uva Hs, United States; [2]Uvahs, United States; [3]Osu, United States; [4]Vcu Hs, United States

Background: The mechanisms of long term allograft dysfunction are not completely understood. Early graft insults like ischemia/reperfusion injury followed by course of its response/repair could involve changes in molecular determinants including DNA methylation (DNAm) which influence long term allograft function. In the current study we assessed the dynamics of DNAm across 1) pre-implant biopsies post-ischemic injury (PI) 2) allograft biopsies post-reperfusion (PR) and 3) >24 months post kidney transplantation (KT).
Methods: Infinium 450K methylation (n = 96) and gene expression (n = 182) arrays were performed in PI, PR and KT renal allograft biopsies and analyzed. Genome runner was used to assess distribution and enrichment of differentially methylated (Dme) CpG sites along regulatory features. Integrative analyses of Dme CpGs and corresponding differential gene expression were performed at each matched time points.
Results: PI allografts, when classified based on progression to allograft dysfunction vs. normal function, showed 1188 Dme CpGs mapped to genes involved in inflammation and metabolism. When paired PI and PR allografts were compared there was apparent change in DNAm of genes involved in pathways like *NRF2*-mediated oxidative stress response and functions like cellular assembly and organization, cell death and survival. Integration analysis showed Dme and expression of genes involved in energy metabolism, transporters and transcription factors important in regulation of immune response. Further, comparison of post-KT allografts with differential outcomes revealed 21 351 Dme CpG sites. The Dme CpGs observed at early time points were mostly hypomethylated and promoter associated. However, a shift in the pattern was observed in later stages. Dme CpGs were interestingly located in gene bodies and in evolutionarily conserved tissue specific regions. Integration analysis corroborated with findings.

Clinical Kidney Immunosuppressive agents

OS033

DO CLINICAL TRIALS REFLECT REALITY? A SYSTEMATIC REVIEW OF INCLUSION/EXCLUSION CRITERIA IN TRIALS OF RENAL TRANSPLANT IMMUNOSUPPRESSION

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Background: Renal transplant recipients and donors are becoming increasingly more marginal, with more expanded criteria (ECD) and donation after circulatory death (DCD) donors and older recipients. Despite this, high risk donors and recipients are often excluded from clinical trials, leading to uncertainty about the generalisability of findings.
Methods: We searched the Transplant Library database for reports from randomised controlled trials comparing immunosuppressive interventions in adult renal transplant recipients published between January 2010 and December 2014. Trial registries were also searched for protocols linked to published reports. Data regarding demographics and inclusion/exclusion criteria were extracted and analysed.

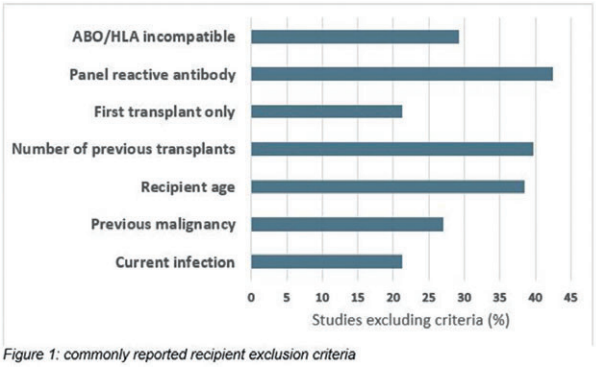

Figure 1: commonly reported recipient exclusion criteria

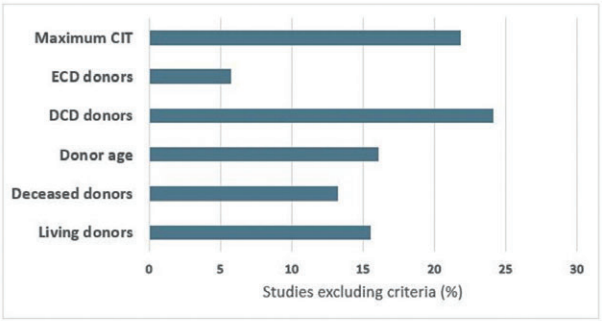

Figure 2: commonly reported donor exclusion criteria

Results: Literature search identified 213 reports from 174 trials. Common recipient inclusion criteria included upper age limit (39%), previous transplantation (40%), immunological risk and current infection/malignancy (*figure 1).* Many studies also specified donor exclusion criteria, including age (16%), donor type and cold ischaemic time (22%) (*figure 2).* 77 (44%) studies had a published protocol available. Inclusion/exclusion criteria recorded in the trial protocol matched those reported in the manuscript in only 6 (8%) trials. of those with published protocols, 51 (66%) trials included additional criteria in the manuscript, 51 (66%) were missing criteria in the manuscript specified in the protocol, and in 19 (25%) key criteria changed from the protocol to the manuscript.
Conclusion: Many recent immunosuppression trials have restrictive inclusion criteria which do not reflect the changing nature of current donor and recipient populations. Discrepancies between protocols and trial reports raise the possibility of selection bias. Caution is advised when applying the results of these trials to older, higher risk recipients and recipients of more marginal organs. Future trials need to consider inclusion of these populations.

Translational Kidney Immunosuppressive agents

OS034

A PHASE-TWO, RANDOMISED, PLACEBO-CONTROLLED TRIAL OF BELIMUMAB IN RENAL TRANSPLANTATION SUGGESTS DE NOVO ANTIBODY FORMATION IS REDUCED IN BELIMUMAB TREATED PATIENTS

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Background: HLA and non-HLA antibodies produced by B-cells are an important contributor to graft loss in kidney transplantation. Antibody profiling using protein microarrays was conducted as part of BEL114424, a phase 2, double-blind, randomised controlled study of the addition of belimumab to standard of care in renal transplantation (ClinicalTrials.gov NCT01536379; EudraCT 2011-006215-56). Belimumab is a monoclonal antibody neutralising B Lymphocyte Stimulator (BLyS; BAFF), a cytokine that enhances B-cell survival and proliferation. This post-hoc analysis was designed to establish whether belimumab post-transplantation had an impact on the persistence of pre-transplant non-HLA antibodies or the development of *de novo* non-HLA antibodies post-transplant.
Methods: Patients were randomised to intravenous belimumab 10 mg/kg (n = 14), or placebo (n = 14) on the day of renal transplant and at weeks 2, 4, 8,

12, 16 and 20 in addition to a standard regimen of basiliximab, mycophenolate mofetil, tacrolimus and prednisolone. Serum samples taken at the day 0, weeks 24 and 52 visits from 16 subjects (8 belimumab and 8 placebo) were applied to ProtoArrays (Invitrogen). A global threshold for significant antibody binding was obtained by comparing day 0 and week 24 samples (independently of treatment). The number of unique targets with antibody binding above threshold were then analysed by treatment and time point. Funding provided by GSK.
Results: The number of ProtoArray antigens with above threshold antibody binding was reduced in Belimumab treated patients at week 24 (not significant), with the trend still evident at week 52. This trend became stronger when examining *de novo* post-transplant antibody binding at week 24 ($p = 0.047$). Similar differences were seen when only kidney-specific antigens were considered.
Conclusions: This post-hoc analysis suggests that adding belimumab to standard immunosuppression may inhibit the generation of *de novo* non-HLA alloantibodies post-transplantation.

Clinical Kidney Immunosuppressive agents

OS035 EFFICACY AND SAFETY OF IGURATIMOD IN HIGHLY SENSITIZED PATIENTS WITH OR WITHOUT RENAL GRAFT: A PRELIMINARY RETROSPECTIVE CASE SERIES

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Objective: Effective therapies are still sparse in pre-sensitized patients. Here we reported the efficacy and safety of Iguratimod, an approved anti-B cell drug in rheumatoid arthritis, in highly sensitized renal transplantation candidates and renal transplantation recipients in a small retrospective cohort.
Methods: The case series included 28 highly sensitized patients. All patients received off-label use of 50 mg/day Iguratimod in addition to their routine therapy. The clinical data were collected, including gender, age, graft status, baseline panel reactive antibody (PRA). PRA was tested post Iguratimod therapy monthly. Response was defined as 30% or more decrease in PRA. Our hospital board approved this clinical trial. All patients signed informed consent.
Results: In the 28 cases, the median follow-up was 13.7 months and the overall response rate was 71.4%. There were 10 cases of renal transplantation candidates, 5 males and 5 females. 4 cases of PRA descending after application of Iguratimod, 1 case >30% and the remaining 3 cases ranged from 20% to 30%. There were 18 renal transplantation recipients, 13 males and 5 females, of which 12 cases of PRA decreased >30%, and 3 cases decreased between 20% and 30%. There were 2 cases of Grade1 liver injury, as slightly elevated transaminase and 2 cases of Grade1 gastrointestinal events. No any other common adverse events reported.
Conclusion: Iguratimod can reduce the PRA in highly sensitized patients, especially when combined with routine immunosuppressive drugs. Iguratimod was well tolerated in renal transplantation candidates and renal transplantation recipients. Further prospective trials and basic research are needed to verify our results.

OS036 TACROLIMUS AND MYCOPHENOLATE REGIMEN AND SUBCLINICAL TUBULO-INTERSTITIAL INFLAMMATION IN LOW IMMUNOLOGICAL RISK RENAL TRANSPLANTS

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The aim was to evaluate the relationship between maintenance immunosuppression, subclinical tubulo-interstitial inflammation and interstitial fibrosis/tubular atrophy (IF/TA) in surveillance biopsies performed in low immunological risk renal transplants at two transplant centers. The Barcelona cohort consisted of 109 early and 66 late biopsies in patients receiving high tacrolimus (TAC-C0 target at 1-year 6 to 10 ng/mL) and reduced MMF dose (500 mg bid at 1-year). The Oslo cohort consisted of 262 early and 237 late biopsies performed in patients treated with low TAC-C0 (target 3 to 7 ng/mL) and standard MMF dose (750 mg bid). Subclinical inflammation, adjusted for confounders, was associated with low TAC-C0 in the early (OR: 0.75, 95%CI: 0.61- 0.92; $p = 0.006$) and late biopsies (OR: 0.69, 95%CI: 0.50–0.95; $p = 0.023$) from Barcelona. In the Oslo cohort, it was associated with low MMF in early biopsies (OR: 0.90, 95%CI: 0.83–0.98; $p = 0.0101$) and with low TAC-C0 in late biopsies (OR: 0.77, 95%CI: 0.61–0.97; $p = 0.0286$). MMF dose was significantly reduced in Oslo between early and late biopsies. IF/TA was not associated with TAC-C0 or MMF dose in the multivariate analysis. We were not able to explore whether minimization of both drugs, this means, MMF dose $\leq$1 g/day and TAC C_0 levels <5 ng/mL, is associated with a higher risk of subclinical inflammation since this schedule was not followed at any of both centers. In summary, our data suggest that in low immunological risk renal transplants treated with TAC and MMF based regimens, TAC-C0 levels are associated with subclinical inflammation in patients receiving reduced MMF.

Translational Kidney Immunosuppressive agents

OS037 KIDNEY RECIPIENTS WITH 10 YEAR BELATACEPT-TREATMENT DISPLAY AN ALTERED T CELL SUBSET COMPOSITION AND LOW PLASMA CYTOKINE LEVELS COMPARED TO MATCHED PATIENTS WITH CNI-BASED IMMUNOSUPPRESSION

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Background: More than 10 years ago, Belatacept (Bela)-based immunosuppression was investigated in the BENEFIT trial of kidney transplantation (KTx) compared to CNI-based immunosuppression. Bela inhibits T cell costimulation by blocking the binding of CD28 to CD80/CD86. This specific interaction is supposed to affect CD28-dependent de novo T cell responses and, thus, may have less side effects in contrast calcineurin inhibitors (CNI). Therefore, we investigated the long-term effects of Bela on lymphocyte subset composition and plasma cytokine/chemokine levels compared to the CNI group.
Methods: Peripheral blood samples of 5 kidney recipients with Bela- and 10 matched recipients with CNI-treatment were collected, PBMCs were analysed by flow cytometry for lymphocyte subsets using a newly developed Lyotube panel and plasma by multiplex technology for cytokine/ chemokine levels.
Results & Conclusions: In the T cell compartment, Bela-treated patients show some differences to CNI-treated patients: Frequencies of CD56 + CD4 + T cells and HLA-DR+CD45RO+ memory Tregs were significantly lower ($p < 0.03$) in the Bela than in the CNI group. Naïve, central, effector memory and TEMRA T cell subsets showed no differences between the two groups. Neither CD27-CD28- "virus-specific" memory T cells nor CCR7-CD57 + CD4 + "senescent" T cells, discussed to be responsible for early rejection upon Bela-treatment, are altered.. Slightly reduced plasma levels were detected for many cytokines like IFN-g, TNF-a, IL-1, 4, 10, IL-17 and chemokine like CCL2-4, CXCL8-12. Only MIF was significantly lower in plasma of Bela-treated patients. Importantly, the creatinine levels in both groups were equal. Taken together, long-term treatment of KTx patients with Bela is associated with lower frequencies of activated effector and memory Treg subsets accompanied by low levels of cytokines/chemokines indicating that systemic immunosuppression with equal kidney function can be achieved by a CNI-free regimen.

Translational Others Immunosuppressive agents

OS038 ANTI-GAL AND ANTI-NEU5GC RESPONSES IN NON-IMMUNOSUPPRESSED PATIENTS FOLLOWING TREATMENT WITH ANTI-THYMOCYTE GLOBULIN

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Background: Anti-lymphocyte or anti-thymocyte globulins (ATG) are polyclonal animal-derived IgGs, widely used as immunosuppressive drugs in the prevention or treatment of organ or bone-marrow allograft rejection, graft vs. host disease, and some autoimmune diseases. However, animal-derived glycoproteins are also strongly immunogenic and rabbit ATG induce serum sickness disease in patients when no additional immunosuppressive drugs are used.

In this study, we analyzed sera from patients of the START randomized phase II clinical trial, which evaluated the effect of Thymoglobulin® therapy in the auto-immune context of new-onset type 1 diabetes. The aim was to analyze various anti-ATG specificities developed by the patients, and especially anti-galactose-α1-3-galactose (Gal) and anti-Neu5Gc. These two xeno-carbohydrate epitopes are present on rabbit IgG glycans and are lacking in humans.
Methods: Serial sera from patients at pre- or post-ATG infusion time points (1, 3, 6 and 12 months) were analyzed by ELISA for anti-ATG, anti-Gal and anti-Neu5Gc IgGs and IgMs. Results were compared to placebo-treated patients and healthy donors matched for gender and age.
Results: We showed that diabetic patients have pre-existing antibodies against the three specificities before treatment, although levels are similar to healthy individuals. ATG treatment resulted in highly significant increases of both IgMs (for anti-ATG and anti-Neu5Gc) and IgGs (for anti-ATG, -Gal, and -Neu5Gc), peaking at one month and still detectable one year post-infusion.
Conclusions: Treatment with rabbit polyclonal IgGs in the absence of additional immunosuppression results in a vigorous humoral response against Gal and Neu5Gc epitopes, contributing to an inflammatory environment that may compromise the efficacy of ATG therapy. Moreover, as diet-derived Neu5Gc is found on endothelial cells, elicited anti-Neu5Gc antibodies could play a role in vascular inflammation, with potential long-term clinical consequences.

OS039 TRANSIENT ANTIBODY TARGETING OF CD45RC INDUCES TRANSPLANTATION TOLERANCE AND POTENT DONOR ANTIGEN-SPECIFIC REGULATORY T CELLS

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Rat CD4 + and CD8 + CD45RClow/- have been described as Tregs whereas CD45RC+ are Th1 cells. We reasoned that depletion of CD45RC+ cells with a MAb would eliminate T cell involved in graft rejection and spare Tregs. Transient administration (10 or 20d) of an anti-rat CD45RC MAb in a rat cardiac allotransplantation model (2 different strain combinations in both cases complete MHC mismatch) induced transplant tolerance (>83% >120 days survival, $n = 9$) whereas isotype-treated controls rejected in <14d ($n = 10$). Long-term allograft recipients showed complete inhibition of alloantibodies but primary and memory humoral responses against cognate antigens were maintained. Anti-rat CD45RC MAb induced apoptosis of only CD45RC+ T cells *in vitro* and *in vivo* through intrinsic CD45RC+ signaling. *In vivo* anti-rat CD45RC treatment increased the number of CD4 + and CD8 + CD45RClow/- Tregs, potentiated there *in vitro* suppression, modified their transcriptional signature and potentiated adoptive transfer of donor-specific tolerance to grafted recipients vs. Tregs from controls. We also demonstrate that human CD45 isoforms are expressed differentially by Tregs. Human CD4 + and CD8 + Foxp3 + Tregs were both largely CD45RClow/- and CD45RA+R-B+RO+. Anti-human CD45RC treatment inhibited GVHD in immune-humanized NSG mice both, when CD45RC+ cells were depleted before and after *in vivo* PBMC administration ($n = 4$). Anti-human CD45RC MAb induced apoptosis of only human CD45RC+ T cells. In conclusion, short-term anti-CD45RC MAb administration eliminates cells implicated in organ rejection and GVHD while preserving CD4 + and CD8 + CD45RClow/- Tregs that become primed to donor alloantigens and is thus a potent novel therapeutic candidate to favor transplantation tolerance in humans.

Basic Kidney Immunosuppressive agents

OS040 IMMUNOSUPPRESSORS (CSA, MCA, IVIG) DIRECTLY ACT UPON ENDOTHELIAL CELLS RESULTING IN ALTERED ABILITY TO TRIGGER CD4 + T CELL INFLAMMATORY RESPONSES

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Background: The allograft endothelium forms an interface with recipient leukocytes and regulates the immune response. We have shown that microvascular endothelial cells (mECs) simultaneously induce expansion of FoxP3hiTreg and of Th17 (Taflin et al, PNAS 2011). Moreover mECs allogenicity was modified by HLA-DR antibody binding that led to increased Il-6 secretion and Th17 expansion (Lion et al Am J Transplant 2016). Although the outcome of immunosuppression has been extensively studied in circulating leukocytes, the effect of immunosuppressors (IS) on the graft endothelium has not been examined. This study determined whether commonly used IS alter the ability of mECs to orientate lymphocytes towards an inflammatory or regulatory profile.
Methods: We investigated the effect of cyclosporine A (CsA), mycophenolic acid (MCA) and intravenous immunoglobulins (IVIgs) on the phenotype, IL-6 secretion and allogenicity in an experimental model of the human mECs interaction with allogenic PBMC in an inflammatory setting.
Results: Both MCA and CsA significantly reduced HLA-DR expression while IVIgs increased it. All IS amplified CD54 expression. Both MCA and IVIgs reduced mECs secretion of IL-6. Concerning mEC immunogenicity, expansion of FoxP3hiTreg was significantly diminished after CsA or MCA treatment although CsA increased expansion of IFNy producing cells. Both MCA and CsA reduced IL-6 production by mECs co-cultured with allogeneic PBMC. In contrast to both MCA and CsA, incubation with IVIgs induced proliferation and expansion of FoxP3hiTregs.
Conclusion: Immunosuppressors such as MCA and CsA modified the immunogenic function of mECs leading to a predominantly pro-inflammatory CD4 + T cell response. In contrast, low concentrations of IVIgs promoted a regulatory response. Results obtained with CsA and MCA treatment may explain the inefficiency of these therapies on long-term graft survival and identify a hitherto unknown regulatory pathway

Clinical Pancreas/Islet Donation and donor types

OS041 DEVELOPMENT OF AN MRI SCORE TO ASSESS THE QUALITY OF PANCREAS GRAFTS PRIOR TO TRANSPLANTATION

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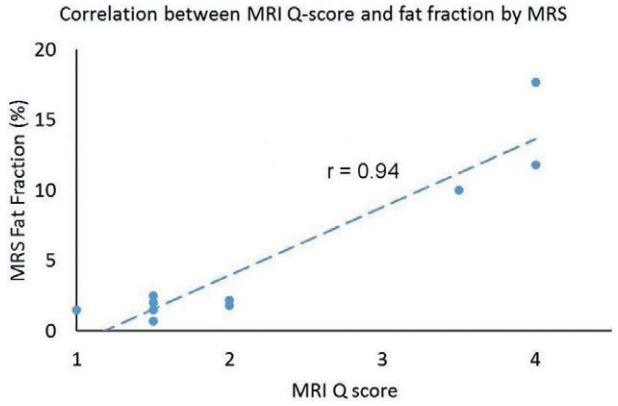
Background: Assessment of the pancreas grafts prior to transplantation is difficult and fatty infiltration is one of the main reasons for organ discards. We developed an MRI score for objective assessment of the pancreas grafts prior to transplantation.
Methods: Ten pancreases not suitable for transplantation underwent a macroscopic assessment, MRI scanning and histopathological assessment. MRI was undertaken using structural T2-weighted images in axial and coronal orientation. A single voxel MR spectroscopy (MRS) scan was acquired from selected areas in head, body and tail of parenchymal tissue. MRS fat fraction (FF) was calculated as: 100% * fat signal/(water signal + fat signal). The structural MRI were independently scored by two radiologists blinded to the macroscopic appearance of the graft using a four-point quality (Q) score (1-normal parenchyma, 2- minor fat infiltration, 3-medium fat infiltration, 4-inhomogeneous appearance and significant fat infiltration). The Q-score was compared with the calculated FF and the macroscopic assessment.
Results: Two grafts had no macroscopic fat infiltration whilst the remaining eight had moderate ($n = 5$) or severe ($n = 3$) fat infiltration in and around the graft as judged by the surgical team. In contrast, only one of the five moderately fatty grafts were considered fatty by MRS scoring (FF 11.8%) compared with a mean MRS FF of 1.875% (1.5%–2.5%) for the other four grafts. Similarly, two of the three severely steatotic grafts were confirmed by MRS scoring (FF 13.85%). There was a very good correlation between the MRI Q-score and the FF by MRS as shown in figure 1 ($R^2 = 0.8813$).



Conclusions: Fatty macroscopic appearance of the graft does not reflect the actual deep fat infiltration and therefore surgical macroscopic assessment may be inaccurate and may lead to unnecessary organ discards. MR imaging and spectroscopy scoring may provide additional information to assist the decision to accept an organ for

Clinical Pancreas/Islet Other

OS042 IDENTIFYING A METABOLIC SURROGATE MARKER FOR PANCREAS GRAFT FAILURE

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Introduction: The lack of a validated measure of graft function after pancreas implantation has hindered our ability to monitor recipients post-transplant and identify declines in function before graft failure (return to insulin) occurs. Further clinical trials have been hindered by the lack of a surrogate end-point for graft failure.
Methods: Longitudinal metabolic measures taken pre-discharge and at 3 monthly intervals post-transplant according to clinical protocol, including Hba1c, fasting and stimulated glucose and insulin were recorded for a cohort of 500 pancreas transplant recipients between 2002- 2011 with at least 4 years follow-up data. 118 graft failures were included in the cohort and compared to those with ongoing good pancreas function for patterns of functional decline. Data was censored at graft failure or last follow-up.
Results: Fasting and stimulated glucose pre-discharge was associated with graft failure ($p < 0.05$). Insulin and c-peptide level had no association to graft failure at any time-point. HbA1c increased incrementally in the group with subsequent graft failure and HbA1c >5.9% at 1-year post-transplant predicted graft failure (AUC 0.842, $p = 0.005$) with 83.3% sensitivity and 94.7% specificity in ROC analysis. Cox regression and Kaplan-Meier analysis showed 1 year HbA1c >5.9% to predict graft failure (HR 37.5, $p = 0.001$) and 5-year graft survival of 62.3% vs. 98.6% for HbA1c < 5.9% ($p < 0.001$).
Discussion: We have shown that 1-year HbA1c >5.9% is a strong predictor of graft failure and can be used as a reliable surrogate end-point for graft failure in clinical trials. We have seen that insulin and c-peptide are not useful predictors of graft failure. However, rises in glucose or HbA1c post-transplant should serve as early warnings of risk of graft failure, and could be considered as triggers for intervention.

OS043 THE 10 YEARS OUTCOME OF PANCREAS TRANSPLANT ALONE (PTA) IN TYPE 1 DIABETES (T1D)

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Background: the long-term safety and efficacy of PTA in T1D subjects is still debated. In the present study we evaluated the outcome at 10 years follow-up of 60 consecutive PTA performed in T1D patients at our center.
Methods: The 60 T1D individuals had the following pre-transplant characteristics: age, 38 ± 8 years; 29 males/31 females; BMI, 23.2 ± 2.8 kg/m^2, duration of diabetes, 24 ± 8 years. The PTA surgical technique consisted of transplantation of the whole pancreas with the duodenum, with portal or systemic drainage of endocrine secretion and enteric drainage of the exocrine pancreas. Immunosuppression was based on basiliximab or ATG and high dose steroid as induction, whereas maintenance treatment mostly consisted of the calcineurin inhibitor tacrolimus, the anti-proliferative agent mycophenolate (mofetil or sodium) and low dose steroid. Data were analyzed after 10 years from transplant.
Results: At the end of follow-up, survival of PTA recipients was 91.7% (55 out of 60), with, therefore, a mortality rate of 0.83% per year. Causes of death (all occurring in patients with functioning graft) were cardiovascular disease (3 cases), viral infection (1 case) and lung cancer (1 case). Graft function at 10 years in living recipients was 63.6%, with full insulin independence in 55% of cases, which was accompanied by robust endogenous insulin secretion (C peptide: 3.1 ± 1.5 ng/ml) and sustained normoglycemia (fasting plasma glucose: 94.6 ± 15.6 mg/dl; HbA1c: 5.7 ± 0.5%). Total cholesterol (159 ± 33 vs. 204 ± 48 mg/dl) and LDL cholesterol (93 ± 23 vs. 129 ± 43 mg) improved significantly (both $p < 0.01$) after transplantation. Two patients developed end-stage renal disease (both at 4 years post-transplant). In the remaining recipients with functioning graft, the MDRD calculated glomerular filtration rate showed a yearly decrease of 2.1 ± 0.4 ml/min.
Conclusion: The results of this single center experience indicates that PTA can be considered a safe and effective procedure in selected T1D subjects.

OS044 OUTCOMES AFTER BLADDER AND ENTERIC DRAINAGE FOR PANCREAS TRANSPLANTATION ONLY

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Background: There is still controversy around the best technique for drainage of exocrine secretions in pancreas transplantation alone (PTA). The aim of this study is to compare the outcomes after the enteric drained (ED) and bladder drained (BD) PTA.
Methods: A prospectively-maintained database of pancreas transplant recipients for the period from 07/2004 to 08/2016 was analysed. Groups were compared for demographic and transplant variables, and for patient and graft survival using Kaplan-Meier and Cox regression analyses.
Results: 178 PTA were performed: 128 ED and 50 BD, 58% were PTA, 36% were PAK and 6% were pancreas after SPK (PASPK) in the ED, and 94% PTA, 4% PAK and 2% PASPK in the BD cohort. Demographic data for recipients showed no statistical difference. The donor BMI and the percentage of DCD donors were statistically higher for the ED group. The cold ischemic time was similar.

There was no significant difference in patient 5-year survival and graft survival. After adjustment for demographic variables in a multivariable Cox regression analysis, BD was not independently associated with a favourable outcome. The number of treated episodes of rejection was numerically, but not significantly, higher in the BD group (32.3% vs. 24.3%; $p = 0.287$). Readmission rates were significantly higher in the BD group (66% vs. 45%; $p = 0.01$), with mean total length of hospital stay in the first year being more than double (23 vs. 10 days; $p = 0.002$), this included an enteric conversion rate of 46% (23 patients).
Conclusion: There is no statistically significant difference in patient and graft survival. Bladder drainage is associated with higher complication rate, hospital readmissions and enteric conversions. This analysis suggests that increased monitoring of exocrine function and treatment of rejection episodes may not result in improved graft survival and may have negative impact in other respects.

Clinical Pancreas/Islet Immunology

OS045 AUTOANTIBODIES AGAINST PANCREAS PREDICT WORSE GRAFT FUNCTION AND INCREASED PRO-INFLAMMATORY STATUS AFTER PANCREAS-KIDNEY TRANSPLANTATION

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Background: Following GAD65 and I-A2 AAb positivity, pancreatic endocrine function worsens. However, it remains uncertain how pancreatic AAb affect pancreatic graft function and whether AAb positivity promote an underlying inflammatory process after simultaneous Pancreas-Kidney transplantation (SPKT). Thus, we aimed to investigate whether pancreatic AAb positivity promoted an impairment of the endocrine pancreatic graft function and also an underlying inflammatory process after SPKT.

Methods: We prospectively evaluated 80 matched SPKT recipients in whom pancreatic AAb were consecutively positive or negative after SPKT. HbAc1 and c-pep serum levels were evaluated at 12, 24, 48 and 60 months after AAb became positive. Further, 38 of those recipients were evaluated in a cross-sectional study. Patients with normal fasting glucose and c-pep serum levels with either negative of positive AAb were evaluated for $CD14^+CD16^+$ monocytes by flow cytometry. 10 healthy subjects served as controls.
Results: of the 80 recipients prospectively evaluated, 50% became AAb positive after transplant. Among them 42.5% (n = 17) were GAD65 + , 42.5% (n = 17) IA-2 + and 15% (n = 6) were positive for both AAb. Patients with positive AAb showed higher levels of Hb1Ac and lower c-peptide at 24, 48 and 60 months after AAb seroconversion ($p < 0.001$ for all comparisons). In the cross-sectional analysis, patients with positive pancreatic AAb showed a higher percent of $CD14^+CD16^+$ monocytes compared to those with negative (6.7 ± 4.1% vs. 4.0 ± 1.9%, p = 0.03) and the healthy controls (6.7 ± 4.1% vs. 3.4 ± 0.9%; p = 0.01). In the positive AAb group, monocytes correlated with Hb1Ac (r = 0.40, p = 0.01) and c-pep (r = -0.37, p = 0.02). AAb positivity was independently associated with an increased percent of $CD14^+CD14^+$ monocytes (OR 1.92, CI 1.1–3.1, p = 0.01).
Conclusion: Post-transplant pancreatic AAb positivity are surrogators of beta-cell dysfunction; besides, are associated with increased pro-inflammatory CD14 + CD16 + monocytes after SPKT.

Clinical Pancreas/Islet Other

OS046 PREDICTING 1-YEAR INSULIN INDEPENDENCE BY SINGLE FASTING BLOOD SAMPLE BASED INDICES IN TYPE 1 DIABETIC ISLET ALLOGRAFT RECIPIENTS

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Background: The aim of the study was to identify predictors of long-term insulin independence in pancreatic islet transplant (ITx) recipients among single fasting blood sample based indices: Secretory Unit of Islet Transplant Objects (SUITO), transplant estimated function (TEF), homeostasis model assessment (HOMA)2-B%, C-peptide/glucose ratio (CP/G), C-peptide/glucose creatinine ratio (CP/GCr) and BETA-2 score compared to mixed meal tolerance test (MMTT).
Methods: We determined the correlation of MMTT 90-min and peak glucose and the six surrogate indices estimated on day 75 post ITx with insulin-free period, areas under receiver operating characteristic curves (AUROC) to find, which assay best predicts return to insulin therapy, and Kaplan-Meier curves for insulin-independent survival according to optimal cut-offs for all indices.
Results: We analyzed values from 22 MMTT tests in 13 recipients with up to 3 year follow up performed on day 75 post ITx. MMTT peak glucose was best predictor of insulin-free period (r = -0.77, $p < 0.001$) and anticipated loss of insulin independence at 1 year (AUROC 0.94, 95% CI 0.89 - 1.0, $p < 0.001$). BETA-2, SUITO, CP/G and HOMA2-B% were well correlated with the length of insulin free-period (r 0.57– 0.75, $p < 0.001$) and the values estimated on day 75 differed significantly between patients who were on and off insulin 1 year after ITx ($p < 0.01$). of all surrogate tools BETA-2, SUITO, CP/G and HOMA2-B% estimated on day 75 seemed equally good predictors of insulin independence 1 year after ITx (with AUROCs>0.81–0.94, $p < 0.001$). Insulin-free survival differed significantly between patients whose BETA-2, SUITO, CP/G, CP/GCr and HOMA-2B values measured on day 75 were below and over the cut-off.
Conclusions: MMTT peak and 90-min glucose estimated 75 days after ITx best predicted loss of insulin independence at 1 year post ITx. BETA-2, SUITO, CP/G also proved to be robust predictors and their values were positively correlated with duration of insulin independence.

Clinical Pancreas/Islet Surgical technique

OS047 DOES THE CAUSE OF PRIMARY GRAFT FAILURE AFFECTS LONG TERM RESULTS IN PANCREAS RE-TRANSPLANTATION?

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Introduction: The late increase in the number of pancreas transplantations has lead to an increase in potential candidates for retransplantation (PRT) after graft failure due to technical complications or chronic immunological rejection.
Material and Methods: We did a retrospective study to analyze PRT done from 2001 to 2016. The mean time between the first and second transplant was 57.3 ± 51.1 months. The back table end-to-end splenic with distal mesenteric artery anastomosis technique was used in 85.7% of the transplants. The cold ischemia mean time was 11.8 ± 2.8 h. Exocrine drainage was managed with a duodenojejunostomy in all cases. We used SPSS v20 for statistical analysis
Results: In a period of 16 years 35 retransplantations were done in our center. The group of PRT had mean age of 40 years old. Most of the primary graft failure was due to immune causes (57.1%), 40% was related to technical complications and in one patient the graft had to be removed because a lymphoma in the graft. In four cases (11.4%) a simultaneous pancreas-kidney retransplantation was done and in 31 patients a pancreas alone retransplantation was done with a functional kidney graft. The most common surgical related complication was vascular thrombosis without difference due to the primary graft failure. After a following of 82 ± 47 months, the five-year survival was 94% in the group of immune cause and 92% when primary graft failure was associated with surgical technical complications without significant difference. One year, 3 and 5 years graft survival was 79%, 73% and 61% respectively when primary graft failure was due to immune causes and 71%, 71% y 63% respectively when associated with technical complications as the cause of primary graft failure without significant difference.
Conclusions: PRT can be considered as an effective and safe second option in patients with previous primary graft failure independently of the primary graft failure cause.

Clinical Pancreas/Islet Histology

OS048 EFFECT OF INTRAPANCREATIC FAT ON DIABETES RISK AFTER TOTAL PANCREATECTOMY WITH ISLET AUTOTRANSPLANTATION

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Background: While intrapancreatic fat is postulated to impair b-cell mass and function in type 2 diabetes, via local release of non-esterified fatty acids and pro-inflammatory factors, the impact of intrapancreatic fat has never been studied in patients with pancreatitis undergoing total pancreatectomy with islet autotransplantation (TPIAT) for chronic pancreatitis.
Material and Methods: We studied the association between intrapancreatic fat and diabetes outcomes in 87 patients undergoing TPIAT between 2009 and 2016 who met the following criteria: marginal islet mass transplanted (2000–5000 islet equivalents/kg), non-diabetic prior to TPIAT, with low ("LPF", n = 53) or high ("HPF", n = 26) intrapancreatic fat content. Intrapancreatic fat was initially evaluated by gross examination during islet isolation and later validated using histomorphometric analysis of archived pancreas biopsies taken just prior to isolation (n = 44). Samples were paraffin-embedded and sections stained with hematoxylin and eosin prior to digital image analysis and fat area quantification.
Results: Differences in fat content were confirmed with histomorphometry (2.1 + /- 4.3 vs. 10.6 + /-8.9%; $p < 0.001$). Patient demographics and islet isolation data was similar between groups. Insulin independence or low-dose partial insulin supplementation was more frequent at 1 year with LPF (p = 0.016); 1 and 2-h glucose levels during mixed meal tolerance tests were higher in the HPF group (p = 0.027, p = 0.016) while Beta-score (a composite marker for islet function) was significantly better in the LPF group (6.08 ± 1.73 to 4.58 ± 1.93, p = 0.028).
Conclusion: Patients with HPF were more likely to be insulin dependent, with higher post-prandial glucose excursion, suggesting that intrapancreatic fat might lead to b-cell dysfunction with detrimental effects on diabetes outcomes after TPIAT. Alternatively high intrapancreatic fat may be a marker for patients with greater visceral adiposity and insulin resistance.

Basic Kidney Immunology

OS049 CD4 + CD28NULL T CELLS NEED EXOGENOUS CYTOKINES TO BECOME ALLORESPONSIVE AND SHOW AMBIGUOUS SUPPRESSIVE CAPACITY

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Background: $CD4^+$ T cells lacking the costimulatory molecule CD28 ($CD28^{null}$) increase with age and under inflammatory conditions. They have been associated with increased as well as decreased risk for rejection. The aim of this study was to investigate the alloreactive potential of $CD4^+CD28^{null}$ T cells.

Materials and Methods: FACS-sorted $CD4^+CD28^{null}$ T cells were stimulated with HLA-mismatched CD3-depleted cells in the absence or presence of exogenous cytokines. The alloreactive potential was evaluated by measuring proliferation, degranulation, cytotoxicity and cytokine production. Furthermore, the suppressive capacity of $CD4^+CD28^{null}$ T cells was evaluated by measuring inhibition of proliferation of T cells depleted from $CD4^+CD28^{null}$ T cells.
Results: $CD4^+CD28^{null}$ T cells showed an almost absent proliferation, degranulation and cytokine production in response to allogeneic stimulation. Addition of IL-15, but not IL-21 alone, increased the frequency of proliferating $CD4^+CD28^{null}$ T cells significantly ($p < 0.05$) up to 30% without altering CD28 expression. The combination of IL-15 and IL-21 increased CD107a expression within the $CD4^+CD28^{null}$ T cells ($p < 0.001$). Furthermore, granzyme B and perforin positivity seemed to be higher when IL-15 and IL-21 were added to the allogeneic condition within $CD4^+CD28^{null}$ T cells. $CD4^+CD28^{null}$ T cells also produced more IFN-γ and TNF-α ($p < 0.001$ for IFN-γ and $p < 0.05$ for TNF-α) after alloantigen stimulation in the presence of IL-15 & IL-21. Finally, allogeneic expanded, but not unexpanded, $CD4^+CD28^{null}$ T cells possessed ambiguous allogeneic suppressive potential.
Conclusion: $CD4^+CD28^{null}$ T cells represent a heterogeneous population with low alloreactive potential harboring ambiguous suppressive properties that might explain their association with a reduced risk for rejection.

Translational Kidney Immunology

OS050

GENERATION OF TIGIT+ ITREGS BY HUMAN REGULATORY MACROPHAGES BEFORE KIDNEY TRANSPLANTATION

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Background: The human regulatory macrophage (Mreg) is already far advanced in its development as a cell therapy for use as an adjunct immunosuppressant in organ transplantation. Preclinical experiments in mice showed that donor-strain Mregs given prior to transplantation prolonged allograft survival beyond the apparent lifespan of the transferred cells. This protective effect depended upon administration of living, iNOS-expressing cells suggesting that, unlike immature DC treatment, allogeneic Mregs might shape recipient T cell responses through direct pathway interactions. To address this hypothesis in humans, characteristics of $CD4^+$ T cells exposed to allogeneic Mregs in culture were examined in patients after Mreg treatment.
Methods: Changes in $CD4^+$ T cells caused by 5-day coculture with allogeneic Mregs were characterized by flow cytometry, gene expression profiling and suppressor assays. Patients were treated with Mreg_UKR cell products within the *ONEmreg12* trial (NCT02085629).
Results: Coculturing naïve human $CD4^+$ T cells with allogeneic Mreg led to emergence of IL-10-producing, $BTNL8^+$ $TIGIT^+$ $FoxP3^+$ induced regulatory T cells (iTregs) that suppressed polyclonally stimulated T cell proliferation and inhibited mo-DC maturation. This induction of Tregs depended upon TCR-, B7-, IDO- and notch- signaling. Administering allogeneic Mregs to NSG mice reconstituted with human naïve $CD4^+$ T cells resulted in $TIGIT^+$ $FoxP3^+$ Treg generation and systemic human IL-10 production. An acute increase in $FoxP3^+$ Tregs was observed after donor-derived Mreg treatment in two prospective living-donor kidney transplant recipients. Investigation of one Mreg-treated kidney transplant recipient with long-term stable graft function revealed an oligoclonal expansion of TCR-Vβ13.1$^+$ $TIGIT^+$ Tregs at 8-years post-treatment.
Conclusion: This study hints at a feed-forward mechanism by which Mreg treatment could promote allograft acceptance through rapid induction of direct alloreactive Tregs.

Basic Heart Immunology

OS051

LOSS OF BAT3 PROMOTES TRANSPLANT TOLERANCE BY REGULATING CD4 + T CELLS FUNCTION

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Objective: To explore the effect of Bat3 on T cells and its function in transplant tolerance induction.
Methods: We generated Bat3flox/flox CD4-Cre + mice, sorted WT and Bat3cko naïve T cells and differentiated them into different T cell subsets *in vitro*. *In vivo*, we generated heart transplant models between WT and Bat3cko mice, checked the graft survival and the T cell function in the allograft. Further, the RNA-seq was performed between WT and Bat3cko graft infiltrating T cells. We further checked the memory precursor T cells in the early, middle and late stage during LCMV Armstrong infection; at last we tested the relationship between Bat3 and mTOR complex by Western Blot and co-IP.
Results: Bat3cko T cell could express more IFN-γ, Tim-3 and IL-10, but less IL-2 and TNF-α than the WT controls during *in vitro* differentiation. No differences of IL-17 and Foxp3 expression were detected between WT and Bat3cko T cells. In the heart transplant model, the graft could survive longer in Bat3cko mice, and *ex vivo* analysis showed that Bat3cko T cells in the allograft expressed less IFN-γ, but more Tim-3 and IL-10 than cells in the WT mice. In the LCMV Armstrong infection model, there were much less virus-specific T cells and memory precursor T cells in Bat3cko mice;. The co-IP experiments showed Bat3 could bind to Rictor, and then regulate the function of mTORC2 complex and downstream molecules.
Conclusion: Bat3 could bind to Rictor and regulate the mTORC2 function. Loss of Bat3 could inhibit the T cell function and induce transplant tolerance.

Basic Cell Immunology

OS052

GZMB+ B CELLS, A KEY FACTOR OF CELL IMMUNITY IN HUMAN ?

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Background: We identified specific B cell transcriptional signature and emergence of B cells with suppressive regulatory functions in the blood of transplanted patients with long-term graft outcome. These B cells inhibit T cell response through a granzyme B (GZMB+) dependent mechanism. We hypothesize that GZMB+ B cells are key factor of cell homeostasis in healthy individuals and key regulator of immune response in chronic inflammation, by a GZMB dependent mechanism, still not understood.
Methods: GZMB+ B cells that represent around 1% of circulating B cells. We propose a protocol to expand them. We characterize their phenotype and their function after expansion.
Results: GZMB+ B cells could be expended by 10 fold *in vitro*. Expended GZMB+ B cells express high level of regulatory, activatory and differentiation molecules and keep ability to produce immunoglobulin. After 3 days expansion, expanded GZMB+ B cells maintain their regulatory capacities. They block CD4 + CD25- effector T cell proliferation in a GZMB B dependent manner, whereas has no effect on T cell apoptosis. This regulatory effect is maintained through an amplification loop of regulation/amplification that is dependent on GZMB but independent from Notch-1, a master regulator of GZMB.
Conclusion: Ability to expand these cells demonstrates their potential for cell therapy and future clinical development. These data provide novel insights into the characterization of B cell–mediated immune-regulation in tolerance in clinic and may constitute a useful therapeutic tool in solid organ transplantation and autoimmune diseases.

OS053

PROMOTION OF TOLERANCE-INDUCING CELL SUBSETS FOLLOWING HEART TRANSPLANTATION: THE FINE DIFFERENCE BETWEEN MTOR- AND CNI-INHIBITION

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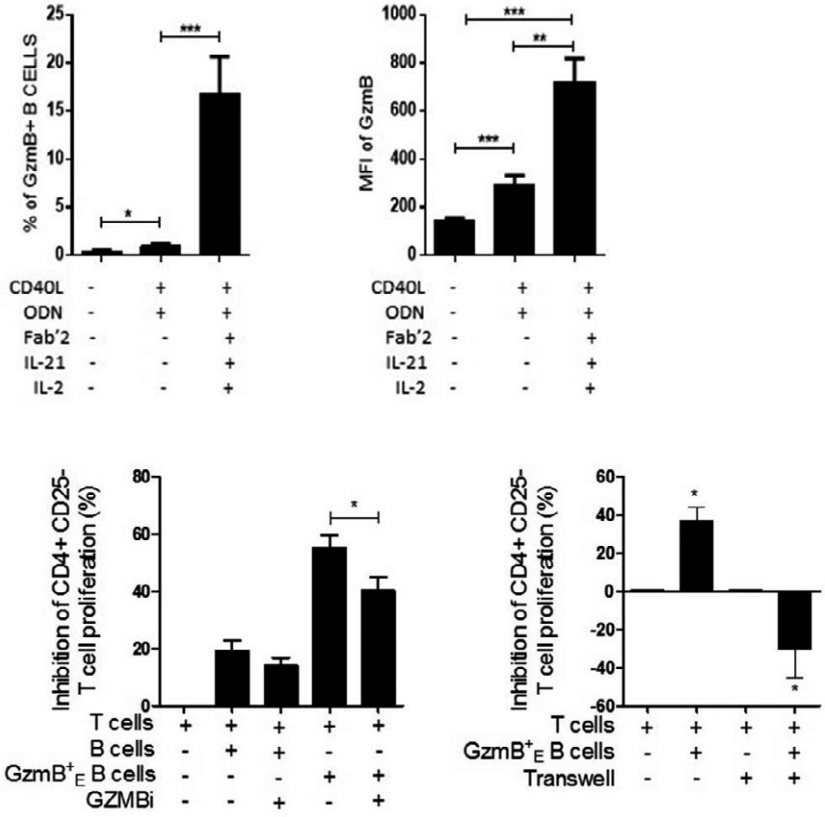
Introduction: Tolerance-inducing properties have been attributed to the immunosuppression based on inhibitors of the mammalian target of rapamycin (mTOR). The present study investigated the differences in regulatory T cell (Treg) and dendritic cell (DC) subsets as well as on the immune balance in comparison to CNI-based immunotherapy following heart transplantation (HTx).
Methods: HTx patients with either mTORI- ($n = 20$) or CNI-based immunotherapy ($n = 20$) were included. Flow cytometric analyses for the DC subsets expressing BDCA-1, -2, -3, -4 and for the Treg subsets expressing CD39, CD62L, CD120b and CD147 were performed. The immune balance (IL-2, IL-4, IL-10, IFN-g) and IL-34 levels were multiplexed.
Results: Age at HTx (mTORI: 54.7 $\pm$ 9.9 years, CNI: 53.3 $\pm$ 8.9 years) and at study begin (mTORI: 59.7 $\pm$ 10.2 years, CNI: 57.0 $\pm$ 9.0 years) were comparable in both groups. BDCA-1 + und -3 + myeloid DCs were higher and BDCA-2 + and -4 + plasmacytoid DCs were lower in mTORI-treated HTx patients. The total percentage of Tregs (mTORI: 11.4 $\pm$ 3.4%, CNI: 8.7 $\pm$ 2.4%, $p = 0.006$) as well as the percentage of the CD39 + Treg subset (mTORI: 35.4 $\pm$ 15.9%, CNI: 27.1 $\pm$ 10.8%, $p = 0.060$) was increased in HTx patients with mTORI-based immunosuppression compared to CNI-based immunosuppression. Serum levels of the pro- and anti-inflammatory cytokines as well as the Treg-specific cytokine IL-34 were higher in patients treated with CNI-based immunosuppression suggesting that these patients suffer from an immune imbalance. Furthermore, the rejection rate of CNI-treated patients was higher than the rate of mTORI-treated patients (CNI: 55.0%, mTORI: 31.6%).
Conclusion: Inhibition of mTOR following HTx promotes changes of distinct tolerance-inducing cell subsets of Tregs and DCs, an immune imbalance determined by increased cytokine levels and a lower rate of rejections compared to CNI-treated patients.



Basic Cell Immunology

OS054 IMMUNOREGULATORY ROLES OF CD137 SIGNALING IN GRAFT-VS.-HOST DISEASE

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CD137 functions mainly as a costimulatory molecule for T cell activation. However, its functions have been found in a variety of other immune and nonimmune cells and its immunoregulatory functions have also been revealing. In this study, we investigated the role of CD137 in the BM12-to-unirradiated, MHC II-mismatched C57BL/6 chronic graft-vs.-host disease (GVHD) model. This lupus-like chronic GVHD occurs because donor CD4 + T cells break host B-cell tolerance with help from host CD4 + T cells. We found that chronic GVHD was inhibited when CD137-/- mice were used as the host in this chronic GVHD model. Instead, they exhibited evident loss of body weight, lymphodepletion in the spleen, and intestinal and liver GVHD, characteristic features of acute GVHD. Consistent with these phenotype changes, there was progressive preferential differentiation of Th1 and Th17 cells in the spleen of CD137-/- recipient mice. This pattern of helper T-cell differentiation was associated with replacement of splenic CD11b+ dendritic cells with CD8 + dendritic cells in CD137-/- mice. Importantly, absence of CD137 signaling resulted in reduction in IDO-expressing B cells and FoxP3 + regulatory CD4 + T cells. These data indicate that CD137 signaling was critical in the generation of regulatory B cells and CD4 + T cells, without which donor T cells are activated, instead of entering into anergy, and attack host target tissues. Overall, our results suggest that host CD137 signaling is a key factor to determine the fate of donor CD4 + T cells during GVHD course.

OS055 IL-22 ANTIBODY ATTENUATES ACUTE GRAFT-VS.-HOST DISEASE VIA INCREASING FOXP3 + T CELLS THROUGH MODULATING THE FUNCTION OF CD11B+ CELLS

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Background: The transfer of splenocytes isolated from B6 mice into normal B6D2F1 mice induces acute graft-vs.-host disease (aGVHD), which is mediated by the elimination of recipient B lymphocytes by donor cytotoxic T cells. IL-22 is a cytokine that is structurally related to IL-10 and is secreted by Th1 cells, Th17 cells and innate immune cells.
Method: To investigate the association between IL-22 and aGVHD, anti-mouse IL-22 antibody (IL-22Ab) was used to ablate the activity of this cytokine in a mouse model of aGVHD, CD25 and CD11b cells were depleted in the model of aGVHD to determine the mechanism of IL-22 Ab in protecting aGVHD. *In vitro* experiments were done by co-culture the naïve T cells and CD11b cells obtained from aGVHD to generate the iTregs.
Result: Our results proved that administration of IL-22Ab significantly reduced the progression of aGVHD in B6D2F1 recipients of B6 grafts. In addition, IL-22Ab treatment decreased the percentage of interferon-γ+ and tumor necrosis factor-α+ T cells but increased the numbers of forkhead box p3 + regulatory T cells (Tregs) *in vivo*. In the presence of Tregs and donor CD11b+ cells, IL-22Ab protected against aGVHD. Furthermore, the process of Treg induction was more efficient when CD4 + CD25- T cells were differentiated in the presence of CD11b+ cells obtained from IL-22Ab-treated GVHD mice compared to untreated control cell co-culture.
Conclusion: IL-22Ab may represent a valid approach towards aGVHD prevention.
Keywords: IL-22, aGVHD, Treg, Foxp3, CD11b.

OS056 GENERATION OF POTENT AND STABLE *EX VIVO*-EXPANDED REGULATORY T CELLS BY MODULATING CD27 SIGNALLING

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Background: Regulatory T cell (Treg) therapy is a promising strategy to improve outcomes after transplantation. Ligation of CD70 to CD27, a costimulatory molecule member of the tumour necrosis factor superfamily, supports T cell responses by providing survival signals. In human Tregs, CD27 expression correlates with suppressive potency after *in vitro* expansion. We hypothesised that modulation of the CD27/CD70 pathway may allow for the generation of Tregs with enhanced suppressive properties after *in vitro* expansion.
Methods: $CD4^+CD127^{low/-}CD25^+$ Tregs were sorted from healthy donors PBMCs and expanded for 14 days *in vitro* via αCD3/αCD28 stimulation in the presence of IL-2. Cells were then flow sorted according to CD27 expression and expanded for a further 14 days. Phenotype, suppressive function and

cytokine production were analysed after expansion. Additionally, levels of activation, proliferation and death were analysed by flow cytometry in Tregs or $CD4^+$ T cells after *in vitro* αCD3/αCD27 stimulation.
Results: CD27 expression correlated with epigenetically stable FOXP3 expression, measured by TSDR demethylation. Suppressive activity was confined to expanded $CD27^+$ Tregs, while $CD27^-$ Tregs promoted T cell proliferation and produced high levels of IL-17. On ligation of CD27, there was a robust activation and proliferation response in conventional T cells, but high death levels in Tregs. Moreover, blocking the CD27/CD70 pathway within an *in vitro* suppression assay potentiated T cell proliferation and Treg suppression.
Conclusion: Selection on CD27 may allow the generation of a more potent and stable Treg product for cellular therapy. Since CD27 costimulation may activate distinct intracellular pathways in conventional and regulatory T cells, CD27/CD70 axis could be targeted to regulate the balance between proinflammatory and regulatory T cell responses. CD27/CD70 pathway seems to play a role in the activity of human Tregs, and its modulation may increase their suppressive properties.

Basic Composite Tissue Immunology

OS057

EX VIVO EXPANDED REGULATORY T CELLS COMBINED WITH SHORT-TERM COSTIMULATION BLOCKADE PREVENT REJECTION OF VASCULARIZED COMPOSITE ALLOGRAFTS

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Background: Reconstructive transplantation represents a valid therapeutic option after devastating tissue loss. Routine clinical application, however, is hampered by the toxicity of long-term maintenance immunosuppression. The current study investigated to a novel approach using *ex vivo* expanded regulatory T cells combined with short-term immunomodulatory strategy in a murine hind limb transplantation model.
Methods: Fully MHC-mismatched orthotopic hind limb transplants were performed from Balb/C to C57BL/6 mice. Recipients in the experimental groups received various combination regimen consisting of 0.5 mg CTLA4 Ig on day 0, 2, 4 and 6 post-transplant and, 20 mg/kg anti-Thy 1.2 mAb on POD-1 and 1 mg/kg Rapamycin (POD 0–9) and 1 week expanded Treg cells. Allograft survival was monitored and flow cytometric analysis was performed to evaluate mixed chimerism and clonal deletion of alloreactive T cells.
Results: Combination of T cell depletion and CTLA4-Ig plus short-course of Rapamycin increased VCA survival significantly while untreated control

Figure 1

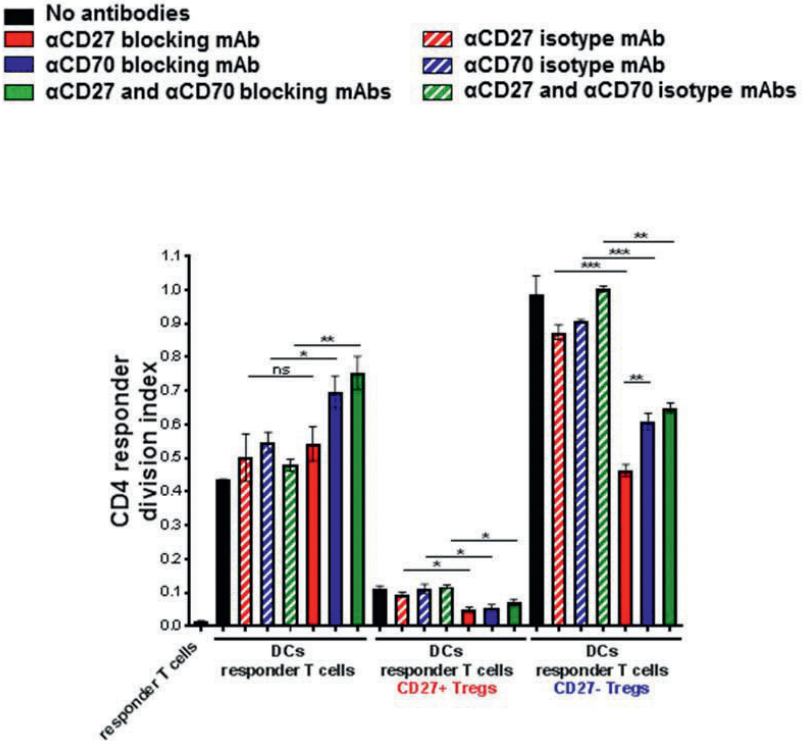

Figure 1. Blocking the CD27/CD70 pathway potentiates T cell proliferation and Treg suppression.
Suppressive capacity of expanded CD27+ Tregs and CD27- Tregs was analysed in the absence (black) and in the presence of 10ug/ml of isotype (striped) or αCD27 (red), αCD70 (blue) or αCD27+αCD70 (green) blocking mAbs. $10x10^4$ CD27+ Tregs or $10x10^4$ CD27- Tregs were incubated with $10x10^4$ autologous CD3+ cells (responder T cells) labelled with VPD and $2x10^4$ dendritic cells (DCs) for 80-96h. The graph represents the division index of responder cells; the average number of cell divisions that a cell in the original population has undergone. Mean with SEM is represented and statistical significance was assessed by a Mann-Whitney test (*p<0.05, **p<0.01, ***p<0.001). No statistical differences between different isotype mAbs and control media were observed. 1 representative donor is displayed.

rejected allografts (MST 105 days vs. MST 9 days; $p < 0.01$). Mixed chimerism was detected in recipients receiving the combined treatment protocol with 5.013 ± 1.23% of donor derived CD11b+ cells on POD 55. Vβ – TCR staining profiles in recipients after full treatment showed 1.570 ± 0.3700% of νβ5 + CD4 + T cells, while naïve C57BL/6 express 3.567 ± 0.3690% of νβ5 + CD4 + T cells, suggesting the actuation of central deletion of developing donor-reactive T cells. The addition of *ex vivo* expanded regulatory T cells further significantly increased VCA survival to 200 days and induced long-term stable mixed chimerism.
Conclusion: The combination of T cell depletion, costimulation blockade, and a short-course of Rapamycin prevents VCA rejection and significantly prolongs graft survival without the need for myeloablative conditioning or maintenance therapy. regulatory T cells added in the early post transplant period further optimize regulation.

Basic Cell Immunology

OS058 DHRS9 IS A SPECIFIC AND STABLE MARKER OF HUMAN REGULATORY MACROPHAGES

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Background: The human regulatory macrophage (Mreg) has emerged as a promising cell type for use as a cell-based adjunct immunosuppressive therapy in solid organ transplantation. A therapeutic cell product, known as Mreg_UKR, is presently being investigated in a Phase-I/II trial as a means of safely minimising maintenance immunosuppression in kidney transplant recipients. Mregs can be distinguished from macrophages in other polarisation states by their unique mode of derivation, a constellation of surface markers and suppressor function; however, until now, no single marker was available to specifically and stably identify human Mregs.
Methods: By immunoprecipitation and MALDI-MS sequencing, dehydrogenase/reductase 9 (DHRS9), a little-studied retinol dehydrogenase of the SDR family of NAD(P)(H)-dependent oxidoreductases, was identified as the cognate antigen of a mouse monoclonal antibody raised against human Mreg lysates. DHRS9 expression within a panel of human monocyte-derived macrophages and dendritic cells (DC) was investigated by q-PCR, immunoblotting and flow cytometry.
Results: DHRS9 expression discriminated human Mregs from a broad panel of *in vitro*-derived macrophages and human monocyte-derived tolerogenic DC, including Tol-DC, Rapa-DC, DC-10 and PGE_2-induced MDSC. Expression of DHRS9 was acquired gradually during *in vitro* development of Mregs from $CD14^+$ monocytes and was further enhanced by IFN-γ stimulation. Treating Mregs with 100 ng/ml lipopolysaccharide for 24 h did not extinguish DHRS9 expression. A population of $DHRS9^+$ human splenic macrophages was discovered by immunohistochemistry. Although it cannot be inferred that these naturally-occurring $DHRS9^+$ macrophages are a physiological equivalent of *in vitro*-derived Mregs, their presence suggests that DHRS9 expression by cultured Mregs is not an artefact.
Conclusion: DHRS9 is a specific and stable marker of human Mregs that should be useful in future studies, especially searching for a natural counterpart.

OS059 BTNL8 IS EXPRESSED BY HUMAN MREG-INDUCED FOXP3 + TREGS

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Background: The human regulatory macrophage (Mreg) has emerged as a promising cell type for use as a cell-based adjunct immunosuppressive therapy and is presently being investigated in a Phase-I/II trial as a means of safely reducing maintenance immunosuppression in kidney transplant recipients. Coculturing naïve human CD4 + T cells with allogeneic Mreg led to their conversion into IL-10-producing $FoxP3^+$ Tregs capable of suppressing polyclonally-stimulated T cell proliferation. To discover novel markers of Mreg-induced iTregs, whole-genome gene expression profiling studies were performed, leading to identification of butyrophilin-like 8 (BTNL8).
Methods: A microarray dataset was generated comprising 5 replicates of 4 human cell types – namely, (1) flow-sorted fresh $CD4^+$ T cells, (2) $CD4^+$ T cells after 5d coculture with allogeneic human Mregs, (3) $CD4^+$ T cells after control macrophage coculture, and (4) $CD4^+$ T cells cultured alone for 5d. BTNL8 expression in T cells was investigated by q-PCR, immunoblotting and flow cytometry.
Results: BTNL8 stood out as a highly discriminatory marker of Mreg-generated iTregs with likely immunological relevance. Up-regulation of *BTNL8* mRNA in Mreg-cocultured T cells was corroborated by qPCR using primers amplifying both the BTN-like and B7-like variants of BTNL8. By sequencing, it was shown that Mreg-cocultured T cells expressed only the B7-like variant. *BTNL8* was quantified in $CD4^+$ $CD25^+$ $CD127^{int}$ Treg and non-Treg from blood. *BTNL8* was not reliably detected in freshly-isolated Tregs or non-Treg; however, PHA-treatment strongly induced *BTNL8* expression in Tregs and more weakly in non-Treg. Immunoblotting revealed stronger expression of the B7-like (37kD) isoform of BTNL8 in Mreg-cocultured $CD4^+$ T cells than controls. By flow cytometry, stronger BTNL8 expression was found in Mreg-induced iTregs compared to $CD25^+$ $FoxP3^-$ or $CD25^-$ non-Tregs.
Conclusion: The 37-kD variant of BTNL8 is a useful marker of human activated, Mreg-induced Treg.

Basic Others Immunology

OS060 *IN VIVO* TREG EXPANSION UNDER COSTIMULATION BLOCKADE TARGETS EARLY REJECTION AND IMPROVES LONG-TERM OUTCOME

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Background: Early allograft rejection is a major obstacle under costimulation blockade-based immunosuppression. We have previously shown that the immunosuppressive effect of CTLA4Ig monotherapy is Treg-dependent at low (LD) but not high doses. Therefore, we aimed at increasing CTLA4Ig's efficacy by targeting recipient's Tregs through adoptive transfer and *in vivo* Treg expansion.
Methods: Cardiac allograft transplantation was performed (Balb/C à C57BL6) under CTLA4Ig monotherapy, modeled after the clinically approved dosing regimen (LD). In groups of mice treated with LD CTLA4Ig, 3x106 recipient Tregs were transferred early (D-1, $n = 6$) or late (D8, $n = 10$) or Tregs were expanded *in vivo* by using IL2/aIL2 complexes (D-3, D-2, D-1; $n = 5$).
Results: Transferred Tregs were viable and traceable in various compartments including the spleen, lymph nodes, blood and bone marrow. However, neither early, nor late Treg transfer prolonged allograft survival under LD CTLA4Ig therapy (MST 24.5 vs. 33.5 vs. 52.5; $p = n.s.$). By treating mice with IL2/aIL2 complexes the deleterious effect on Treg numbers under costimulation blockade was abolished. Moreover, CD80 expression on dendritic cells, which was significantly increased by CTLA4Ig treatment, was lowered to levels observed in naïve animals. Notably, addition of IL2/aIL2 complexes significantly prolonged heart graft survival (MST >100 days) compared to CTLA4Ig monotherapy (MST: 52.5 days) or IL2/aIL2 complexes only (MST: 14 days) ($p < 0.001$).
Discussion: Whereas Treg transfer didn't result in an improved allograft outcome, *in vivo* Treg expansion by using IL2/aIL2 complexes resulted in long-term graft survival with low dose CTLA4Ig treatment. These results suggest a clinically promising strategy to improve outcome with costimulation-blockade-based immunosuppression.

Basic Lung Immunology

OS061 SYSTEMIC TREG LEVELS EARLY AFTER LUNG TRANSPLANTATION ARE ASSOCIATED WITH THE RISK FOR ACUTE REJECTION EPISODES

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[1]Ludwig-Maximilians-Universität München, Germany; [2]Medizinische Hochschule Hannover, Germany; [3]Helmholtz-Zentrum München, Germany

Background: Regulatory T cells (Treg) are key modulators of the immune response in lung transplantation (LTX). It is unknown, whether systemic Treg levels early after LTX are (i) indicative for their systemic frequency over time and (ii) correlate with the incidence of immunological events. Hence, systemic Treg levels were analyzed prospectively in LTX recipients and correlated with the occurrence of acute rejection (AR) episodes.
Methods: In total, 116 (m/f: 55/61, age: 52 ± 1y, LAS: 47 ± 2) patients undergoing single ($n = 33$) or double ($n = 83$) LTX were included. Following FACS-analysis of Tregs in peripheral blood (CD3 + /CD4 + /CD25 + / FoxP3 +) at day 21 after LTX, a low ($n = 29$, lower quartile, ≤1.71% of CD4 +), intermediate ($n = 58$, 50% percentile, 1.71%-5.59% of CD4 +) and high Treg group ($n = 29$, upper quartile, ≥5.59% of CD4 +) were defined. Thereafter, Tregs were monitored at day 90, 180, 270 and 365. Patients treated with steroids due to a biopsy proven (A ≥ 1/ B ≥ 1) and/or clinical rejection

episode (FEV1-loss) were defined positive for AR. Data are given as mean ± SEM.
Results: Age, LAS and trough-levels of FK506 were not significantly different between the groups. Treg levels remained significantly different between the high and low Treg group throughout day 270 (3.1 ± 0.5 vs. 5.4 ± 0.5% of CD4 +) and maintained the same trend up to 365 days after LTX. Interestingly, within the high Treg group a drop of individual Treg levels to the range of the lower quartile (and *vice versa*) was never observed. Furthermore, there was a clear trend for an increased AR only in the low-Treg group (low/intermediate/high: 48.26% vs. 25.86% vs. 27.59%).
Conclusion: Systemic Treg frequency measured as early as 3 weeks after LTX seems to be indicative for Treg levels in the ensuing post-LTX period. Hence, early Treg levels may indicate the immunological risk in LTX. Recipients with a persistently low Treg level carried the highest risk for AR, while continuously high Treg levels appeared protective.

Clinical Lung Immunology

OS062 NUMBER OF CD8 + CD27 + CD28- EFFECTOR MEMORY T CELLS PRIOR LUNG TRANSPLANTATION AS BIOMARKERS OF SEVERE ACUTE REJECTION

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Introduction: Non-invasive biomarkers before lung transplantation could be useful to identify patients at risk of acute rejection (AR) with poor prognosis and could tailor immunosuppression to avoid early AR. Several biomarkers of AR were identified and our group described an increased number of CD8 + TEM cells prior lung transplantation in patients with risk of subsequent acute rejection (1). We ought to immunophenotype CD8 TEM in an independent cohort of lung transplant candidates.
Material and Methods: 52 lung transplant candidates were recruited in the study, and CD8 + T cell subpopulations were identified by multiparametric flow cytometry. Biopsy protocol was scheduled 21 days after lung transplantation and reported following ISHLT criteria. A 61.5% of lung transplant patients had an AR episode, 4 patients had A1 (mild), 19 had A2 (moderate) and 9 had A3 or A4 (severe) AR.
Results: The median of CD8 + TEM before lung transplantation in patients with severe AR was 155.8 (47.2–229.7) vs. 74.3 (43.7–103.6) in non-severe AR patients; $p = 0.046$. Within the CD8 TEM subsets, those with CD27 + CD28- phenotype were also higher in patients with severe AR than with non-severe AR = 25.2 (7.5–27.1) vs. 7.24 (4.3–16.5); $p = 0.037$. After ROC analysis of CD8 + TEM CD27 + CD28- levels and severe AR, the AUC was: 74.6%, and a value of 18.8cells/uL CD8 TEM CD27 + CD28- was able to discriminate with 71.4% of Sensitivity and 82.2% of Specificity the patients with severe AR. Those patients with higher levels of CD8 TEM CD27 + CD28- than 18.8 cells/uL were at risk of severe AR [OR 11.56 (1.89–70.59), $p = 0.008$].
Discussion: The measurement of CD8 TEM prior lung-transplantation was confirmed as a biomarker of severe AR in an independent cohort, and the exhausted phenotype CD27 + CD28- of CD8 TEM has an increased association with severe AR. The utility of monitoring CD8CD27 + CD28- in patients on waiting list of lung transplantation should be confirmed in multicentre studies.
(1) San Segundo et al. PLoS One (2013)13;8(11):e80601

Clinical Lung Immunosuppressive agents

OS063 CONVERSION TO EXTEND RELEASE TACROLIMUS IN EARLY POST- LUNG TRANSPLANTATION PERIOD

Alessandro Palleschi, Letizia Corinna Morlacchi, Valeria Rossetti, Paolo Tarsia, Rosaria Carrinola, Lorenzo Rosso, Davide Tosi, Paolo Mendogni, Margherita Cattaneo, Mario Nosotti
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Tacrolimus, an immunosuppressive agent, has been studied in lung transplantation (LuTx), but it is currently off-label. An extended release (ER) formulation allows once-daily dosing, improving adherence and reducing maximum concentration, with comparable area under the curve from 0–24 h. The aim of this study was to report the clinical experience of switching from tacrolimus bis in die (BID) to ER-tacrolimus in stable early LuTx recipients.

Study subjects were adult patients underwent bilateral LuTx in 2016 with early regular post-operative course; patients with an intensive care unit stay >14 days were excluded. Data were collected from our dedicated database. The switching from tacrolimus BID to ER-tacrolimus was carried out for all patients on 16th day after surgery, dosed 1 : 1 ratio. Dosage adjustment was based on trough concentrations (Cmin). We consider as range a Cmin of 10–15 ng/ml, acceptable 8–10 and 15–18 ng/ml, extra-range a value outside of the above intervals. Cmin at the day of switch (T0), 1st (T1) and 2nd day (T2), 1 (T3), 2 (T4), 3 (T5) and 4 weeks (T6), and 2 months (T7) were analyzed.

Twenty-one patients were observed, 17 female, a median age of 40 years. The indications were cystic fibrosis, emphysema and interstitial lung disease in 13, 3 and 8 cases, respectively. All patients received fungal prophylaxis with azole. The median intensive care unit stay was 4 days. The 3-months mortality was 4.7% (1 patient). Excluding two patients with preoperative renal failure, we observed a reduction of renal function in two patients. Table 1 shows the respiratory functional and Cmin trends of patients.

To our knowledge, we report the first experience of early switch to ER-tacrolimus. We observed a low rate of extra-range Cmin and we do not recorded severe side effects. Further research should focus on the acute and chronic lung allograft dysfunction onset.

OS064 PHASE II PROSPECTIVE PILOT STUDY TO COMPARE PHARMACOKINETICS, SAFETY AND TOLERABILITY BETWEEN TWO FORMULATIONS OF ONCE-DAILY EXTENDED- RELEASE TACROLIMUS

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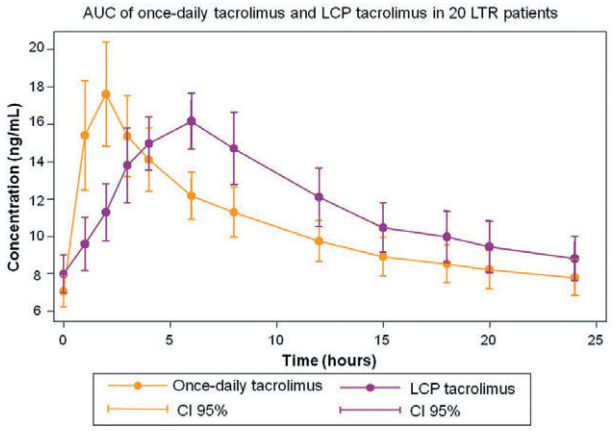
Background: once-daily dosing tacrolimus is widely used in lung transplantation (LT). The aim of this study was to compare the pharmacokinetic (PK) profile, tolerability and safety of novel once-daily extended-release tacrolimus (LCPT; Envarsus®) compared to once-daily prolonged-release tacrolimus (ODT; Advagraf®) in stable adult LT recipients (LTR).
Methods: phase II, open-label, single-center, prospective pilot PK study. Twenty stable LTR were recruited, mean age 55.9 (r: 38–67) years, 13 (65%) men, under immunosuppressive treatment based on ODT and more than 6 months of post-operative follow-up. At this point, patients were switched to

	T0 (%)	T1(%)	T2(%)	T3(%)	T4(%)	T5(%)	T6(%)	T7(%)	T8(%)
FEV1 median value (range)							58 (45–98)		77 (45–117)
FVC median value (range)							59 (43–89)		75 (49–110)
FK: Range N/CF	50/38	43/38	29/31	38/33	75/38	88/15	75/50	38/50	
FK: Acceptable N/CF	25/46	43/54	58/62	38/58	25/62	12/85	25/50	50/42	
FK: Extra-range N/CF	25/16	14/8	13/7	24/9	0/0	0/0	0/0	12/8	

Table 1. N = not cystic fibrosis; CF = Cystic fibrosis; T0-T7 = see the text; T8 = 3 months after LuTx



LCPT on a 1: 0.7 (mg/mg) conversion dose. For study purposes follow-up was 6 months and cystic fibrosis (CF) patients were excluded. Two 24-h PK profiles were obtained in each patient, the first one on the day - 14 and the second one on the day + 14 after switching to LPCT. PK parameters, safety and tolerability were compared.
Results: Mean (SD) AUC 0–24 h was 254.21 (61.78) ng mL/hr for ODT and 281.72 (68.52) ng mL/hr for LCPT showing similar bioavailability (Schuirmann's Two One-sided test). Mean (SD) dose in ODT was 5.05 (1.67) mg and in LCPT 3.36 (1.03) mg (p: 0.0002). Time to maximum concentration (Tmax) was 125 min for ODT and 325 min for LCPT. Correlation between AUC 0–24 and C24 was (r = 0.947) for ODT and (r = 0.945) for LCPT. Switch was safe and well tolerated. There were no differences in side effects between the two formulations.
Conclusions: Switching from ODT to LCPT was safe and well tolerated in stable non-CF LTR. A lower dose of LCPT allows similar bioavailability.

Basic Lung Histology

OS065 CHANGES IN THE EXTRACELLULAR MATRIX - SIGNS OF REMODELING LEADING TO CHRONIC REJECTION AFTER LUNG TRANSPLANTATION

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Background: About 50% of lung transplanted patients develop chronic rejection in the form of bronchiolitis obliterans syndrome (BOS) within 5 years after transplantation. BOS is characterized by a decrease in lung function, caused by progressive fibrosis. However, little is known about its initiation. We hypothesize that changes in the distribution of extracellular matrix proteins might be a marker for the disease process.
Methods/Material: Our study aimed to map total collagen, collagen type IV, biglycan and periostin in transbronchial biopsies taken at 3 and 12 months after transplantation using Masson's Trichrome staining and immunohistochemistry. Staining patterns were quantified and related to patient data (n = 58) in a 5-years follow-up.
Results: Compartment specific patterns could be revealed between 3 and 12 months post-transplantation. Alveolar total collagen (p = 0.019) and small airway biglycan (p = 0.02) increased in BOS-developing patients. Alveolar collagen type IV increased in BOS-free patients (p = 0.01) (3 vs. 12 months). Individual calculation of the change in protein content (12 minus 3 months for the respective patient) confirmed the increase in biglycan (p = 0.012) and showed a trend for increased periostin (p = 0.057) in the small airways of BOS patients compared to BOS-free patients (BOS vs. BOS-free). Already at 3 months, before onset of BOS, increased total alveolar collagen (p = 0.036) and small airway collagen type IV (p = 0.034) could discriminate between patients developing less severe and severe forms of BOS (BOS grade 1 + 2 vs. 3).
Conclusion: The results show distinct alterations of the extracellular matrix which might be part of the complex remodeling processes that eventually lead to BOS.

Clinical Lung Immunology

OS066 LONGITUDINAL DATA FROM A PROSPECTIVE OBSERVATIONAL STUDY OF HYPOGAMMAGLOBULINEMIA (HGG) AT 18 MONTHS AFTER LUNG TRANSPLANTATION (LT)

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Background: Immunosuppressive therapies in LT have been linked to the development of secondary HGG. The large prospective studies have not been performed to evaluate the clinical relevance of HGG in LT recipients.
Methods: This is a single center prospective observational study of LT recipients at the University of Pittsburgh Medical Center. Pre- and post-transplant IgG levels were measured and related to infection, antibiotic use, and immunosuppression. Analysis was performed using non-parametric tests.
Results: 135 LT recipients were prospectively evaluated. The mean age at transplant was 56.8 years. 62.2% of subjects were males and 91.8% were Caucasian. The primary reasons for transplant were IPF, COPD, and CF (34.1%, 31.1%, and 9.6% respectively). 66.7% were induced with Alemtuzumab and 33.3% with Basiliximab. Median IgG levels increased from 496.5 mg/dl at the time of transplant to 675 mg/dl at 18-months post transplant. 10 subjects were deceased by 18 months (7.4%). Post-transplant subjects receiving Basiliximab had significantly lower IgG levels at 3, 6, and 9 months than those induced with Alemtuzumab, but those differences were absent at 12, 15, and 18 months after transplant. Severe HGG (IgG < 400 mg/dl) was associated with 2 or more pneumonias (p = 0.0006) and higher number of antibiotic courses (p = 0.003) compared to the subjects without severe HGG. One-year and 18-month mortality were associated with lower IgG levels at 3 months post-transplant (p = 0.04). Furthermore, severe HGG tended to associate with more mortality at any time during 18 months post-transplant (p = 0.07). There was no relationship between IgG levels and CMV viremia, steroid use, or presence of acute rejection.
Conclusions: Our data suggest that LT recipients with severe HGG are at increased risk for recurrent pneumonias, more antibiotic courses, and worse survival. Additionally, low IgG level at 3 months post-transplant appears to be a predictor for increased mortality at 12 and 18 months post-transplant.

Clinical Lung Infection

OS067 CHARACTERISTICS AND OUTCOMES OF *STREPTOCOCCUS PNEUMONIAE* INVASIVE INFECTION IN LUNG TRANSPLANT RECIPIENTS

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Lung transplant recipients (LTR) have an increased risk of streptococcus pneumoniae (Sp) invasive infection (SPII).

We performed a retrospective analysis of any consecutive patient with at least one Sp isolate in bacteriological sample and/or urinary antigen in 538 LTR followed in a French center between 2010 and 2016. Patients with asymptomatic colonization, bronchitis and SPII are described.

83 isolates were obtained in 60 patients (11%) after a median time of 7.5 months post LT (IQR, 3.6; 12.4). Among them, 21 patients remained asymptomatic, 12 patients had bronchitis and 27 patients had at least one episode of SPII, mostly pneumonia. Sp was isolated in the immediate post-operative course in 12 patients (20%). Strains were susceptible to penicillin G and A in respectively 68 and 89% of the cases. Patients with isolates had another potential factor of colonization in 48% of the cases, such as the presence of bronchial stent or tracheostomy (23%), current tobacco use (15%) and pulse steroids in the previous 2 months (15%). Biopsy proven acute cellular rejection occurred simultaneously in 20% the patients. SPII incidence was 1.72 cases/100 patient-years. 80% of the cases of SPII occurred in the first 3 years post LT. Co-infection with various respiratory virus was documented in 29% of the cases. Co-infection with chronic colonizing bacteria, such as *Pseudomonas* or *staphylococcus* was present in 35%. None of the patients with SPII had received previous combined pneumococcal vaccination and only 6 (22%) of them were under azithromycin at the time of SPII. 19% of the patients required ICU admission, due to shock. None of them died.

Colonization of the lung allograft with Sp may occur very early and is frequently associated with bronchial stent, tobacco exposure or previous pulse steroids. SPII occurs in half of the cases. As previously described in the immunocompetent host, viral co-infection may be critical in the occurrence of SPII.

OS068

IMPACT OF RESPIRATORY SYNCYTIAL VIRUS INFECTION ON LONG-TERM OUTCOMES IN LUNG TRANSPLANT RECIPIENTS

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Acute respiratory virus infections have been associated with lung function decline at time of infection in lung recipients (LTR). An increased risk of acute cellular rejection (ACR) and chronic lung allograft dysfunction (CLAD) has also been reported following viral infection. We report on the lung function at time of infection and 6 months after respiratory syncytial virus (RSV) infection.

We performed a retrospective analysis of all consecutive patients with at least one positive PCR for RSV on a respiratory sample in 439 LTR followed between 2013 and 2016. At the time of infection, decliners, defined as patients with a drop of FEV1 > 10% from baseline, were compared to non-decliners. At 6 months, the occurrence of ACR, anti-HLA DSA and the occurrence/evolution of bronchiolitis obliterans syndrome (BOS) were assessed.

RSV infection occurred in 42 patients (9.7%; incidence 3.95/100 patient-years) at a median time post LT of 760 days (IQR, 272; 1432). 30 (71%) were decliners and 12 (29%) non-decliners. Decliners had more frequently a past history of similar episode than non-decliners (respectively 16/30, vs. 2/12; $p = 0.036$) and had more frequently pre-existing BOS stage 1 or more (8/30, vs. 0/12; $p = 0.08$). The diagnosis, the immunosuppression, co infection with bacteria or other viruses and concomitant ACR did not differ between the two groups. At 6 months, ACR occurred in 1 patient in each group ($p = 0.48$), and *de novo* or aggravating BOS stage 0p or more occurred equally in both groups (10/30, vs. 4/12; $p = 0.99$). 7/30 (23%) of the decliners had *de novo* or increasing DSA (*vs.* 1 non-decliners; $p = 0.4$), and 2 of them experienced antibody-mediated rejection in the following 6 months.

RSV infection in LTR is frequently associated with an acute drop in FEV1, especially in case of pre-existing BOS and past history of similar episodes. *De novo* or aggravating BOS occurs in 1/3 of patients in the following 6 months independently of the occurrence of decline at the time of infection.

Clinical Lung Rejection

OS069

DONOR SPECIFIC HLA ANTIBODY-MEDIATED COMPLEMENT ACTIVATION IS A SIGNIFICANT INDICATOR OF ANTIBODY-MEDIATED REJECTION AND POOR LONG-TERM GRAFT OUTCOME DURING LUNG TRANSPLANTATION

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It has been demonstrated in heart and kidney transplantation that anti-HLA DSA mediate damage to the allograft via multiple mechanisms, including complement-dependent and independent actions. The transplant community is now in pursuit of new tools or technologies that will allow for stratification of DSA+ patients for antibody mediated rejection (AMR). C3d assay allow direct measure of DSA activation of complement.

According to routine DSA detection strategy (Single Antigen One Lambda), 105 patients within our Foch Lung transplant cohort (September 2008-December 2013) were considered as DSA positive patients and further tested using the Immucor® LSA Lifecodes bead-based assays for single antigen and C3d testing. AMR diagnosis associated graft failure and DSA presence and histological lesion compatible with AMR and/or C4d positive staining. DSA positivity was defined by BCM > 500 (Background corrected MFI). C3d ratio was calculated as BCM of patients beads/BCM of negative control

Among 105 patients, 25 were considered DSA+AMR- and 15 DSA+AMR+. Comparison of donor specific beads BCM and donor specific beads C3d ratio between DSA+AMR+ and DSA+AMR- patients show a significantly higher value in DSA+AMR+ patients. BCM and C3d ratio of donor specific beads show strong correlation in DSA+AMR+ patients (R = 0.6). Within DSA+AMR- group the correlation was weaker (R = 0.09). Within our study population, immunodominant DSA C3d ratio > 4 was significantly associated with graft loss.

DSA capacity to bind C3d is clearly associated with AMR and graft loss in lung transplantation. These results need to be validated in larger multicentric study.

Clinical Lung Other

OS070

UPPER LIMB REHABILITATION AFTER LUNG TRANSPLANTATION (BSLTX) - A RANDOMISED CONTROLLED TRIAL

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Exercise rehabilitation is a key element in recovery after adult lung transplantation (LTX). Whilst lower limb endurance exercise is an accepted component, the role of upper limb (UL) exercise is not clear.

Study aimed to investigate effects of a supervised upper limb exercise program (SULP) vs. no supervised upper limb (NULP) rehabilitation program after LTX.

Method: Post-LTX patients >18 years were randomised to either supervised upper limb training program (SULP) or no UL (NULP) program as part of post LTX rehabilitation program. Randomisation was stratified for incision type either clam shell or bilateral anterior thoracotomies. Exercise sessions were thrice weekly & consisted of cardiovascular training on bike & treadmill & lower limb strength training. Those participants randomised to SULP completed a progressive UL strength training component according to protocol.

Outcome measures were taken at baseline, 6 wks, 12 weeks & 6 months by assessors blinded to group allocation. Bodily pain was scored on a visual analogue scale (VAS) with anchors of no pain & maximal pain & pain sited on body chart. Strength of shoulder flexion and abduction was measured using a hand held dynamometer. Quality of life (QOL) was assessed.

Results: Participants ($n = 80$) had mean age 56 years (SD 11), 57% male and 55% had a primary diagnosis of COPD. After 6 weeks of training, participants in the SULP had significantly less pain on VAS than those performing no UL exercises (NSULP mean 3.8 cm (SD1.7) vs. SULP 2.05 cm (SD 1.3) $p < 0.001$). At 6 weeks the SULP participants had greater UL strength (peak force Nm) than NULP participants (SULP 8.4Nm (SD4.0) vs. NULP 6.7Nm (SD 2.8) $p = 0.037$). After 12 weeks of training the SULP participants had less posterior thoracic pain sited on body chart (SULP 1 (SD 2.6) vs. NULP 8 (SD 22) $p = 0.026$). At 6 months, there was no significant difference between groups for all outcomes.

After LTX a supervised UL exercise program results in short term improvement in pain & muscle strength

Clinical Lung Surgical technique

OS071

LOBAR TRANSPLANTATION DOES NOT AFFECT EARLY OUTCOME COMPARED TO FULL LUNG TRANSPLANTATION

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Background: The shortage of donor pool for lung transplantation led to an increasing waiting list mortality, in particular in selected sub-groups of patients created by introduction of the Lung Allocation Score era. Several strategies have been proposed to overcome this scenario, one of them is lobar transplantation. The aim of this study was to compare early outcome of lobar lung transplantation vs. full lung transplantation in our center.

Methods: We performed a retrospective analysis of our experience with lobar lung transplantations (Study group), compared with full lung transplantations (Control group). Primary endpoint was 3-months survival. Secondary endpoints were: grade 3 primary graft dysfunction within the first 72 h, intensive care unit stay, postoperative length of stay, bronchial healing problems, overall survival.

Results: From January 2011 to September 2016, we performed 120 consecutive lung transplantations. of them, 110 (91.7%) were full lung and 10 (8.3%) were lobar transplantations. Causes of lobar transplantations were: donor-recipient size mismatch (5) and graft parenchymal or vascular damages (5). Recipient and donor characteristics resulted homogeneous in two groups. In lobar transplantations for size mismatch, the difference between donor and recipient vital capacities were 1.48 $\pm$ 1 liters vs. 0.26 $\pm$ 0.86 liters in Control group ($p = 0.0028$). The 3-months survival rate wasn't statistically different in two groups. Extracorporeal life support and total ischemic time were higher in Study group ($p = 0.043$ and $p = 0.03$ respectively). No statistically significant differences were found regarding secondary endpoints, including overall survival.

Conclusions: Lobar lung transplantation has comparable early outcome with full lung transplantation. Our clinical experience confirmed lobar transplantation as a valid tool to shorten the waiting list in the Lung Allocation Score era, in particular for recipient with small chest cavities.

Translational Lung Biomarkers and molecular changes

OS072

BLOOD GENE EXPRESSION PREDICTS BRONCHIOLITIS OBLITERANS SYNDROME APPEARANCE AFTER LUNG TRANSPLANTATION

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Background: Bronchiolitis obliterans syndrome (BOS) is the main manifestation of chronic lung allograft dysfunction responsible for the poor long-term outcome after lung transplantation. While physiopathological mechanisms are poorly defined, identification of harbingers of BOS is therefore essential to prevent the progression of the disease before irreversible damages appear.
Methods/Materials: we performed gene expression analysis from peripheral whole blood of 80 lung transplanted recipients (LTR) using whole genome microarrays. Using an independent set of patients, including 13 LTR without and 11 with BOS 6 months before the clinical diagnosis, we identified differential genes between the two populations of patients that were validated by qPCR.
Results: Overall, 3 genes, POU Class 2 Associating Factor 1 (*POU2AF1*), T-cell leukemia/lymphoma protein 1A (*TCL1A*) and B-cell lymphocyte kinase (*BLK*), were identified as predictive biomarkers of BOS 6 months before the clinical diagnosis, with AUCs of 0.83, 0.77 and 0.78 respectively. These 3 genes allow stratifying upon CLAD risk (log-rank test $p < 0.01$) and are not associated with time post-transplantation.
Conclusion: These biomarkers could provide clinicians with new tools to adapt treatment and to improve long-term follow-up of LTR.

Basic Kidney Histocompatibility

OS073

VALIDATION OF A COMPUTATIONAL SCORING SYSTEM FOR PREDICTING HLA IMMUNOGENICITY BASED ON QUANTIFICATION OF SURFACE ELECTROSTATIC POTENTIAL DIFFERENCES BETWEEN DONOR AND RECIPIENT HLA MOLECULES

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Introduction: Building on our previous research in HLA immunogenicity, we have now created a novel computational algorithm to quantify structural and surface electrostatic potential differences between donor and recipient HLA and applied it to predict alloantibody responses in a unique patient cohort.
Methods: We examined 191 patients that underwent treatment for infertility with lymphocyte immunotherapy (LIT). Patients were injected intradermally with partner's lymphocytes, and serum samples collected prior to and after LIT to assess HLA-specific sensitisation (Luminex). Following two field HLA typing, HLA structural modelling and calculation of HLA electrostatic potential, donor-recipient HLA comparisons were performed to determine the electrostatic mismatch score (EMS-3D) and assess its ability to predict donor-specific antibody (DSA) development and overall sensitisation to HLA post-LIT (cPRA).
Results: The EMS-3D of mismatched HLA ranged 0 to 0.488 (median: 0.268, IQR: 0.200–0.344). Increasing EMS-3D was strongly associated with higher risk of DSA development against HLA-A and -B (OR: 1.70 per 0.1 unit increase, 95% CI: 1.35–2.15, $p < 0.0001$) and against HLA-DR and -DQ (OR: 2.35 per 0.1 unit increase, 95% CI: 1.94–2.84, $p < 0.0001$). Notably, physicochemical differences between donor and recipient HLA-DQ were higher compared to other loci (EMS-3D median: 0.346, IQR: 0.200–0.421) and donor HLA-DQ with the highest EMS-3D (fourth quartile) were highly likely to induce a DSA response (OR: 30.8, 95% CI: 11.6–81.9, $p < 0.0001$). Finally, the overall physicochemical disparity between donor and recipient HLA types was an independent predictor of the risk of developing high sensitisation levels to HLA (cPRA≥85%, OR: 1.09 per 0.1 unit increase in EMS-3D, 95%CI: 1.01–1.17, $p = 0.02$).
Discussion: We developed and validated a novel HLA immunogenicity algorithm to enable better assessment of transplant immunological risk and help inform future deceased-donor kidney allocation policies.

Clinical Intestine Histocompatibility

OS074

THE IMPORTANCE OF DONOR-SPECIFIC ANTIBODIES MONITORING AND ANTI-MICA ANTIBODIES IN INTESTINAL TRANSPLANTATION

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Background: Intestinal transplantation (IT) is the most immunogenic among organ solid transplantation. Rejection episodes are currently treated with immunosuppressive therapy focused on cellular immune response. However, the presence of frequent rejection episodes refractory to this treatment, suggest that humoral mechanisms probably participate in rejection. Nowadays, donor-specific antibodies (DSA) monitoring is the only tool to diagnose antibody mediated rejection due to the lack of consensus in histological markers.
Methods: We analyzed the role of DSA and anti-MICA antibodies in graft rejection and survival of the unique Spanish IT cohorts: H. 12 de Octubre for adults ($n = 21$) and H. La Paz Infantil for children ($n = 56$).
Results:

- The presence of pre-transplant (preTx) DSA constitutes a risk factor in the adult cohort from the 3rd month post-transplant (posTx) ($p = 0.021$), being more significant at 1 year ($p = 0.0072$). In addition, the number of rejection episodes is higher in recipients with preTx DSA ($p = 0.04$).
- In both adult and children, posTx DSA associate with higher rejection rates and less graft survival (Figure 1A). We also observe that SFI of LSM (LABScreen Mixed) and MFI of Single-Antigen correlate with rejection grade.
- The rejection rate and graft survival of desensitized DSA+ recipients are similar to DSA- patients and significantly different from non-desensitized DSA+ recipients (Figure 1B).
- Liver-inclusive grafts show a protective role in the generation of *de novo* DSA ($p = 0.0004$), with less allograft rejection and higher survival.
- None of the recipients with anti-MICA antibodies suffered any rejection episode ($p = 0.0032$), which suggests a protective role in IT.

Conclusions: PreTx and posTx DSA play an important role in intestinal rejection and graft survival. Monitoring DSA is essential to prevent, identify and treat the humoral component of rejection. Desensitization protocols and liver-inclusive grafts should be considered in high risk recipients.

Translational Kidney Histocompatibility

OS075

PREDICTING KIDNEY ALLOGRAFT OUTCOME BY MEASURING DE NOVO DONOR SPECIFIC ANTIBODIES: BY CYTOTOXIC AND IGG FCXM ON REAL DONOR CELLS; C3D AND IGG-MFI BINDING ON SINGLE ANTIGEN

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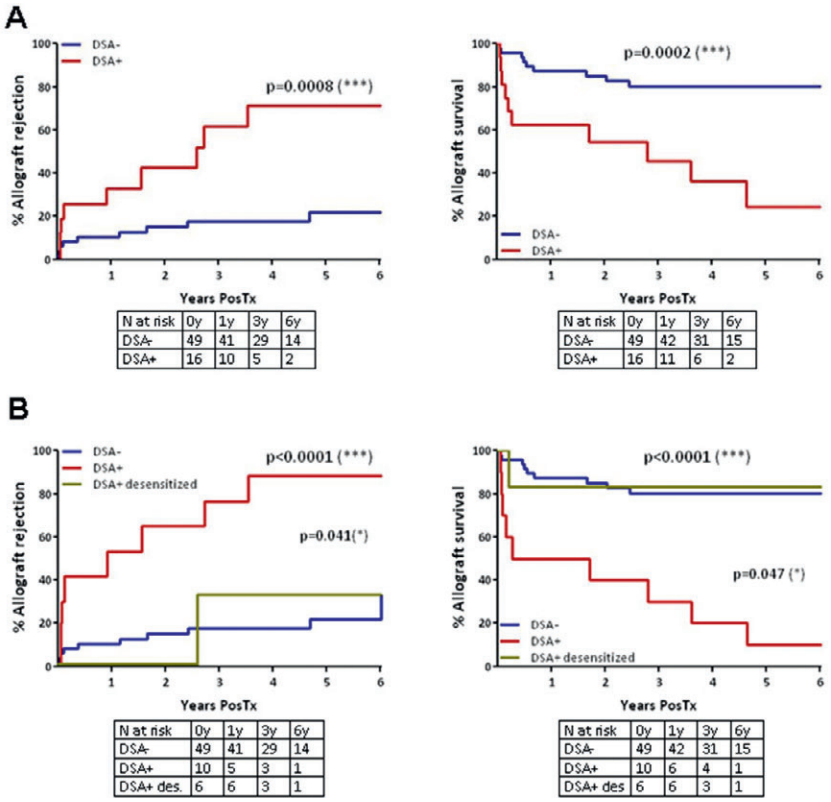
Background: The detection of de novo Donor Specific Antibodies (dnDSA) after kidney transplantation has been associated to worse graft outcome. However, not all patients with dnDSA lose their graft. Thus, a better understanding of the biological properties of dnDSA is highly needed to refine current risk stratification.



Methods: 409 consecutive kidney transplant patients transplanted between 2010 and 2013 were screened for the presence of IgG-dnDSA using Single Antigen Bead assays. The capacity of those antibodies to fix C3d and to be cytotoxic on real donor cells frozen in liquid nitrogen was analyzed.
Results: 32/409 (7.8%) of patients developed dnDSA, being 25/32 (78%) C3d positive. 80% of *p* Patients with C3d positive dnDSA developed subsequent rejection in 80% of cases, while only 29% of patients with non-complement fixing antibodies rejected their graft ($p = 0.019$). Patients with C3d positive dnDSA showed significantly lower free rejection time free and a poorer allograft survival than those with non-complement-fixing dnDSA ($p < 0.001$). of note, mean fluorescence intensity (MFI) of 7500 discriminated those dnDSA with C3d binding capacity with high accuracy (AUC 0.952). Patients with dnDSA having both C3d-binding capacity and cFCXM positive tend to lose the graft first at earlier time.
Conclusion: An approach based on MFI, C3d fixation and real cytotoxic capacity of post-transplant sera can better predict the outcome of kidney graft, and guide treatment strategies.
Funding: European Union's Seventh Framework Program [FP7/2007-2013] grant agreement HEALTH-F4-2012-305385.

Clinical Kidney Histocompatibility

OS076

BROAD ANTIGEN MISMATCHES AND EPITOPE MISMATCHES IN THE PRACTICE OF ONE TRANSPLANTOLOGY CENTRE

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Selection using epitope mismatches (EpMM) has good potential in recipients with pre-existing antibodies, and also in kidney allocation in network of transplant centres with a large common waiting list. Is the use of EpMM advantageous compared to the use of broad antigen mismatches in a single transplant centre?

We have analysed the link between the risk of losing a transplant and EpMM and broad antigen mismatches. The results of 347 recipients who had a first cadaveric kidney transplant were analysed. The recipients did not have any pre-existing antibodies. HLA-genotyping of recipients was performed using the sequence specific primers method.

The five-year survival rate decreased as the number of broad antigen mismatches increased (log rank $p < 0.001$). Univariate analysis showed a higher number of HLA-A, -B и -DR mismatches to be associated with an increased risk of transplant loss ($p = 0.015$; $p = 0.001$; $p < 0.0001$). However, multivariate adjusted Cox proportional hazard regression showed HLA-B and -DR mismatches ($p = 0.001$; $p < 0.0001$) to be associated with higher risk, but not the HLA-A ($p = 0.146$). There was a linear relationship between the number of broad antigen mismatches and the risk of transplant loss. Increased EpMM were exponentially, not linearly related to the risk of transplant loss. Nevertheless, the number of EpMM remains a risk factor, even when adjusted for the number of broad antigen mismatches in the multivariate analysis ($p < 0.001$).

EpMM allow for more accurate prediction of the risk of transplant loss: the area under the ROC curve was 0.812 [0.766; 0.858] vs. 0.649 [0.59; 0.707] in broad antigen mismatches. This approach allows to identify patients at high risk of transplant loss (over 20 EpMM) amongst patients, who were previously considered to have low immunological risk (i.e. 1–2 broad mismatches).

Basic Others Histocompatibility

OS077

HLA EPITOPE FREQUENCY ON SINGLE ANTIGEN BEAD TESTING PANELS VARIES SIGNIFICANTLY - HLA EPITOPES SHOULD BE CONSIDERED WHEN ASSESSING MFI

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Introduction: Single-antigen bead (SAB) assays are frequently used to characterise HLA antibody levels in terms of Median Fluorescence Intensity (MFI), despite the test being semi-quantitative and poor correlation between crossmatch results and MFI. MFI values are influenced by HLA density on beads, denatured antigen and blocking of secondary detection antibodies. We have investigated the influence of epitope frequency within the SAB testing panels on MFI values of reactive serum.
Method: A characterisation of the frequency of HLA epitope registry defined HLA class I epitopes on two commercially available SAB assays was performed. HLAMatchaker and 3D models generated within Swissmodeller and viewed in Swissviewer were used to identify epitopes within HLA class I reactive sera, this data was used to determine an epitope corrected MFI in reactive serum.
Results: The number of times an epitope is represented varies from 1–88 and 0–87 for kit 1 and kit 2 respectively. The number of times an epitope is present only once is 52 times on kit 1 and 39 on kit 2. The mean class I epitope number is 9.04 for kit 1 and 9.0 for kit 2. The mean epitope number for HLA-A is 9.8 (kit 1) and 9.3 (kit 2), for HLA-B 11.2 and 11.0 and HLA-C 6.0 and 6.7. Assessing reactive sera enabled MFI values to be derived from all beads containing the

epitope, providing an epitope corrected MFI (eMFI) value. For example, epitope correction of a serum reacting with the 62GE epitope demonstrated an eMFI of 60 000 in comparison to an MFI of ~7000 when donor specific antigen alone was used.
Conclusion: The frequency of HLA class I epitope representation differs between and within the SAB panels. Consideration of the frequency of epitopes is important when assigning MFI values as antibody reactivity will be spread across all HLA antigens expressing the reactive epitope. In cases where epitope reactivity is clearly defined knowledge of epitope frequency in SAB kits may help

Translational Kidney Histocompatibility

OS078 NOVEL ENDOTHELIAL CELL BASED ASSAY TO STUDY COMPLEMENT DEPENDENT CYTOTOXICITY

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Introduction: Donor specific anti-HLA antibodies (DSA), blood group antibodies and anti-endothelial cell antibodies (AECA) can mediate antibody-mediated rejection (ABMR). Complement involvement is indicated by complement activation products such as C4d along the endothelium of the microvasculature in the rejected kidneys. However, endothelial cytotoxicity of the various antibodies and the role of complement (regulation) is not entirely clear yet.
Methods: Next to the diagnostic complement dependent cytotoxicity (CDC) test on donor lymphocytes (L-CDC) and the luminex immunoassay we developed an endothelial CDC (EC-CDC) using primary endothelial cells (EC) cultured from donor kidney perfusate after machine perfusion, circulating human EC progenitors or conditionally immortalized human glomerular EC. Antibody binding and complement activation was evaluated by FACS analysis for immunoglobulins, activated C3 and neoantigen C9.
Results: ABO incompatible serum caused complement mediated cell cytotoxicity in the EC-CDC comparable to the L-CDC. In contrast, L-CDC negative sera containing DSA against HLA I and II as shown by the luminex immunoassay, show complement dependent cytotoxicity in the EC-CDC. Incubation with serum suspected of containing AECA show abundant cell death in the EC-CDC whereas no cytotoxicity was seen in the L-CDC. More cell death was seen in the primary EC and EC progenitors compared to the immortalized EC-line. FACS analysis with primary EC showed strong IgG binding after incubation with serum containing DSA and showed activation of C3 without C9 neoantigen deposition.
Conclusions: We were able to successfully perform endothelial based CDCs and thereby show antibody mediated complement dependent cytotoxicity, also using sera containing DSA that do not show cytotoxicity in an L-CDC. Furthermore, we show that AECA are cytotoxic for EC in a complement dependent manner, confirming the pathogenicity of such antibodies.

Clinical Lung Histocompatibility

OS079 PERSISTENT DE NOVO DONOR-SPECIFIC ANTIBODIES ARE ASSOCIATED WITH DECREASED SURVIVAL IN LUNG TRANSPLANT RECIPIENTS

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Background: The impact of de novo donor-specific (DSA) and non-donor-specific (nDSA) anti-HLA-antibodies diagnosed by solid-phase assays on outcome in lung transplant patients is still a matter of debate. We hypothesize that differentiating DSA by persistent and transient appearance may offer a better risk assessment.
Patients and Methods: We investigated the clinical relevance of HLA-antibodies on lung allograft outcome prospectively in 72 recipients who were transplanted between 2013 and 2015. The presence of HLA-antibodies was analyzed by Luminex Single Antigen Bead assay regular prior and after (3 weeks, 3 months, 6 months, 9 months, 12 months and 18 months) transplantation and on demand in case of graft dysfunction. Lung function, patient survival and risk factors for the development of donor specific antibodies (DSA) were assessed within a median follow-up of 21 months.
Results: Time to first DSA appearance was earlier in case of transient DSA compared to persistent DSA (51.9 $\pm$ 62.1 vs. 177.3 $\pm$ 156.2 days, $p = 0.035$). In 13 out of 23 (56%) patients DSA disappeared after a median of 114 days. Forty-four % (10/23) of patients had persistent DSA post-transplant. Risk factors for DSA development seem to be the concurrent existence of non-donor specific antibodies ($p < 0.001$) and change in the immunosuppressive regime from Tacrolimus to Cyclosporine A in the first 3 months after transplantation ($p = 0.03$). The majority of DSA were HLA-antibodies class II (91%), 90% of them were anti-DQ antibodies (19/21). DSA impaired patient survival in comparison to controls (1-year patient survival 83% vs. 97%; $p = 0.078$). Remarkably 1-year survival of patients with persistent antibodies was only 60%. Patients with persistent DSA had significantly reduced overall survival compared with those without DSA and with transient DSA ($p < 0.001$).
Conclusion: Persistence of de novo DSA in the first year after lung transplantation is associated with reduced patient survival.

Clinical Kidney Histocompatibility

OS080 VALUE OF DONOR-SPECIFIC ANTIBODIES CHARACTERISTICS AT TIME OF KIDNEY ALLOGRAFT BIOPSY

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Background: Donor-specific antibodies (DSA) detected by single antigen flow beads (SAFB) are imperfectly associated with antibody-mediated rejection (AMR) and kidney allograft survival. Several SAFB adaptations were proposed in order to improve clinical outcomes prediction: serum ethylenediamine tetraacetic acid (EDTA) treatment, C1q and C3d binding assays, or DSA intra-graft detection (gDSA assay).
Methods: Seventy-seven kidney transplant recipients with an allograft biopsy for cause and serum DSA were included. Serum IgG DSA mean fluorescence intensity (MFI) with or without EDTA treatment, DSA ability to bind C1q or C3d, and DSA intra-graft detection were correlated with AMR and kidney allograft survival.
Results: The median time between transplantation and biopsy was 25 months (range: 0.5–251), and the median follow-up was 24 months (range 0–125). Forty percent of biopsy specimens were in favor of AMR. The sensitivity and specificity of the C1q, C3d and gDSA assays for predicting AMR were 68%/61%, 52%/70% and 65%/57%, respectively. Serum MFI, whether EDTA-treatment was performed or not, did not allow AMR prediction using a ROC approach. In univariate analysis, DSA MFI over 2500 without serum treatment, over 3800 with EDTA-treatment, DSA C3d positivity and intra-graft detection were associated with death-censored graft survival (DCGS), whereas DSA C1q positivity was not. Using multivariate models, the independent factors associated with DCGS were estimated glomerular filtration rate, interstitial fibrosis and tubular atrophy score, and C4d positivity on the biopsy.
Conclusion: At the time of an allograft biopsy for cause, estimated glomerular filtration rate and histopathologic criteria are the best prognosis factors for subsequent kidney allograft loss. Our findings weaken the rationale for implementing any of the C1q, C3d or gDSA assays at the time of the biopsy because they do not seem capable of predicting AMR or graft loss.

Basic Kidney Histocompatibility

OS081 A NEW TOOL FOR QUANTIFICATION OF THE DONOR HLA-SPECIFIC MEMORY B CELL REPERTOIRE IN IMMUNIZED PATIENTS

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Background: Pre-existing or *de novo* donor-specific HLA antibodies (DSA) represent an important risk factor affecting transplant outcome. Patients with a history of immunization but lacking serum DSA may harbor dormant memory B cells which can rapidly produce DSA upon re-encounter with the same HLA. Current methods to detect memory B cells mainly utilize synthetic monomeric/tetrameric HLA molecules which generally do not represent the complete HLA repertoire of an individual. Here, we present a donor-specific HLA-ELISPOT assay enabling the screening for HLA-specific memory B cells in peripheral blood of immunized individuals using cell lysates as a natural source of both HLA class I and II.
Methods: Peripheral blood mononuclear cells or splenocytes were treated with non-ionic detergents to obtain HLA-containing lysates. Human B cell hybridomas producing specific HLA antibodies were tested against these lysates for validation purposes. Next, polyclonally activated peripheral blood B cells from women ($n = 22$) with a history of pregnancy were tested for the presence of HLA-specific memory B cells against paternal cell lysates as the source of HLA. Autologous lysates served as negative controls.
Results: For all hybridomas tested, we detected spot formation against the lysates containing the corresponding HLA specificities whereas no spots were

observed against lysates with irrelevant HLA, indicating the specificity of the assay. In women with a history of pregnancy, we found a median frequency of 31 (range: 0–802) HLA class I and 89 (range: 0–1050) HLA class II specific memory B cells per million IgG producing cells directed at paternal HLA.
Conclusion: This novel lysate-based ELISPOT assay allows for the first time to quantify all donor HLA class I and II-specific memory B cells and may predict anamnestic responses in transplant recipients with a history of immunization by serving as a memory B cell cross-match assay.

Clinical Kidney Histocompatibility

OS082

SHARED EPITOPES CONTRIBUTE TO ACCUMULATION OF HIGHLY SENSITIZED PATIENTS IN KIDNEY PAIRED DONATION PROGRAM

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Introduction: Our Kidney Paired Donation (KPD) program (called the Alliance for Paired Donation; APD) arranges exchanges among patients with incompatible live donors. We evaluated the sensitization of APD patients. Methods/Results: Since 2010, the APD registered 1122 patients and arranged 418 transplants (Tx). APD patients had 40% highly sensitized (HS; cPRA of 80%–100%) and 30% very highly sensitized (VHS; cPRA of 95%–100%) patients. Since Tx patients had only 22% HS with half of them VHS, there was an accumulation of HS/VHS patients. We examined the HLA sensitization pattern: >85% HS had IgG to HLA-A; >90% to -B, 60% to -C; 82% to -DR; 85% to -DQB, 49% to -DPB, and 30% to -DQA. Sensitization was lower in HS Tx patients (Fig. 1A): the median cPRA was reduced for each HLA locus in HS Tx patients compared to the waiting HS patients (all $p < 0.05$; Fig. 1B). The IgG levels to cross-reactive antigen groups (CREGs) were very similar in HS against most and less frequent HLAs within the same CREG family. Indeed, as shown in Fig. 1B, CREG-A1C had similar IgG levels to very frequent HLA-A1 (23.5% of population) and to low frequent A36 (1% of population) or A80 (0.3% of population). Identical patterns were observed for class I CREGS (CREG2, CREG5, CREG7, CREG8 and CREGCw4) and class II cross-reactive HLAs (DR and DQB). Shared epitopes in CREG-A1C included 44KM3, 76ANT, 144KR, 166DG, 17RS and 63EN (Fig. 1B). Similar analyses confirmed sets of shared epitopes for all class I CREGs and cross-reactive class II groups. Conclusions: 1) APD accumulates HS/VHS patients; 2) cross-reactivities within CREG groups for class I and cross-reactive HLAs for class II contribute to sensitization in HS/VHS patients; and 3) shared epitopes among HLAs are involved in the mechanism of sensitization.

Clinical Pancreas/Islet Histocompatibility

OS083

EARLY FORMATION OF DE NOVO DONOR SPECIFIC ALLOANTIBODIES FOLLOWING KIDNEY AND COMBINED KIDNEY PANCREAS TRANSPLANTATION

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Background: The development of de novo donor-specific antibodies (dnDSA) in solid organ transplantation has been shown to have a negative impact on allograft survival. We compared rates of dnDSA formation in a single-centre population of kidney and simultaneous pancreas-kidney (SPK) recipients.
Methods/Materials: Data was collected retrospectively on all kidney and SPK recipients transplanted between May 2015 and August 2016 with routine HLA antibody testing using Luminex solid phase assay performed within six months following transplant. SPK recipients were maintained steroid-free postoperatively with Alemtuzumab induction, whereas kidney only patients routinely received Basiliximab induction and maintenance triple therapy. For the purposes of this study, patients were only considered positive for dnDSA if antibodies developed within six months of transplantation (MFI > 1000) with no evidence of DSA prior to surgery.
Results: of the 178 kidney and 24 SPK recipients included, four kidney patients and six SPK recipients developed dnDSA during the study period (2% vs. 25%, $p < 0.001$). No significant association was found between the development of dnDSA and exposure to sensitising events ($p = 0.282$), pre-existing non-donor specific anti-HLA antibody ($p = 0.900$), total number of HLA mismatches ($p = 0.518$) or level of HLA mismatch ($p = 0.816$). De novo DSA appeared within three months of transplantation in all but one patient.
Conclusion: De novo DSA formation occurs more frequently following SPK rather than kidney only transplantation, most likely reflecting the difference in immunosuppression regimes used.

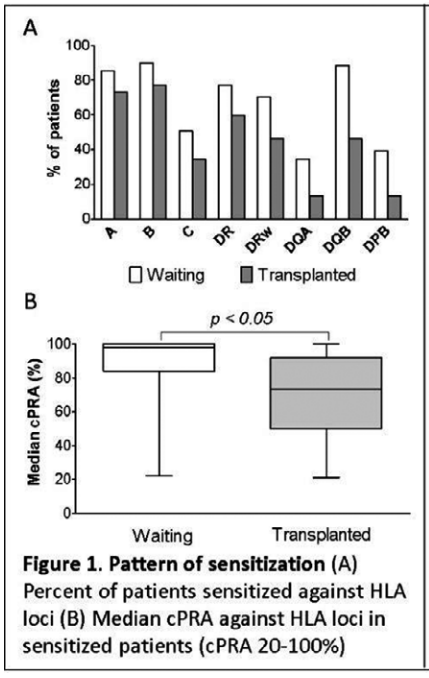

Figure 1. Pattern of sensitization (A) Percent of patients sensitized against HLA loci (B) Median cPRA against HLA loci in sensitized patients (cPRA 20-100%)

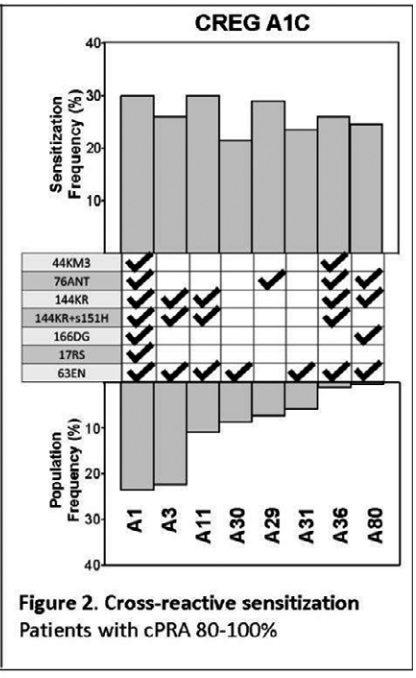

Figure 2. Cross-reactive sensitization Patients with cPRA 80-100%

Clinical Kidney Histocompatibility

OS084

DONOR RECIPIENT MATCHING BASED ON HLA EPITOPES IMPROVES OUTCOME IN KIDNEY TRANSPLANT RECIPIENTS

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Background: HLA mismatches of the donor and recipient causing *de novo* donor-specific HLA antibodies (dnDSA) are a risk factor for immunologic complications and poor graft survival. Evaluating histocompatibility based on HLA epitopes may improve outcomes after kidney transplantation and better prevent sensitization than classical matching of HLA class I and II antigens. To date there is very few data examining clinical outcomes based on HLA epitope matching.
Methods: 2787 consecutive adult kidney transplants performed 1995–2015 without preformed DSA have been included. *De novo* DSA were detected by Luminex single antigen assay. HLAMatchmaker score was calculated as the weighted sum of eplets of high resolution patient and donor typing.
Results: The distribution of the HLA epitope mismatch (assessed by the HLAMatchmaker algorithm) and the correlation to the count of mismatched A, B,C,DR,DQ-HLA molecules is shown in Fig. 1a and Fig. 1b. Categorization by HLAMatchmaker epitopes significantly predicted the incidence of dnDSA (Fig. 1c) and allograft survival (Fig. 1d). In a multivariate Cox regression analysis adjusted for the number of antigen mismatches the HLAMatchmaker score could be identified as an independent risk factor for dnDSA (HR per 10 increment 1.269 ($p < 0.0001$) adjusted for A,B,DR-antigen mismatches; HR 1.270 ($p < 0.0001$) per 10 increment adjusted for A,B,C,DR,DQ-antigen mismatches).
Conclusion: HLAMatchmaker epitopes have a strong predictive value for dnDSA independently from the antigen mismatch. Allocation strategies based on HLA epitopes may result in improved donor recipient matching with a smaller amount of immunogenicity leading to less dnDSA and thus improve long-term kidney allograft survival.

Clinical Kidney Infection

OS085

BOOSTING THE VZV-SPECIFIC MEMORY T AND B CELL RESPONSE PREVENTS THE HIGH INCIDENCE OF HERPES ZOSTER AFTER TRANSPLANTATION

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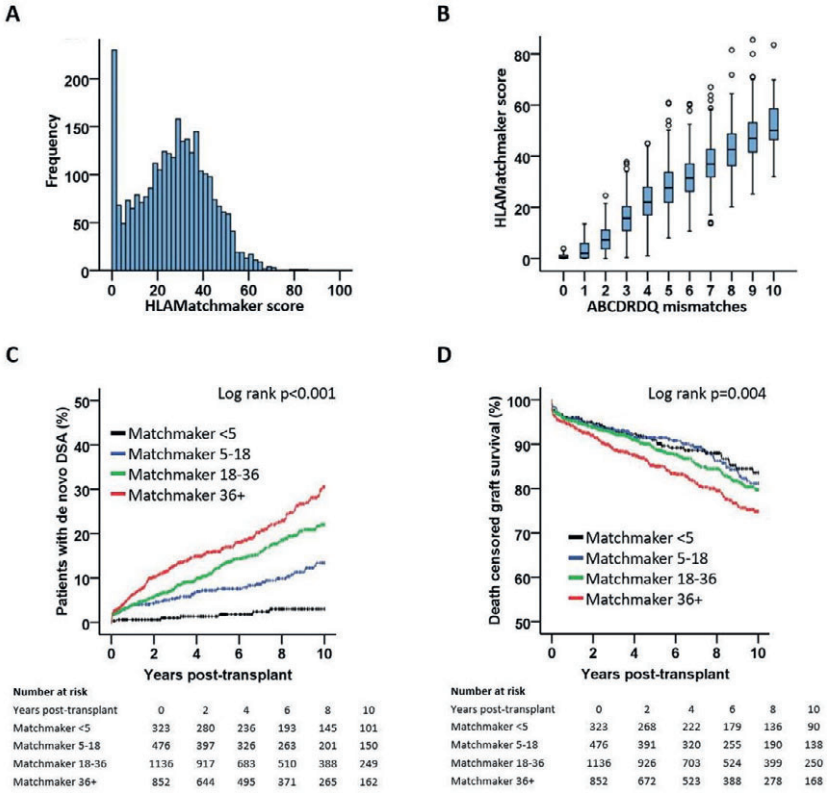
Background: Transplant patients are at high risk to develop herpes zoster (HZ) and severe complications. Reactivation of varicella zoster virus (VZV) could be prevented by booster vaccination. However, end stage renal disease (ESRD) patients are known to respond significantly poorer to vaccinations against hepatitis B and influenza, than healthy individuals. First, we investigated the incidence of HZ after transplantation. Second, we studied the effect of VZV booster vaccine on B and T cell memory responses in patients with ESRD and healthy controls.
Methods: The medical records after first kidney (KTx: $n = 420$), liver (LTx: $n = 224$), heart (HTx: $n = 195$) and lung (LuTx: $n = 119$) transplantation were analyzed for HZ. The VZV-specific T and B cell responses before and 1 year after Zostavax® vaccination were analysed in 19 patients, aged ≥50 years, awaiting renal transplantation, by flow cytometry and Elispot. Twenty gender and aged-matched living donors served as controls.
Results: The overall incidence rate of HZ post-KTx (14.4 cases/1000 PY), LTx (24.5 cases/1000 PY), HTx (30.8 cases/1000 PY) and LuTx (38.2 cases/1000 PY) was significantly higher than in the general population of 50–70 years of age (7–8 cases/1000 PY). One year after vaccination, the percentage of CD4 central memory had increased in both patients ($p = 0.004$) and donors ($p = 0.004$) and the CD4 effector memory were increased in donors ($p = 0.009$) compared to before vaccination, while the VZV-specific IgG producing cells only increased in the first 3 months after vaccination in patients ($p = 0.007$) and donors ($p = 0.0001$) and remained stable thereafter.
Conclusion: HZ is a frequent complication after transplantation. VZV booster vaccination equally increases VZV-specific IgG titers and VZV-specific T-cell and B-cell memory for at least 1 year after vaccination in ESRD patients compared to healthy individuals. Prophylactic VZV vaccination before transplantation could reduce HZ incidence and severity after transplantation.

Figure 1



Translational Liver Infection

OS086

BACTERIAL TRANSLOCATION IN RECIPIENTS IS ASSOCIATED WITH BILIARY COMPLICATIONS AFTER LIVER TRANSPLANTATION

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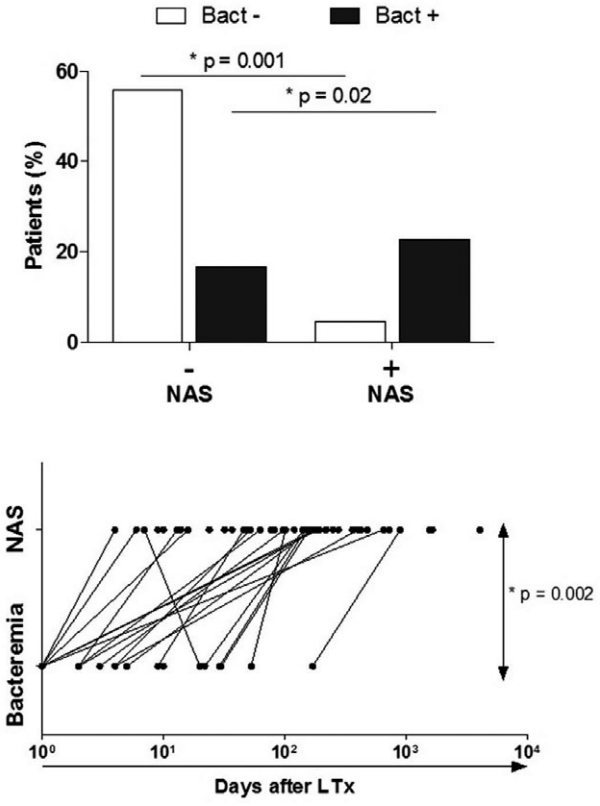
Introduction: The intestinal microbiome and the translocation of intestinal bacteria to the portal circulation are more and more recognized as important pathogenic factors in liver diseases pre-transplantation. The role of microbial translocation on liver transplantation outcomes however, including biliary complications, has not yet been established. Therefore, the aim of this study is to investigate the incidence of bacteremia after liver transplantation and explore a link with biliary complications.
Methods: From 1989 – 2010 all liver transplants were analyzed retrospectively for donor and recipient characteristics and positive bacterial cultures in serum. Patients with non-anastomotic strictures (NAS) were compared to patients with anastomotic strictures (AS) or patients without NAS or AC.
Results: of 600 patients, 123 had positive blood cultures (29%). NAS was diagnosed in 67 patients of which 49 patients (73%) had positive cultures. In the non-NAS group patients, only 43 had positive cultures (11%, *Figure 1*). Multivariate analysis showed bacteremia, high donor age and longer warm ischemia times as independent risk factors for NAS (*Table 1*). Most patients had bacteremia prior to the diagnosis of NAS (*Figure 2*). AS was not associated with bacteremia after transplantation or before diagnosis, suggesting a different etiology.
Conclusion: Bacterial translocation occurs in approximate 30% of recipients after liver transplantation and is associated with an increased risk of non-anastomotic biliary complications. Most patients have a bacteremia preceding the diagnosis of NAS. Further studies of 16S bacterial DNA in serum samples is ongoing.

	Univariate	Multivariate	HR
Bacteremia	0.001	0.01	2095
Donor Age	0.002	0.01	1.017
WIT	0.007	0.05	1.022



Clinical Kidney Infection

OS087

EFFICACY OF INTRAVENOUS IMMUNOGLOBULIN IN THE TREATMENT OF BK VIRUS ASSOCIATED NEPHROPATHY IN RENAL TRANSPLANT RECIPIENTS

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Background: BK virus infection can cause significant nephropathy in renal transplant recipients leading to allograft dysfunction and loss. There is no standard treatment other than reduction of immunosuppression (IS). Different adjuvant treatment like leflunomide, cidofovir, Intravenous immunoglobulin (IVIG), fluoroquinolones have been attempted with mixed outcome.
Methods: A single-centre retrospective study was performed on all cases diagnosed with BK-virus associated nephropathy (BKVAN) from 2005 to 2015 for evaluation of the impact of reduction of immunosuppression alone vs. patients who received IVIG in addition to the reduction of Immunosuppression.
Results: Of 1708 kidney transplants, 37 (2.1%) cases of BKVAN were diagnosed at a mean of 23.37 months after transplant, mostly on indication biopsy. 10 patients (27%) were managed with immunosuppression (IS)-reduction alone (IS-r group) and 26 patients (70.3%) received IVIG (1–2 gm/kg) in addition to IS reduction (IVIG group). One received leflunomide and hence excluded. Both groups were comparable in terms of type of induction and maintenance IS therapy, mean serum creatinine and quantitative BKV DNA (copies/ml) at the time of diagnosis of BKVAN, and proportion of IS reduction after the diagnosis of BKVAN. The actuarial patient survival after mean of five years follow up in IVIG and IS-r alone group was 100% and 90% ($p = 0.085$), and graft survival was 96.15% and 62.5% ($p = 0.01$). Mean time for plasma BKV DNA to fall below 5000 copies/ml in IVIG group was 5.86 months compared to 15.6 months in IS-r group.
Conclusion: Intravenous immunoglobulin treatment in addition to usual reduction in immunosuppression resulted in significantly better graft survival and early resolution of BK viremia. We strongly recommend IVIG adjuvant treatment in patients with BKVAN.

Clinical Liver Infection

OS088

PRE-TRANSPLANT SERUM PROCALCITONIN LEVEL FOR PREDICTION OF EARLY POST-TRANSPLANT SEPSIS IN LIVING DONOR LIVER TRANSPLANTATION

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Introduction: Sepsis is a frequent cause of in-hospital mortality after liver transplantation (LT). Therefore, elimination of possible risks in the pre-transplant period, early diagnosis of post-transplant sepsis, and prompt administration of antimicrobial agents are important. The objectives of this study were to analyze the impact of early post-transplant sepsis on outcomes and to clarify the value of predictive factors for early post-transplant sepsis.
Methods: The study included 136 patients who underwent initial living donor LT (LDLT) at our institute from April 2009 to December 2016. Sepsis was defined using the third international consensus criteria. The results of biochemical tests at the introduction of anesthesia before LDLT were collected for pre-transplant evaluation.
Results: Post-transplant sepsis was found in 50 patients (36.8%), and these patients had a higher MELD score (19 [7–47] vs. 15 [7–39]; $p = 0.01$) and greater blood loss (7.3 [1.9–52.0] vs. 5.1 [0.5–37.0] l; $p = 0.02$) compared to those without sepsis. More patients had a pre-transplant serum procalcitonin (PCT) level >0.5 ng/ml in the sepsis group than in the non-sepsis group (14 [28.0%] vs. 6 [7.0%]; $p = 0.001$). The 1-, 3- and 5-year survival rates in the sepsis group were significantly lower than those in the non-sepsis group (59.4% vs. 89.0%, 54.0% vs. 85.9%, 49.5% vs. 75.9%; all $p < 0.001$). Multivariate analysis identified pre-transplant serum PCT >0.5 ng/ml (odds ratio 4.0, 95% confidence interval 1.3–12.5; $p = 0.02$) as the only independent risk factor for post-transplant sepsis.
Conclusions: Survival of patients with early post-transplant sepsis was poor and the incidence of sepsis was associated with the pre-transplant serum PCT level. Re-evaluation of the general condition and rescheduling of LT should be considered in a patient with pre-transplant serum PCT >0.5 ng/ml, regardless of systemic symptoms.

OS090 POOR OUTCOME OF POLYOMAVIRUS -ASSOCIATED NEPHROPATHY WITH GLOMERULAR PARIETAL EPITHELIAL CELLS INFECTED BY POLYOMAVIRUS

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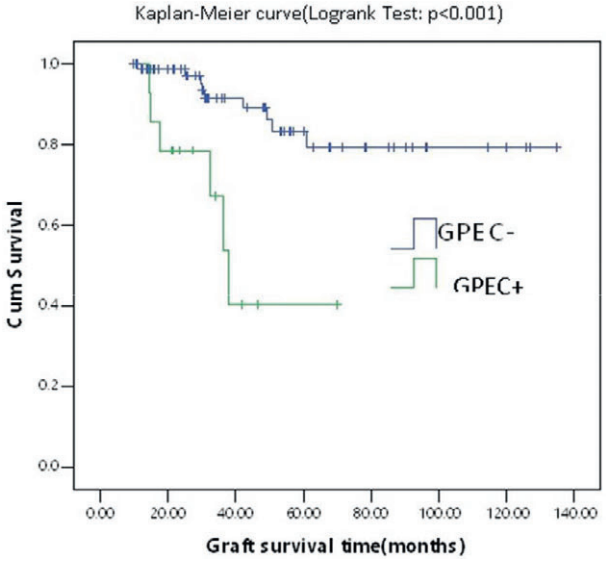
Background: Bowman's capsular epithelium infected by polyomavirus(Py) in polyomavirus -associated nephropathy (PyVAN) is infrequent and considered as the advanced stage of the disease. The aim of this study is to identify the characteristics and outcomes of this subset of patients with PyVAN.
Methods: Between 2007 and 2016, we diagnosed PyVAN in 103 patients. Immunohistochemistry ever showed infection of Bowman's capsular epithelium in 15 (14.6%) patients. Clinical parameters at diagnosis, and long-term graft survival rates were compared between glomerular parietal epithelial cells infected by Py (GPEC+) and GPEC- groups.
Results: There were no difference between the two groups in gender, donor source, immunosuppressive regimen, the mean level of serum creatinine at diagnosis and the rate of acute rejection and delayed graft function, etc. The median viral load in urine and plasma at diagnosis were higher in GPEC+ group than those in GPEC- group but without statistical significance. Patients in GPEC+ group were characterized by the higher mean scores of viral cytopathic changes (cy) and interstitial inflammation (i). After 28.6 ± 30.2 months follow-up, frequencies of graft loss was higher in GPEC+ group, which showed worse graft survival rates ($p < 0.05$) [Table 1].

	GPEC+ ($n = 15$)	GPEC- ($n = 88$)	p
Scr at diagnosis (μmol/l)	217.4	189.1	0.184
BK viruria	1.94 × 10e9	9.72 × 10e8	0.361
BK viremia	6.04 × 10e4	2.07 × 10e4	0.080
Graft loss at the latest follow-up[*n* (%)]	46.2(0)	9(11.0)	0.002
Scr at the latest follow-up (μmol/l)	187.5	185.1	0.933

The 1, 3, 5 year graft survival rates in GPEC+ group were only 92.9%, 53.9% and 40.4%, respectively [Figure 1]

Conclusions: PyVAN with GPEC infected by Py is characterized by extensive viral cytopathic effect and interstitial inflammation in graft biopsy. Although this subset of PyVAN is uncommon, it means the advanced stage of the disease with poor outcome.



OS091 IMPACT OF URINARY TRACT INFECTIONS IN KIDNEY TRANSPLANT RECIPIENTS DURING THE FIRST YEAR ON LONG-TERM GRAFT FUNCTION

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Background: Urinary tract infections (UTIs) are very common in patients with kidney transplantation and can be associated with significant morbidity. However, the impact of UTI on graft survival is still debated.
Patients and Methods: We analyzed a cohort of 380 patients who received a kidney transplantation at our Center from January 2008 to September 2015. UTI was defined by the evidence of a urine culture with more than 10^5 colony-forming units (CFU) per mL or more than 10^3 CFU/mL with urinary infection symptoms. UTIs in the first post-transplant year were classified into three groups: early (<3 episodes in the first six months), late (<3 episodes between the 7th and 12th month) and recurrent (>3 episodes throughout the whole first year). The primary outcome was graft function over a maximum follow-up of three years.
Results: UTIs occurred in 184 (48.4%) kidney transplant recipients during the first year. 83 patients developed early UTIs (21.8%), 50 (13.2%) late UTIs and 51 (13.4%) recurrent UTIs. Graft function significantly improved in patients with early and late UTIs over three years compared to the Nadir values, but not in patients with recurrent UTIs ($p < 0.001$) (Figure 1)

Kaplan-Meier analysis showed that recipients with recurrent UTI had the worst graft outcome during the follow up period (endpoint: eGFR < 60 ml/min/1.73 m²) ($p = 0.02$) (Figure 2).

Cox regression analysis showed that recurrent UTIs were an independent predictor of graft function at 3 years post-transplantation (hazard ratio, 1.519; 95% CI, 1.033 to 2.232; $p = 0.03$) in a model adjusted for gender, age, BMI, DGF, acute rejection and CMV infections.
Conclusion: Recurrent UTIs during the first year after kidney transplantation were strongly associated with worse long-term graft function and these high-risk patients require close monitoring for an appropriate prevention and treatment.

Clinical Others Infection

OS092 ACCIDENTAL TRANSMISSION OF HEPATITIS C (HCV) VIRUS FROM AN ORGAN DONOR TO FIVE TRANSPLANT RECIPIENTS: EARLY TREATMENT WITH DIRECT ACTING ANTIVIRALS SUCCESSFULLY PREVENTS CHRONIC HCV INFECTION

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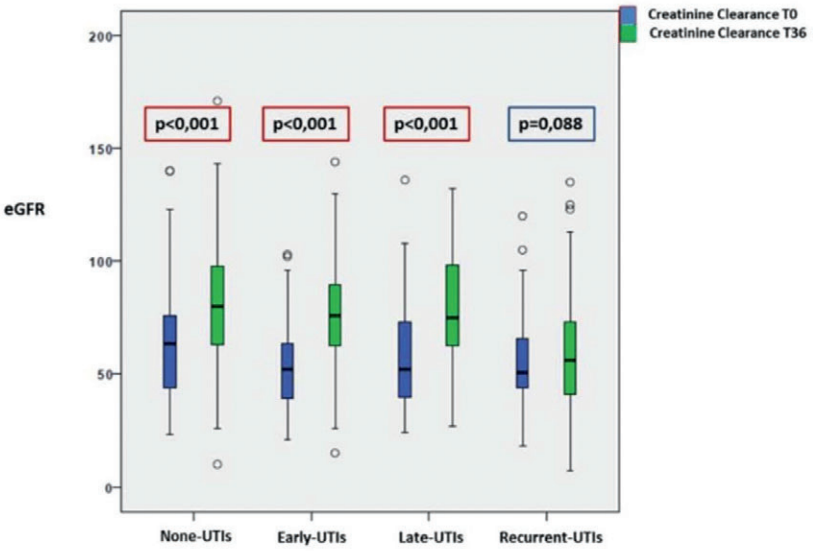
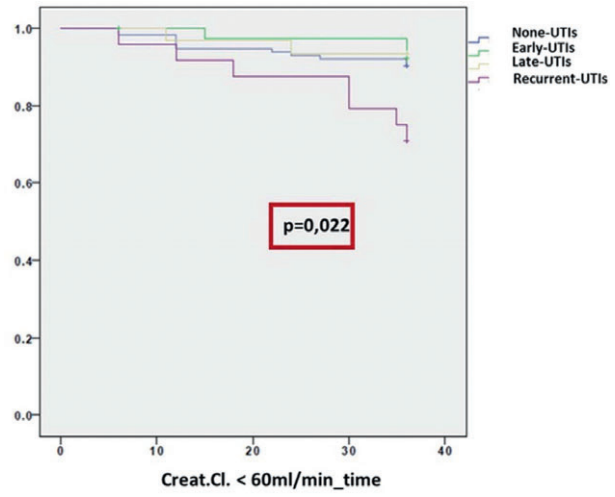
Background: Limited data exist analyzing transmission rates of Hepatitis C virus (HCV) and time course of HCV infection after solid organ transplantation. No data exist on the efficacy and outcome of an early-initiated treatment course with new direct acting antivirals (DAAs) directly after confirmed HCV transmission.
Methods: Clinical information of the HCV-positive organ donor and five recipients in five different transplant centers after accidental HCV transmission were collected. Sera from all recipients and the donor were tested for serologic and nucleic acid tests (NAT) of HCV infection before and 16 weeks post-transplant.
Results: The organ donor was a 55 years old woman who died due to subarachnoid hemorrhage. The donor did not belong to a HCV high-risk group. On day 4 of ICU stay donor received one unit of packed red blood cells. Routine serological testing for anti-HCV IgG at time of donation was negative. NAT for HCV was initially not performed. All 5 transplant recipients were tested negative for anti-HCV IgG and had negative HCV-NAT before transplantation. All patients had detectable quantitative (q) HCV-NAT early post-transplant (Table 1). Retrospective analysis revealed that the organ donor had low level HCV-RNA (genotype 1a) in the blood.

Characteristics of HCV kinetics and response to specific therapy are shown in the Table 1. In 4 patients, a 12 weeks course of different DAA regimens was initiated after a median of 9.5 days with early viral response (EVR) at treatment



. Kaplan-Meier analysis showed that recipients with recurrent UTI had the worst graft outcome during the follow up period (endpoint: eGFR < 60ml/min/1.73m²) (p=0.02)(Figure 2)



week 4. The liver recipient had multiple postoperative complications and died due to septic shock. All other recipients had good graft function 16 weeks post-transplant and achieved a sustained virological response 4 weeks after end of therapy (SVR4).

Discussion: HCV has a high transmission rate in solid organ transplantation with early active replication onset in the recipient. Early initiation of therapy with DAAs seems to effectively prevent chronic HCV infection.

Clinical Liver Infection

OS093

IMPACT OF DIRECT ACTING ANTIVIRAL AGENTS (DAAS) FOR HEPATITIS C VIRUS (HCV)-INDUCED LIVER DISEASES ON REGISTRATION AND OUTCOME ON WAITING LIST (WL) FOR LIVER TRANSPLANT (LT)

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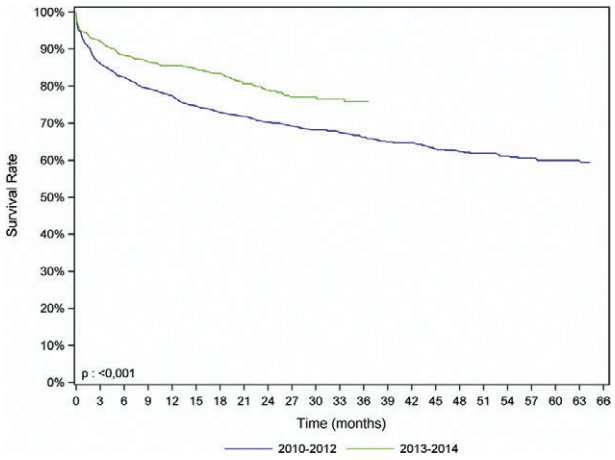
The 2th-generation of DAAs has provided major progress in the therapeutic management of patients with HCV in demonstrating improved sustained virological response. In France, since 2013, the availability and extent use of DAAs for cirrhotic patients lead to eradicate HCV and avoid liver decompensation. We would like to determine the impact of the 2th-generation of DAAs on registration and outcome on the WL for LT.

Patients and Methods: The study included all adult candidates registered on WL for HCV-induced liver diseases between 2000 and 2016 ($N = 5580$). We compared kinetics over time of transplant indications, outcome on WL and 1-year post-transplant survival.

Results: The number of candidates listed for HCV-induced liver diseases has increased of 104% from 2000 ($n = 194$) to 2013 ($n = 395$). We observed an inversion of the indications of transplant, HCC becoming predominant and representing 54% of HCV-candidates in 2016 vs. 30% in 2006. From now, decompensated HCV-cirrhosis represents 38% of candidates and listing for retransplantation decreased of 35% since 2013. We observed i) a significant decrease of WL mortality from 7.4% in 2013 to 3.3% in 2016 (+62%), ii) a decrease of 30% of delisting for worsening condition from 2014 to 2016, iii) an increase of 82% of delisting for improving condition between periods [2011–2013] and [2014 - 2016], iiii) sharp increase of inactive patients on WL from 23% in 2013 to 60% in 2016. From now, HCV -induced liver diseases

	qNAT positive (post-transplant)	Copies/ml	Start of therapy	Regimen of DAAs (12 weeks)	qNAT negative (days after start of treatment)	EVR4	SVR4
Right Kidney	day 3	522	day 4	SOF+DAC	3	Yes	Yes
Left Kidney	day 6	1.12 Mio	day 10	SOF+LDP+ Ribavirin	28	Yes	Yes
Liver	day 5	549.000	-	-	-	-	-
Lungs	day 2	5 Mio	day 10	SOF+LDP	25	Yes	Yes
Heart	day 6	2.2 Mio	day 9	SOF+LDP	7	Yes	Yes



represents no more than 16% of liver transplant between 2014 and 2016, compared to 20% in 2011 and the 1y-graft survival rate is significantly improved between before (2010–2012) and after (2013–2014) extent use of DAAs (Fig)

Our study indicates that patients have been benefiting from therapeutic access to DAAs. The decrease of transplant needs for HCV-induced liver candidates has contributed to the decrease of global waiting list mortality and removal for worsening conditions observed in France since 2 years.

Clinical Kidney Infection

OS094 REFUSAL TO ACCEPT INCREASED-INFECTIOUS RISK KIDNEY OFFERS ASSOCIATED WITH HIGHER MORTALITY

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Background: Infectious risk donors (IRD) are younger and healthier than most deceased donors, but IRD kidneys are discarded at higher rates despite potential benefit to transplant candidates. We aimed to characterize the survival benefit to candidates of accepting vs. declining a IRD of an IRD kidney.
Methods: Using 2010–2014 national registry data from the United States, we identified 107 658 adult kidney transplant candidates who were offered an IRD kidney that was eventually used for transplantation. We used Cox regression to compare mortality between those who accepted an IRD kidney (n = 5821) vs. those who declined (n = 101 837), matching on listing center and time on dialysis and adjusting for candidate characteristics.
Results: Candidates who accepted IRDs had spent more time on dialysis (3.2 vs. 1.9 y, $p < 0.001$) and were more likely to be white (41.6% vs. 39.3%, $p < 0.001$) than those who declined IRDs. of those who declined, 23.6% eventually received non-IRD kidneys and 4.1% received IRD kidneys after waiting an additional 10.9(4.0–21.8) and 11.2 (4.2–22.3) months, respectively. Accepted IRD kidneys had lower median KDPI (32.3 [17.5–52.0]) than non-IRD kidneys received later (51.8[29.7–71.4]) ($p < 0.001$). In the first 30 days, survival was 99.3% and 99.6% among those who accepted and declined IRDs, respectively ($p < 0.001$). Past the first month of perioperative risk, those who accepted IRDs were at 79% lower risk of death [aHR=$_{0.09}0.21_{0.47}$, $p < 0.001$], and past 6 months at 88% lower risk of death [aHR=$_{0.06}0.12_{0.25}$, $p < 0.001$] when compared those who declined IRDs.
Conclusion: Those who accepted and received IRD kidneys experienced long-term improved survival compared to those who declined. Accepting an otherwise high-quality IRD kidney provides survival benefit to transplant candidates while reducing the burden of the organ shortage.

Figure 1. (a) KDPI of accepted IRD kidneys and (b) KDPI of kidneys later received by patients who had declined IRD kidneys

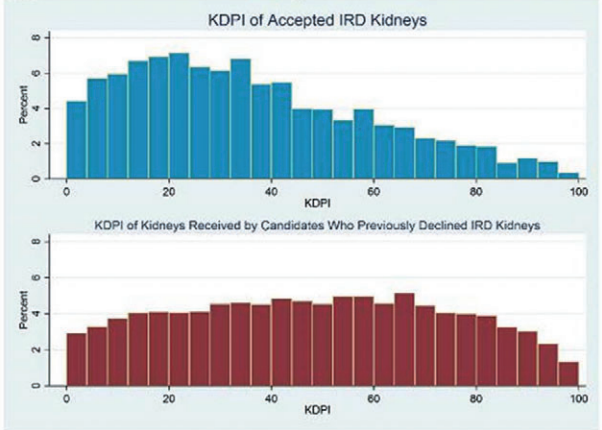
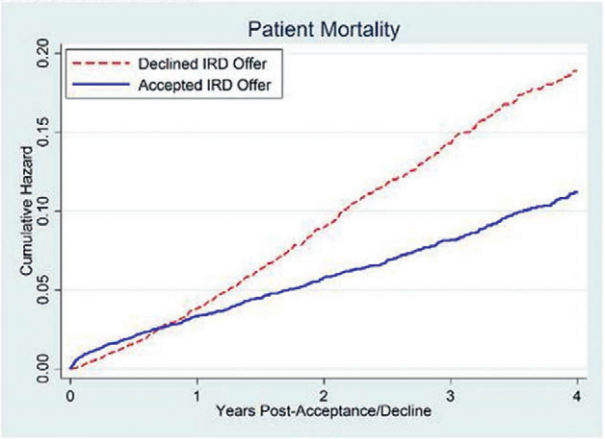


Figure 2. Cumulative hazard of patient mortality between those who accepted IRD kidneys and those who declined IRD kidneys. Candidates matched on listing center and time on dialysis.

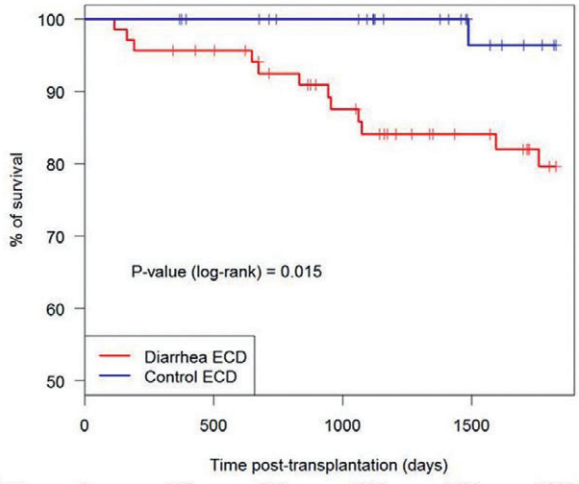


OS095 DONOR CHARACTERISTICS RATHER THAN THE SEVERITY OF POST-TRANSPLANT DIARRHEA DETERMINES LONG-TERM GRAFT OUTCOME

Arnaud Devresse, Florence Aulagnon, Anne Scemla, Lise Morin, Fanny Lanternier, Adel Aidoud, Xavier Lebreton, Rébecca Sberro-Soussan, Renaud Snanoudj, Lucille Amrouche, Claire Tinel, Frank Martinez, Lynda Bererhi, Dany Anglicheau, Olivier Lortholary, Christophe Legendre, Véronique Avettand-Fenoel, Julien Zuber
Necker Hospital, France

Background: The causes and effects of diarrhea on graft outcomes have been poorly investigated in a large cohort of well-phenotyped kidney transplant recipients (KT). The epidemiological burden and presentation of *Norovirus* (Nov) infection in unselected KT also remained to be clarified.

Figure 1 : Death-censored graft survival in the cases (red line) and diarrhea-free controls (blue line) in recipients of ECD allografts



Days	0	365	730	1095	1460	1825
N total	114	110	98	86	71	55
N case	69	65	58	49	41	33
N control	45	45	40	37	30	22

Methods: Between 2010 and 2011, 195 KT who underwent extensive infection workup for post-transplant diarrhea, were enrolled in the study. Patients with NoV infection ("NoV group", $n = 59$) were compared to patients with other causes ("non-NoV group", $n = 136$). A diarrhea-free KT control group was selected from our database (2004–2016) ("control group", $n = 151$), matched by transplant date, and compared to the cases ("diarrhea group", $n = 151$).
Results: NoV was the leading cause (30%). NoV-associated diarrhea ($n = 59$) was associated with longer duration of symptoms (226 ± 352 vs. 128 ± 226 days, $p = 0.003$), higher rates of chronic diarrhea (76% vs. 52%, $p = 0.002$), acute kidney graft failure (59% vs. 38%, $p = 0.006$), hospitalization (61% vs. 36%, $p = 0.002$) and greater weight loss (7%±5% vs. 3%±4%, $p = 0.001$) than non-NoV-related diarrhea. Mycophenolate reduction was more frequent (81% vs. 50%, $p = 0.0001$) and more pronounced (−78%±26% vs. −66%±31%, $p = 0.02$) in the Nov group. When comparing cases with controls, 5 years death-censored graft survival was lower in the cases (91% vs. 98%, $p = 0.01$). The poor functional outcome associated with diarrhea was particularly striking in recipients of grafts from expanded criteria donor (ECD) [Figure 1]

Multivariate analysis retained diarrhea as an independent factor associated with 5 years-graft loss risk in ECD ($p = 0.042$).
Conclusion: NoV is the leading cause of diarrhea after KT and is associated with a more severe presentation. Diarrhea decreases graft survival especially in recipients of ECD allografts.

Clinical Liver Infection

OS096 EFFECTIVENESS OF SUBCUTANEOUS & INTRAVENOUS HEPATITIS B IMMUNOGLOBULIN TO PREVENT REINFECTION AFTER LIVER TRANSPLANTATION: LONG-TERM RESULTS FROM AN INTERNATIONAL MULTICENTER NON-INTERVENTIONAL STUDY

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[1]University Münster, Germany; [2]University Essen, Germany; [3]Biotest Ag, Germany; [4]Addenbrooke's Hospital Cambridge, United Kingdom; [5]Chirurgia Epatica E Del Trapianto Fegato Pisa, Italy; [6]Erasmus Medical Center Rotterdam, The Netherlands; [7]University Zürich, Swaziland; [8]Centre De Transplantation D'organes, Lausanne, Switzerland; [9]Azienda Ospedaliera Policlinico Tor Vergata, Italy

Background: Potent reinfection prophylaxis has improved survival in hepatitis B-transplanted patients. Recurrence rates in HBV-infected patients after liver transplantation (LT) differ among studies, as most of them are monocentric, of small size and with limited follow-up periods.
Aim: To retrospectively evaluate in a large international multicenter patient cohort the effectiveness of subcutaneous (sc) (Zutectra), intravenous (iv) (Hepatect CP) and others hepatitis B immunoglobulins (HBIG), in prevention of reinfection of the liver allograft in the long-term after LT, whether combined with nucleos(t)ide analogues (NUCs) or not.
Methods and Results: Data from 371 patients with HBV-induced cirrhosis ($n = 195$, 52.6%), within Milan criteria HBV-induced hepatocellular carcinoma (HCC) ($n = 147$, 39.6%) and fulminant hepatitis B ($n = 29$, 7.8%) transplanted between 2000 and 2014 and treated with HBIG for at least 1 year post-transplant were analyzed. From 371 patients 30.7% had HBV/HDV coinfection and 27.2% had detectable HBV DNA prior to LT. A total of 347 (93.5%) had concomitant prophylaxis with NUCs (most reported: 60.6% lamivudine, 23.5% entecavir, 23.5% tenofovir), including 28.5% with combined NUCs. HBV recurrence defined as HBsAg positivity and/or detectable HBV DNA occured in 16 patients (4.3%) with a mean time of 36.3 ± 35.6 months. All reinfected patients with available HBV tests pretransplant (14/16) were replicative at time of LT. Incidence of HBV recurrence *per* year was 0.65%. HCC recurrence was documented in 9.5% ($n = 14$) of 147 during a median follow-up of 7 years (range, 1.0 to 15.7 years). In 236 patients treated sc with Zutectra only 1 HBV recurrence was observed during 698 treatment years with home administration in 96.6% of cases.
Conclusion: This large multicenter study conducted in 5 European countries showed that sc or iv HBIG±NUC reinfection prophylaxis is associated with low HBV reinfection (<5%) and HCC recurrence (<10%) rate in the long-term after LT.

Clinical Liver Ischemia-reperfusion and preservation

OS097 THE USE OF NORMOTHERMIC MACHINE PERFUSION IN LIVER VIABILITY ASSESSMENT - CAN WE PREDICT POST-TRANSPLANT OUTCOMES?

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[1]Oxford Transplant Centre, Nuffield Department of Surgical Sciences, United Kingdom; [2]Oxford University Hospitals NHS Foundation Trust, United Kingdom; [3]University Hospitals Birmingham NHS Foundation Trust, United Kingdom; [4]King's College Hospital NHS Foundation Trust, United Kingdom; [5]Cambridge University Hospital NHS Foundation Trust, United Kingdom; [6]Royal Free London NHS Foundation Trust, United Kingdom; [7]The Institute of Biomedical Engineering, University of Oxford, United Kingdom

Background: Normothermic machine perfusion (NMP) may enable an objective assessment of liver quality to aid clinical decision making. However, there is little evidence as to which measures correlate best with outcome. This study aims to identify markers which may be predictive of post-transplant outcome.
Methods: As part of a RCT conducted by the Consortium for Organ Preservation in Europe, 120 NMP livers were transplanted. Biochemical analysis was performed on perfusate collected during NMP from livers with a post-transplant peak aspartate aminotransferase (AST) of <250 U/l (minimal preservation injury [MPI], $n = 28$) and >1000 U/l (significant preservation injury [SPI], $n = 25$). Bile production and post-reperfusion syndrome (PRS) were also compared between the groups.
Results: Groups were matched for donor and recipient characteristics as well as preservation time. There was a significant difference in baseline perfusate alanine aminotransferase (ALT) (MPI 171 U/l vs. SPI 669 U/l; $p = 0.005$) and lactate dehydrogenase (LDH) (MPI 1073 U/l vs. SPI 1838 U/l; $p = 0.01$) between the two groups. These enzymes, along with gamma-glutamyltransferase (GGT), also increased more rapidly during NMP in the SPI group (ALT +56 U/l vs. +461 U/l, $p < 0.001$; LDH +483 U/l vs. +980 U/l, $p = 0.06$; GGT +23 U/l vs. +104 U/l, $p = 0.004$). MPI livers experienced a drop in haemolysis index as NMP progressed in contrast to SPI livers where it rose (MPI −0.04 U/l vs. SPI +0.09 U/l; $p = 0.03$). There was similar lactate clearance by livers in each group.
Bile production was superior in the MPI group (MPI 13.1 ml/hr vs. SPI 7.8 ml/hr; $p = 0.03$). PRS was less common in the MPI group (MPI 0/28 vs. SPI 6/25; $p = 0.007$).
Conclusion: A clear correlation exists between post-transplant outcome and the absolute values and trends in several biochemical parameters and bile production during NMP. These differences can be used to predict organ quality and potentially guide clinical decision making to ensure patients receive an appropriate organ for their clinic.

OS098 PRELIMINARY RESULTS OF THE UK 'REVIVE' TRIAL FOR NORMOTHERMIC OXYGENATED PERFUSION OF DECEASED DONOR LIVERS USING THE PORTABLE ORGAN CARE SYSTEM (OCS™) LIVER

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The Leeds Teaching Hospitals NHS Trust, United Kingdom

Background: OCS Liver REVIVE Trial is a single-arm prospective trial to evaluate the safety and performance of OCS™ Liver system to preserve and assess deceased donor livers for transplantation.
Methods: A total of 25 liver transplant recipients will be enrolled into the trial. All adult donor livers over ≥18 years with less than 50% macrosteatosis suitable for machine perfusion will be considered. Donor exclusions: living or split donors; severe liver injury; DCD donors over 65 years. Recipient inclusion criteria: age ≥ 18 years; registered primary liver transplant candidate; signed written informed consent for the trial. Recipient exclusions: acute, fulminant liver failure; prior transplants; multi-organ transplant; ventilator dependence at time of transplantation. Short-Term endpoints include incidence of Early Allograft Dysfunction within 7 days post-transplant, patient and graft survival at day-30 post-transplant and length of post-transplant critical care and hospital stay. Safety will be assessed by Incidence of device related loss of an organ.
Results: To-date, 11 patients were enrolled in the REVIVE trial. Total cross clamp time was 541.3 ± 61.8 min ranged from 477–636 min, perfusion time on the OCS was 391.5 ± 54.5 ranged from 342 - 518 min, 45% of the Livers were from DCD donors. All livers were safely perfused and demonstrated normal physiologic functions while on the OCS Liver system, producing bile with stable perfusion parameters, and trending down lactate from 6.9 ± 2.8 mmol/l to 1.6 ± 1.0 mmol/l. All livers preserved on OCS system were successfully transplanted. Incidence of EAD was 2/11 patients (18%), 30-day survival is 100%. No serious adverse events regards to use of OCS Liver was noted. ICU stay 33.5 ± 21 h and total hospital stay 8.4 ± 2.6 days.

Conclusion: The portable OCS Liver system has demonstrated safety and reliability to preserve deceased donor livers. Early clinical outcomes of DCD and DBD liver transplant at

OS099 INFLUENCE OF NORMOTHERMIC MACHINE PRESERVATION IN HUMAN LIVER TRANSPLANTATION ON POSTREPERFUSION HEMODYNAMICS

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[1]Liver Transplant Unit Cleveland Clinic, United States; [2]Cleveland Clinic, United States

Background: Graft reperfusion hold a major challenge during liver transplantation and can be associated with hemodynamic instability, post-reperfusion syndrome and coagulation impairment. Normothermic Machine Perfusion (NMP) has been reported to improve post-reperfusion hemodynamics in patients undergoing liver transplantation.
Methods: We summarized amount of vasopressors, arterial blood gas and TEG parameters, as well as blood products transfused during post-reperfusion phase, using standard summary statistics. We descriptively compared matched NMP and control patients on all the above variables using absolute standardized difference (ASD, absolute difference in means or proportions divided by the pooled standard deviation. ASD of 0.2, 0.5, and 0.8 represent small, median, and large differences.
Results: A total number of 50 liver transplant patients with an average age of 61 (SD: 6) and median MELD score of 17.5 [Q1, Q3: 11, 29] were analyzed, including 10 recipients who received grafts preserved with NMP (NMP group) matched with 40 controls who underwent liver transplant after conventional cold storage (CS group). The two groups were comparable on age, MELD, donor risk index, and donor graft type. During the post-reperfusion phase, the matched NMP group received descriptively less amounts of norepinephrine, vasopressin and epinephrine (ASD: 0.35, 0.34, and 0.58), as well as less amount of red blood cell, fresh frozen plasma and cell saver transfusion (ASD: 0.47, 0.86, and 0.42) than CS group. NMP group had descriptively lower base deficit (absolute value, ASD = 0.51), lactic acid level (ASD = 0.23), and higher pH (ASD = 0.27). In addition, TEG R value and MA were descriptively lower and alpha angle was higher in NMP than CS (ASD: 0.07, 0.13, and 0.18).
Conclusion: NMP is associated with more stable hemodynamic, and better metabolic and coagulation profile after reperfusion compared to CS group. These observed benefits need to be investigated in larger studies.

OS100 BILE PRODUCTION DURING NORMOTHERMIC MACHINE PERFUSION OF HUMAN LIVERS FOR TRANSPLANTATION

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Introduction: Normothermic machine perfusion (NMP) involves perfusing a liver with oxygenated blood and additives at 37oC. Animal studies suggest that bile supplementation using bovine sodium taurocholate (BNaT) is necessary to prevent cholestatic injury and maintain bile production (potentially an indicator of organ viability). However, it is unknown whether human livers can uptake and excrete BNaT or whether NMP-bile production correlates with outcome.
Methods: A RCT comparing continuous NMP with Cold Storage in liver transplantation was conducted by the Consortium for Organ Preservation in Europe. Bile production was compared between NMP livers with minimal preservation injury (MPI; AST< 200 IU/l) and significant preservation injury (SPI; AST>1000 IU/l) as determined by post-transplant peak-AST. Bile salt levels were measured in NMP perfusate and bile samples and related to bile production during NMP.
Results: MPI ($n = 25$) and SPI ($n = 27$) donors and recipients were well matched for age, sex, ET-DRI and MELD score. Bile salt analysis revealed that BNaT was taken-up by human livers and secreted in the bile produced. There was a correlation between bile salt uptake from the perfusate and bile production ($r = 0.56$; $p < 0.05$) with bile production < 5 ml/hr causing a progressive accumulation of bile salts in the perfusate. Mean hourly bile production during NMP was better in MPI livers (13.1 ml/hr MPI vs. 7.8 ml/hr SPI; $p = 0.03$) although bile composition was similar. All livers eventually functioned well after transplant.
Discussion: We have demonstrated for the first time that the human liver can take up non-human bile salts (BNaT) and secrete it into bile. It appears that preservation injury causes impaired hepatocellular uptake of bile salts with subsequent accumulation of bile salts in the perfusate and poor bile production during NMP. Absent bile production does not necessarily indicate a non-viable organ but does reflect cellular injury.

OS101 NORMOTHERMIC REGIONAL PERFUSION INCREASES LIVER UTILISATION AND IMPROVES THE OUTCOMES AFTER LIVER TRANSPLANTATION FROM CONTROLLED DCD DONORS

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Background: There is an increased use of normothermic regional perfusion (NRP) for the recovery of organs from donors after circulatory death (DCD). We present a single centre experience with liver transplantation using NRP in category III DCD donors.
Methods: NRP was established via aortic and caval cannulation post-asystole. Blood gases and biochemistry were measured every 30′ during the two-hour NRP. Outcome were compared with a contemporaneous cohort of standard DCD livers transplants.
Results: 49 standard DCD and 15 NRP DCD livers were transplanted between February 2013 and February 2017. The median follow-up was 17 months (range: 0.62–48.6 months). Lier graft utilisation from NRP proceeding donors was 55% (15/27 donors).

The median donor age for the NRP livers was 53 years (range: 28–69 years) whilst the functional warm ischemic time was 26 min. The median peak ALT in the NRP DCD livers in the first week was 473 iu/l (range: 58–3043) compared with 1264 iu/l (range: 120–5462) in the standard DCD group. 2/15 (13.3%) livers in the NRP group developed early allograft dysfunction compared with 15/49 (30.6%) in the standard DCD.

None of the NRP livers developed ischemic biliary strictures compared with 11 patients (22.4%) in the standard DCD group.

There was no primary non-function (PNF) in the NRP group whilst 4 patients had PNF in the standard DCD group (two re-transplanted and two died). All recipients of the NRP livers are alive whilst two patients died in the standard DCD group. Two NRP DCD livers had biliary complications (one bile leak and one anastomotic stricture that resolved with stenting). 9 patients (18.36%) had biliary complications in the standard DCD group requiring stenting (8) and Roux-en-Y hepaticojejunostomy (1).
Conclusions: NRP increases the utilisation of livers from category III DCD donors. NRP DCD liver transplants are associated with a reduced ischemia reperfusion injury and a significantly lower incidence of ischemic biliary strictures.

OS102 FIRST REPORT OF NORMOTHERMIC MACHINE PERFUSION (NMP) FOR HUMAN LIVER TRANSPLANTATION IN THE UNITED STATES

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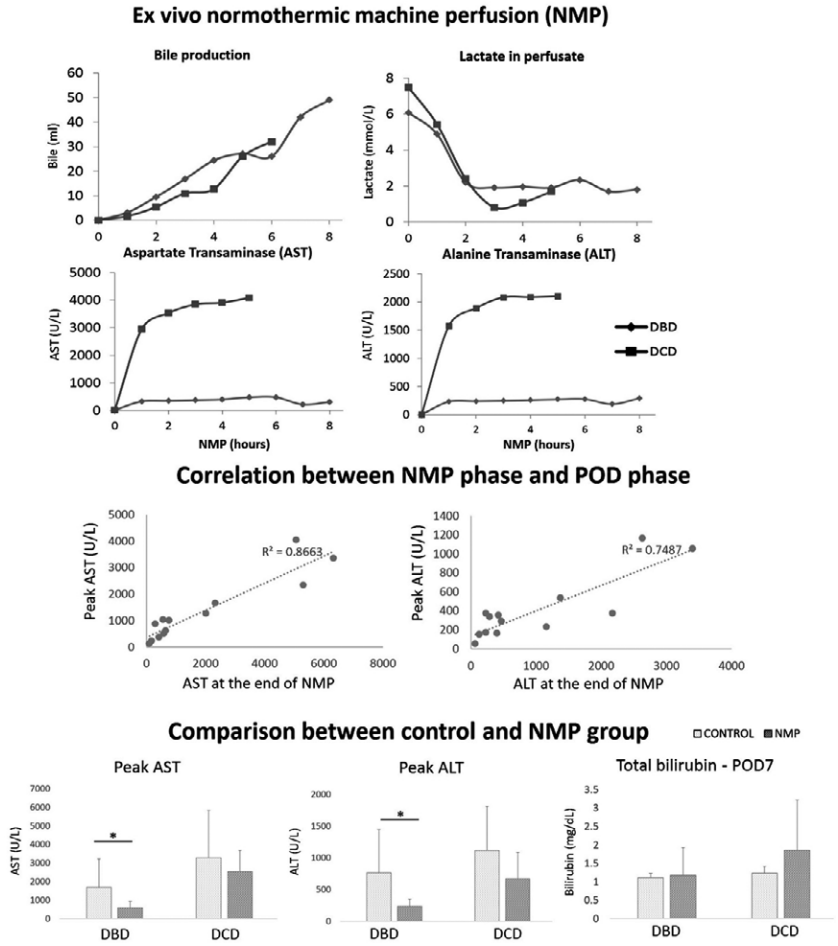
NMP is a novel preservation method for liver grafts. We transplanted 13 human livers after NMP to test the safety and feasibility of NMP on a device developed in our institution. Livers included 8 from donors after brain death (DBD) and 5 after circulatory death (DCD). Cold ischemia time before NMP was 1 hrs 32mins to 3 hrs 57mins. NMP time was 3 hrs 20mins to 7 hrs 52mins. Livers were perfused through portal vein and hepatic artery in physiologic flow rates and pressures with perfusate based on matched human packed red blood cells and fresh frozen plasma. During NMP, bile production was 3–13 ml/h of DBD livers and 1–6 ml/h of DCD livers. All livers displayed lactate clearance [Figure 1]. The alanine and aspartate aminotransferase (ALT, AST) in perfusate at the end of NMP had correlation (both $p = 0.001$) to their peak values in the first 7 post-operative days (POD) [Figure 2]. NMP livers were compared to historic liver transplant controls preserved by cold storage (CS) matched (1 : 4 on DBD, 1 : 2 on DCD) by donor and recipient age, donor risk index, MELD score, total preservation time. Early allograft dysfunction (EAD) was defined as total bilirubin >10 mg/dL or International Normal Ratio (INR) >1.6 at POD7, or peak ALT or AST >2000 U/l until POD7. EAD ratio was 23% in NMP group (3 DCD liver) but was 33% of the controls ($p = 0.02$). NMP group had significant difference compared to the controls on peak AST ($p = 0.001$) and ALT ($p = 0.001$) of DBD livers, but not DCD livers ($p > 0.05$). All DCD-NMP livers had AST decreased rapidly (>1000 U/l) within 1 day after peak compared to only half of DCD-CS livers. These results indicated the potential benefits of NMP preservation on protecting and predicting liver function.



OS103

A PILOT, DOUBLE-ARM, RANDOMIZED, PROSPECTIVE, STUDY ON NORMOTHERMIC *EX-VIVO* PERFUSION OF ELDERLY LIVER GRAFTS (≥70 YEARS)

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Background: CEFEMA is a 24-week, prospective, randomized, double-arm study to evaluate the efficacy and safety of a non-transportable, normothermic *ex-vivo* perfusion device (LiverAssist®) in liver transplantation (LT) with very old donors (≥70 years).
Materials and Methods: A total of 20 consenting, adult (≥18 years) recipients will be enrolled and randomized to normothermic perfusion (NMP) or cold storage (CS). The primary end points are post-transplant AST/ALT peak levels; graft and patient survival; incidence of ischemic type biliary lesion, and adverse events. Liver graft biopsies will be obtained at procurement; bench surgery; after NMP, and before skin closure, and will be evaluated with H&E and PAS-glycogen staining and electronic microscopy with quantitative glycogen and ATP content measurement. Bile duct biopsies (H&E staining) will be obtained at the same time points. IL-6, IL-10, and TNF will be tested in perfusate during NMP.
Results: To date, 14 patients have been enrolled and 6 have been randomized to NMP vs. 8 to CS. Mean (SD) donor age was 82.2(4.0) and 78.3(6.7), respectively ($p = 0.24$). Mean (SD) *ex-vivo* time was 505(101) min for NMP vs. 415(57) for CS ($p = 0.06$). Mean (SD) duration of NMP was 234 (66) min. Mean (SD) AST and ALT peaks were 610(215) and 983(900) UI/l ($p = 0.34$) and 302(82) and 459(138) UI/l ($p = 0.03$) for NMP and CS, respectively. All grafts were successfully transplanted. One patient in the CS was re-admitted for abdominal occlusion on post-operative day (POD) #31 and died on POD #39 for septic shock. Preliminary histologic evaluation (PAS-staining) showed a significant decrease in hepatocyte glycogen concentration at the end of LT for NMP vs. CS. Perfusate IL levels were higher than in serum for grafts on NMP.
Conclusion: Preliminary data show feasibility of NMP for preservation of very old liver grafts. The advantages of NMP over CS await final demonstration.

OS104

EFFECT OF NORMOTHERMIC MACHINE PERFUSION ON OUTCOMES AFTER STEATOTIC LIVER TRANSPLANTATION: A FIRST ASSESSMENT

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Introduction: Steatotic livers are associated with poor early post-transplant outcomes. The aim of this study is to compare post-transplant outcomes from steatotic livers preserved via normothermic machine perfusion (NMP) and static cold storage (SCS).
Methods: As part of the Consortium for Organ Preservation in Europe (COPE) RCT comparing NMP with SCS, 22 matched steatotic livers were transplanted (13 NMP, 9 SCS). Lean NMP and SCS livers were matched with steatotic counterparts (11 NMP, 13 SCS). Peak serum aspartate aminotransferase (AST) in the first 7-days post-transplant, early allograft dysfunction (EAD), post-reperfusion syndrome, duration of critical care stay and primary non-function (PNF) were compared between groups.

Results: Comparison of NMP vs. SCS in steatotic livers showed: (i) a significant reduction in EAD in NMP livers (15.4% NMP vs. 66.7% SCS, $p = 0.03$); (ii) a reduction in median peak serum AST in NMP livers (745 [103–5101 U/l] NMP vs. 2316 [281–5511 U/l] SCS, p = NS); and, (iii) a reduction in the incidence of post-reperfusion syndrome in NMP livers (15.4% NMP vs. 44.4% SCS livers, p = NS).

There was a statistically significant reduction in median peak serum AST between steatotic and lean NMP livers (745 [103–5101 U/l] vs. 320 U/l [173–1493 U/l], respectively; $p = 0.01$). There was an increase in mean critical care duration in steatotic NMP compared to SCS livers (7.231 ± 1.854 days vs. 5.89 ± 1.679 days, respectively; p = NS). However, this was statistically lower in the lean NMP group (2.72 ± 0.407 days, $p = 0.04$). Only one liver developed PNF; this was a severely steatotic liver preserved via NMP.

Discussion: In steatotic donor livers, NMP is associated with improved markers of injury and immediate function compared to SCS. However, a greater improvement in outcomes observed in lean NMP livers highlights a potential need for de-fatting interventions.

OS105 RESULTS OF THE INITIAL PHASE OF THE PORTABLE ORGAN CARE SYSTEM (OCS™) LIVER PROTECT PIVOTAL TRIAL

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Background: The OCS Liver PROTECT Trial is a prospective, international, randomized controlled trial to evaluate the impact of using portable *ex-vivo* warm, oxygenated blood perfusion using OCS Liver System on short and long-term clinical outcomes in liver transplantation as compared to standard cold ischemic storage.

Methods: OCS Liver PROTEC Trial compares preservation of donor livers using OCS-Liver perfusion system (OCS) to cold flush and storage (Control). A total of 300 liver transplant recipients will be randomized into the trial. Donor inclusion criteria: Age ≥40 years old; or total cross clamp time ≥6 h; or DCD ≤55 years old; or ≤40% macrosteatosis. Donor exclusions: Living or split donors; or severe liver injury. Recipient inclusion criteria: age ≥ 18 years; registered male or female primary liver transplant candidate; signed written informed consent for the trial. Recipient exclusions: acute, fulminant liver failure; prior transplants; multi-organ transplant; ventilator dependence at time of transplantation.

Short-Term primary endpoints are incidence of EAD within 7 days post-transplant, patient survival at day 30 and within initial hospital admission. Safety will be assessed by rate of liver graft related (LGR) SAEs within the initial 30 days post-transplant. Long-term endpoints: patient survival at 1 and 2 years.

Results: We are reporting the results of the initial 20 randomized patients in the PROTECT trial (OCS = 8 and Control = 12). Incidence of EAD was 1/8 patients (12.5%) in OCS vs. 5/12 (41.7%) in Control. All patients survived to day 30. There was no LGR SAEs in the OCS vs. 1 LGR SAE in Control. Liver biopsy assessment demonstrated lower IR injury markers and LSEC loss in the OCS arm compared to Control.

Conclusion: The initial experience with the OCS Liver in clinical transplantation demonstrated safety and encouraging early clinical outcomes. The trial is currently expanding enrollment

Translational Liver Ischemia-reperfusion and preservation

OS106 A HISTOLOGICAL AND BIOCHEMICAL ASSESSMENT OF STEATOTIC LIVERS UNDERGOING NORMOTHERMIC MACHINE PERFUSION

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Introduction: Steatotic livers are associated with poor outcomes after transplantation. This study aims to compare histological changes in steatotic livers undergoing normothermic machine perfusion (NMP) and static cold storage (SCS) and compare changes in key lipid metabolites circulating during normothermic preservation of steatotic and lean livers.

Methods: As part of the Consortium for Organ Preservation in Europe (COPE) RCT comparing NMP with SCS, 31 (20 NMP, 11 SCS) moderate and severely steatotic livers (as defined by the retrieval surgeon) were transplanted. The tissue was graded for total macrovesicular steatosis and neutrophil infiltration by an experienced histopathologist. NMP perfusate was analysed for markers of lipid metabolism and function including: triglyceride (TG), 3-hydroxybutyrate (3-OHB) and alanine aminotransferase (ALT).

Results: Thirteen NMP and 9 SCS livers with a mean total macrovesicular steatosis of 39 ± 8% and 34 ± 9%, respectively, were identified. Surgeons over-estimated the presence of steatosis by 34% when compared to histopathological assessment. The degree of steatosis did not change significantly during preservation between the NMP and SCS groups and a similar pattern of neutrophil infiltration was seen in post-reperfusion biopsies.

At the end of NMP (median 554mins [145–1242 min]), mean perfusate TG was significantly higher in steatotic than lean NMP livers (2064 ± 369.5 mmol/l vs. 1017 ± 193.7 mmol/l; $p = 0.02$). Mean 3-OHB levels were also significantly higher in the steatotic liver perfusate (1842 ± 434 mmol/l vs. 605.1 ± 133.8 mmol/l; $p = 0.02$). Mean perfusate ALT was significantly higher in steatotic than lean livers (1846 ± 567.8 U/l vs. 406.4 ± 101.9 U/l; $p = 0.02$).

Discussion: Surgeons grading correlates poorly with histopathological assessment of steatosis. Clear differences in perfusate lipid metabolites highlight potential targets for de-fatting interventions during preservation which may improve outcomes from this group of high-risk livers.

Clinical Liver Ischemia-reperfusion and preservation

OS107 NORMOTHERMIC *EX SITU* PERFUSION PERMITS ASSESSMENT AND TRANSPLANTATION OF DECLINED LIVERS

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Introduction: 19% of DBD and 64% of DCD donor livers in the UK are not used, while 17% of patients either die or are removed from the transplant waiting list. In order to improve our utilisation of livers that might be otherwise declined we initiated a programme of normothermic *ex situ* liver perfusion (NESLiP) using the LiverAssist® device from Organ Assist (Groningen).

Methods: Livers with a long estimated cold ischaemic time, or other higher risk livers, were subjected to NESLiP following arrival at our centre. Perfusion continued until implantation. These livers were compared with a contemporaneous cohort of cold stored livers transplanted before and after each of the NESLiP livers ("Controls").

Results: Twenty livers declined by other centres were assessed with NESLiP, including 4 fast track offers and 2 livers offered for research, and 16 of these were transplanted after a period of normothermic perfusion (Table 1). NESLiP livers were subjected to greater periods of extracorporeal storage, including a median of 308 min (range 122–1561) of normothermic perfusion, with results comparable to cold storage. At a median (IQR) follow up of 421 (261–611) days, the incidence of ischaemic cholangiopathy (MRCP detected) was 31%. Ischaemic cholangiopathy was associated with production of acidic bile (pH ≤ 7.2), but not with bile flow, during NESLiP.

Discussion: NESLiP provided a means of halting cold ischaemia and enabled *ex situ* evaluation of livers that may not otherwise have been used for transplantation. Results are comparable to cold-stored livers but more work needs to be done to identify livers at risk of cholangiopathy, and to improve the outcomes of the perfused livers.

	NESLiP (n = 16)	Control (n = 32)
Liver offer type: DBD or DCD Research/ Fast track/National/Zonal	11 DCD, 5 DBD 2R, 4F, 4N, 6Z	22 DCD, 10 DBD 0R, 5F, 6N, 21Z
US Liver donor risk index (median, range)	2.17 (1.14 - 3.66)	2.18 (1.18–3.82)
UK Liver index (Collett et al.) (median, range)	1.92 (0.80–1.92)	1.82 (0.72–2.93)
Ex vivo storage time (min) (median/range)	778 (564–1561)	439 (333–721)
Donor age (years) (median/IQR)	57.1 (45.8–65.6)	52.8 (45.7–68.4)
UKELD (median/IQR)	56.5 (51.5–63.6)	55.6 (51.5–62.8)
Graft survival (death censored)	14/16 = 88%	30/32 = 94%
Patient survival	15/16 = 94%	100%
Ischaemic cholangiopathy	5/16 = 31%	6/32 = 19%
Peak ALT in first 7 days (median/range)	847 (187–4991)	697 (155–3761)

OS108

5-YEAR EXPERIENCE IN HUMAN EXTENDED DCD LIVER TRANSPLANTATION TREATED BY HYPOTHERMIC OXYGENATED PERFUSION (HOPE) BEFORE IMPLANTATION

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Background: DCD liver transplantation is known for potential worse outcome due to higher rates of graft non-function or irreversible cholangiopathy. We have previously shown in a pilot analysis of the first twenty-five patients that a novel machine perfusion technique, applied after initial cold storage, hypothermic oxygenated perfusion (HOPE), resulted in similar 1y graft survival and no intrahepatic cholangiopathy. We report now on 50 human DCD livers, treated at our center by HOPE, with a cumulative follow up of up to 5 years.
Methods: Fifty HOPE treated DCD liver transplants in Zurich were matched with 50 low risk primary DBD liver transplants, and also with 50 un-perfused DCD livers in Birmingham. Match factors included cold ischemia, donor age, recipient age, and recipient lab MELD. Endpoints were peak liver enzymes, ICU- and hospital stay, graft function, kidney function, complications ranked by comprehensive complications index (CCI), cholangiopathy, patient- and graft survival.
Results: Despite long donor ischemia times (median functional donor warm ischemia 31 min), HOPE treated extended DCD liver transplants achieved similar outcome, compared to standard DBD liver transplants in terms of all endpoints, particularly no graft loss occurred due to intrahepatic cholangiopathy or PNF. In contrast, un-perfused DCD livers developed in 6/50 cases (12%) severe intrahepatic cholangiopathy or PNF, both resulting in graft failure. Five-year graft survival was 78% vs. 79% vs. 68% in HOPE vs. DBD vs. un-perfused DCD liver transplants.
Conclusions: Outcome of HOPE treated human DCD liver transplants maintained over a period of five years comparable with DBD primary transplants, and also superior to un-perfused DCD livers, performed at a highly experienced center. These results suggest strong effectivity of a simple end-ischemic perfusion approach, and may open the field for safe utilization of high risk grafts.

Translational Kidney Metabolic complications

OS109

TACROLIMUS (TAC), NOT CYCLOSPORINE (CSA), INTERACTS WITH METABOLIC STRESS, ENHANCING HUMAN B CELL FAILURE THROUGH BMP SIGNALING

Javier Triñanes[1], Eelco De Koning[1], Peter Ten Dijke[2], Esteban Porrini[3], Françoise Carlotti[4], Aiko De Vries[1]

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Clinical Kidney Metabolic complications

OS110

OXALATE DEPOSITION IN THE RENAL ALLOGRAFT WITHIN 3 MONTHS AFTER TRANSPLANTATION

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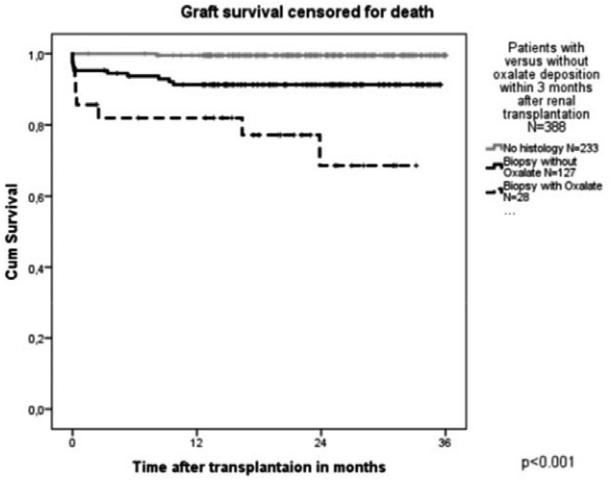
Background: Renal insufficiency causes secondary hyperoxaluria but data regarding prevalence of calcium oxalate deposition (CaOxDep) and its influence on graft survival are scarce.
Methods: We retrospectively analyzed all preimplantation renal biopsies (t0) obtained in 2000–2001 for CaOxDep. In addition, we investigated all for-cause renal allograft biopsies and transplantectomies within 3 months post-transplantation of patients transplanted in 2014–2015. Clinical data were collected. Presence of CaOxDep was studied by means of H&E stained slides using polarized light.
Results: A total of 106 t0 biopsies (56 living, 50 deceased donor) were available for analysis. In 1 biopsy CaOxDep was present. In 2014–2015, 388 patients were transplanted. 155 had at least one for cause renal biopsy or transplantectomy within 3 months after transplantation. In 3 of 8 transplantectomies CaOxDep was found. Twenty-six (17%) patients showed CaOxDep in their biopsy, and 2 additional patients in their transplantectomies (18%). No histologic diagnosis (ATN, rejection or other) prevailed in the population with CaOxDep. Though best eGFR before histology was not significantly different, eGFR at time of biopsy was significantly lower in the group with CaOxDep ($p = 0.016$) and delayed graft function (DGF) was more frequent with CaOxDep ($p = 0.036$). Significantly more patients with CaOxDep had been on dialysis compared to no treatment before transplantation ($p = 0.006$). Other clinical parameters were not significantly different between the groups. Graft survival censored for death was significantly worse in the population with CaOxDep within 3 months ($p < 0.001$).
Conclusion: In 17% of patients with for cause renal allograft biopsy within 3 months after transplantation CaOxDep is present. It prevailed in patients that were on dialysis before transplantation but donor type was not predictive. CaOxDep is recipient derived and may contribute to impaired graft function or even graft failure.



OS111

CARDIOVASCULAR AUTONOMIC FUNCTION AFTER SIMULTANEOUS PANCREAS-KIDNEY AND KIDNEY-ALONE TRANSPLANTATION

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Background: Cardiovascular autonomic dysfunction (CAD) is a common and severe complication of diabetes. In addition, uremia as well as dysglycemia both play a role in the etiology of CAD. Moreover, tissue hypoxia could lead to the development of diabetes complications and CAD. Kidney- alone (KA) transplantation corrects uremia but simultaneous pancreas-kidney (SPK) transplantation also leads to normalization of blood glucose. The aim of this study was to examine whether CAD is improved early after KA with or without diabetes or after SPK transplantation. In addition, we wanted to investigate whether tissue hypoxia is improved after transplantation.
Methods: 43 patients undergoing KA (56.5 ± 10.8 years, mean ±SD; 29 males) and 13 undergoing SPK transplantation (38.4 ± 9.3 years; 11 males) were studied. Baroreflex sensitivity (BRS), heart rate variability (HRV, standard deviation of heart period), tissue (NIRS) and arterial (Sat) oxygenation were measured before and after transplantation. All SPK transplant recipients had type 1 diabetes. Three patients had type 1 diabetes and nine had type 2 diabetes in the KA group. All participants were on dialysis before the transplantation. In addition, we examined 55 healthy controls (CON, 42.1 ± 12.4 years, 33 male).
Results: Before transplantation BRS, HRV and NIRS were reduced in the KA group with and without diabetes and the SPK group compared to the CON group ($p < 0.05$). In the KA patients with diabetes age-adjusted BRS and HRV improved after transplantation and there was a trend of improvement also in the SPK group. Notably, NIRS improved after transplantation when all the patients were pooled together ($p < 0.05$).
Conclusion: CAD was improved in patients with diabetes early after KA transplantation. In addition, we demonstrate improvement of tissue hypoxia in transplanted patients.

OS112

ALTERED BODY COMPOSITION IN PATIENTS AFTER KIDNEY TRANSPLANTATION

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Background: Patients after kidney transplantation treated with glucocorticoids may develop new metabolic diseases like obesity, diabetes and hyperlipidemia. They may also get infections or kidney graft rejection. All these conditions and physical inactivity may lead to increased muscle catabolism and altered proportion of fat and muscle mass compared with people who do not have an organ transplant leading to a doubtable reliability of serum creatinine concentration, creatinine clearance and 24-h creatinine excretion in evaluation of these patients.
Methods: 100 kidney transplant recipients were included in a prospective clinical study. Body composition was measured with bioimpedance analysis. Serum creatinine concentration was determined and creatinine clearance from 24-h urine collection was calculated.
Results: From 53 men and 47 women the mean age was 56 ± 11 years (from 27 to 79 years). The mean time from transplantation was 10 ± 6 years (from 2 to 28 years). The mean body mass index was 25.0 ± 2.6 kg/m^2 (from 19.7 to 30.6 kg/m^2). 75% of patients had reduced proportion, 19% had normal proportion and only 6% had increased proportion of lean body mass (body mass without fat mass) as compared to what would be expected according to their age and sex. The analysis of 24-h urine revealed, that in 45% of the subjects the creatinine excretion per kg of body weight was not in the normal range, these patients had reduced proportion of lean body mass in 80%.
Conclusion: Majority of our renal transplant patients had altered body composition with reduced lean body mass and reduced creatinine excretion per kg of body weight in the 24-h urine. Beside not properly collected urine, the reduced proportion of lean body mass could be an explanation for reduced creatinine excretion. Quantity of excreted creatinine in 24-h urine could not be the measure for proper 24-h urine collection in kidney transplant recipients.

Clinical Kidney Cardiovascular complications

OS113

PLASMA N-6 AND TRANS FATTY ACID LEVELS AND CARDIOVASCULAR RISK MARKERS EARLY AFTER RENAL TRANSPLANTATION

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Background: Cardiovascular disease is the leading cause of death after renal transplantation. In this cohort, we have previously reported lower resting heart rate (rHR) and plasma triglyceride levels with higher levels of marine n-3 polyunsaturated fatty acids (PUFAs) in plasma. Associations with cardiovascular risk markers has, to our knowledge, not previously been studied for the n-6 PUFAs linoleic acid (LA), arachidonic acid (AA) or trans fatty acids (TFAs).
Methods/Materials: In this cross-sectional single center study of 1990 Norwegian renal transplant recipients, transplanted between 1999 and 2011, we assessed associations between plasma levels of LA, AA and TFAs and cardiovascular risk markers ten weeks after transplantation, using multivariate linear regression. Plasma phospholipid fatty acids were determined by gas chromatography.
Results: Plasma HDL cholesterol levels were positively associated with AA (Unstd. β-coeff. −1.03, Std. β-coeff. −0.09, $p < 0.001$) and negatively associated with LA (Unstd. β-coeff. 0.50, Std. β-coeff. 0.09, $p = 0.001$), while not with TFA levels in plasma. Neither LA, AA nor TFAs were associated with plasma levels of triglycerides or LDL cholesterol, rHR, pulse wave velocity, systolic or diastolic blood pressure.
Conclusions: Apart from a positive association between AA and HDL cholesterol, no association with cardiovascular risk markers early after transplantation were found for trans fatty acids and the major n-6 PUFAs LA and AA. Therefore, the findings do not support dietary recommendations for n-6 PUFA and trans fatty acid consumption shortly before or early after renal transplantation for improvement of cardiovascular health.

Clinical Kidney Metabolic complications

OS114

ILIAC PERIPHERAL ARTERIAL DISEASE BEFORE KIDNEY TRANSPLANTATION

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Background: Peripheral arterial disease (PAD) may exclude kidney transplantation when vascular connectivity is hampered. Stenotic or calcified iliac arteries without symptoms are not an indication for vascular treatment. How important is PAD for survival and what is the influence of intervention before transplantation?
Methods: Our retrospective cohort study included 1728 patients transplanted between 2000–2012. PAD was scored as: occlusive or dilating disease, dissection, and arterial intervention in the iliac region. Multivariable Cox proportional hazards analyses were performed to test the independent influence of PAD, corrected for variables with a known significant influence.
Results: There were 325 graft failures and 215 deaths in the period studied. There were missing values in 5 cases. In Cox analysis graft failure censored for death was significantly influenced by PAD ($n = 138$, $p = 0.048$, RR = 1.52). Occlusive disease did significantly influence outcome ($n = 97$, $p = 0.019$, RR = 1.76), while dilating disease ($n = 57$) did not. Treatment of PAD before transplantation did not significantly influence graft failure censored for death. Local interventions on the current side of transplantation had been carried out or were carried out during transplantation in 34 patients. KM showed no difference in patient survival between patients with and without vascular treatment on the side of transplantation. However, compared to patients without PAD the difference was significant ($p < 0.001$, Fig 1). Patient death was significantly influenced by PAD ($p = 0.009$, RR = 1.63) and occlusive arterial disease ($p = 0.004$, RR = 1.85). However, 10-year survival of patients with PAD was more than 50%.
Conclusion: Patients with PAD have significantly worse graft and patient survival than patients without PAD. However, in this vulnerable population more than half of the patients survive more than 10 years after transplantation. These favourable results justify considering patients with PAD for transplantation.

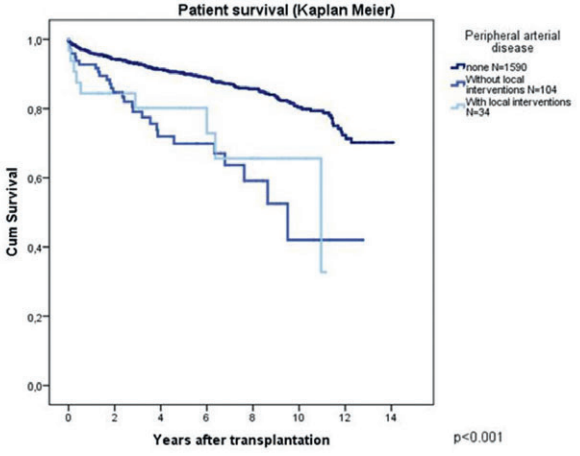

Figure 1. Kaplan-Meier survival curve of the influence of local treatment of PAD on patient survival ($P < 0.001$).

Clinical Kidney Cardiovascular complications

OS115

USEFULNESS OF PRETRANSPLANT AORTIC ARCH CALCIFICATION EVALUATION FOR OUTCOME PREDICTION AFTER DECEASED KIDNEY TRANSPLANT

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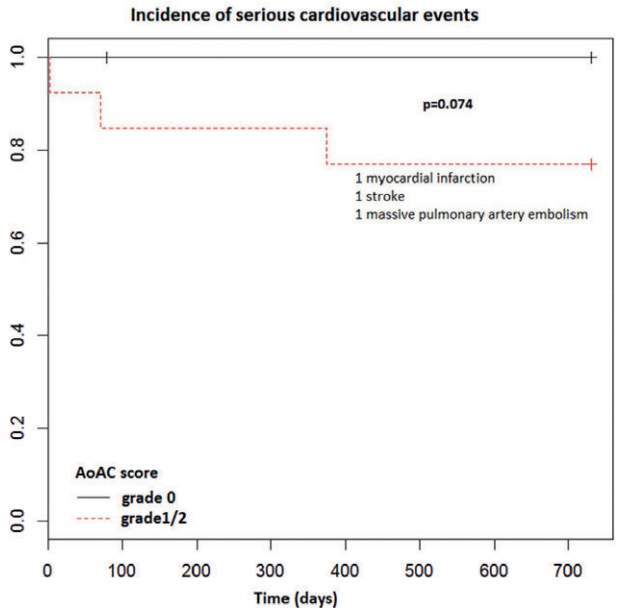
Vascular calcification (VC) remains undervalued burden even after successful kidney transplant (KTx). Aortic arch calcification (AoAC) detected on chest X-ray (CXR) is associated with increased cardiovascular morbidity and mortality and provides supportive information for atherosclerotic risk stratification. We aimed to determine which factors are associated with AoAC evaluated on



pretransplant CXR and determine whether it could predict graft function in 1-year follow-up.
Methods: From 60 KTx recipients 37 without previous vascular events were selected and underwent routine tests before and after deceased KTx. Pretransplant CXR were evaluated by two independent radiologists blinded to patient medical records. AoAC was graded based on a scale from 0 to 3 (0– no visible calcification, 1– <50% calcification in the arch, 2–>50% calcification, 3– circumferential calcification). Carotid-femoral (cfPWV) and carotid-radial (crPWV) pulse wave velocity was measured by using applanation tonometry (SphygmoCor).
Results: AoAC grade 2 was evaluated only in one patient who died 1 month after KTx due to sepsis and cardiovascular decompensation. Grade1 was associated with 3 serious cardiovascular events within more than 1-year follow-up.

We observed that patients with AoAC have higher cfPWV, but lower crPWV values. Therefore, the difference between cfPWV and crPWV was calculated (ΔPWV). The results of univariate and multivariate logistic regression are listed below.

After 1-year follow-up eGFR based on creatinine values were as follows: G1- 23.08%, G2 – 38.46%, G3a – 38.46%. AoAC before KTx. Pretransplant AoAC had no relationship with KTx function.
Conclusions: Although AoAC graded on pretransplant CXR has no predictive value on KTx function in 1-year follow-up, it indicates patients with increased cardiovascular risk. Calculated ΔPWV gives additional information about VC in KTx recipients: higher cfPWV than crPWV suggest the greater extent of calcification.

Variable	Coefficient	SE	*p*	OR	95%CI for OR Lower	95%CI for OR Upper
Univariate logistic regression for AoAC (grade1)						
Peripheral mean arterial BP	−0.097	0.042	0.019	9.066–01	0.823	9.745–01
Central mean arterial BP	−0.083	0.040	0.039	0.919	0.838	9.868–01
Calcium concentration one year after KTx	7.413	3.595	0.039	1.658 + 03	3.726	6.738 + 06
ΔPWV	0.455	0.215	0.034	1.577	1.086	2.568
Multivariate logistic regression for AoAC (grade1). Model 1						
Age	0.082	0.046	0.073	1.086	1.001	1.209
ΔPWV	0.499	0.241	0.038	1.647	1.091	2.866
Model 2						
Age	0.150	0.051	0.003	1.162	1.065	1.312
Urea before NTx	−0.154	0.078	0.047	0.856	0.716	0.981
Model 3						
Age	0.143	0.050	0.004	1.153	1.059	1.300
Time on dialysis	0.001	0.0005	0.045	1.001	1.0001	1.002

Clinical Liver Metabolic complications

OS116

IMPACT OF POST-REPERFUSION HYPERGLYCEMIA ON TRANSIENT POST-TRANSPLANTATION HYPERGLYCEMIA AND POST-TRANSPLANTATION DIABETES MELLITUS AFTER LIVER TRANSPLANTATION

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Introduction: Whilst post-transplant diabetes mellitus (PTDM) is thought to be associated with immunosuppressive medication and metabolic syndrome, impact of early hyperglycemia at reperfusion of liver graft received little attention. This study aims to analyse hyperglycemia at reperfusion and search for potential associations with PTDM and graft quality.
Methods: Post-reperfusion glucose levels and insulin need during first 24 h were collected at regular intervals in a prospective database of primary deceased whole liver transplantations (LT) from January-December 2015 at a single institution. Recipients with pre-transplant DM were excluded. On postoperative day (POD) 1 all patients were started on standard triple immunosuppression, with no induction. Following international consensus, sustained hyperglycemia during POD1-45 was defined as 'transient hyperglycemia' (THG). PTDM was diagnosed after POD45 according to established criteria (any one of: (1) non-fasting plasma glucose levels >11.1 mmol/l ≥ 30 days apart, (2) oral hypoglycemic drugs ≥30 days, (3) insulin therapy ≥30 days, (4) HbA1c ≥48 mmol/l). Associations were sought with patient and graft characteristics and outcomes. Follow-up was at least 1 year.
Results: 117 LTs were studied, including 44 donation-after-circulatory-death and 28 grafts preserved on normothermic-machine-perfusion (NMP). Within 1 h post-reperfusion 60 patients (54%) developed hyperglycemia, and 65% within 24 h. While 13% of patients clear post-reperfusion hyperglycemia on POD0, 81 patients (69%) sustained or developed THG. PTDM occurred in 13 patients (12%).
Conclusion: There is a remarkable hyperglycemic peak post-reperfusion of liver grafts, which predicts transient hyperglycemia, but not PTDM. Occurrence of hyperglycemia post-reperfusion may relate to glucose regulatory function of the graft and insulin resistance during preservation.

Clinical Kidney Metabolic complications

OS117 METABOLIC ACIDOSIS AND OUTCOME IN PATIENTS LONG TERM AFTER KIDNEY TRANSPLANTATION

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Department of Nephrology, Transplantation And Internal Medicine, Poland

Background: Metabolic acidosis (MA) frequently occurs in patients after kidney transplantation (KTx). Results of both experimental and clinical studies suggest that MA may contribute to faster progression of chronic kidney disease. It is unknown however whether or not such relationship occurs also in KTx patients. The aim of this clinical, single center, retrospective, observational study was to examine the relationship between MA and both mortality and renal outcomes in patients after KTx.
Methods: Blood HCO_3^- was measured in 486 patients (290 male; 196 female) aged 48 ± 12 years at least one year after KTx and subsequently all patients were observed during 3 years. MA was defined as the blood HCO_3^- concentration less than 22 mmol/l. The endpoints in survival curves analyses were death or initiation of dialysis therapy. In patients who did not reach above mentioned endpoints the difference between final (after 3 years follow-up) and initial eGFR was calculated (eGFR was estimated according to the MDRD formula). Relative risks (RR) were presented with 95% CI.
Results: MA was diagnosed in 57 (12%) patients being long term after KTx. In patients with MA the risks of death or initiation of dialysis therapy was significantly higher than in patients without MA [RR = 4.11 (1.58–10.67), $p = 0.0038$ and RR = 3.58 (3.58–6.32), $p < 0.001$; respectively]. In KTx patients with MA who did not reach above mentioned outcomes blood bicarbonate concentration at baseline correlated positively with change of eGFR values (R = 0.48, $p = 0.002$, $n = 36$). Such correlation was not found in patients without MA ($n = 386$).
Conclusions:

1 MA increases the risk of mortality and worsens graft survival in patients after KTx. 2. The intensity of MA is associated with faster progression of kidney dysfunction in KTx patients.

Clinical Liver Cardiovascular complications

OS118 A SHIFT IN CARDIAC SYMPATHOVAGAL BALANCE TOWARD SYMPATHETIC PREDOMINANCE IS ASSOCIATED WITH A REDUCTION IN THE HEPATIC ARTERIAL BLOOD FLOW OF A PARTIAL LIVER GRAFT DURING THE NEOHEPATIC PHASE

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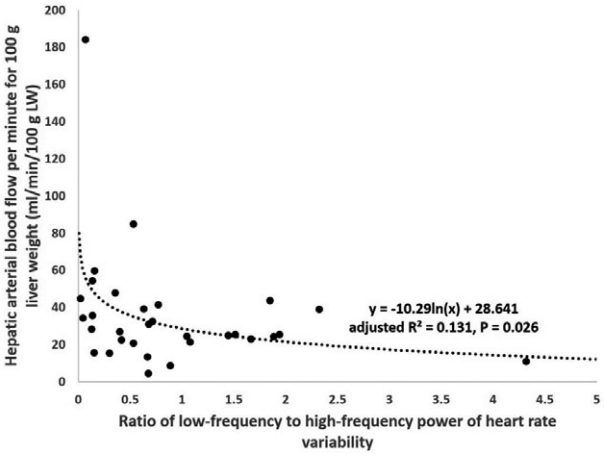
Background: The sympathetic neural pathway which regulates hepatic arterial blood flow (HAF) in a native liver remains lost in a liver graft by the 1st year after liver transplantation. However, in the absence of the hepatic sympathetic nervous system, the effects of systemic autonomic nervous activity on the hepatic hemodynamics of the liver graft have not been elucidated. Therefore, we investigated the relationships between systemic autonomic nervous activity and hepatic blood flow during the neohepatic phase.
Methods/Materials: Thirty one cirrhotic patients undergoing living donor liver transplantation were analyzed. Following reconstruction of the hepatic artery and bile duct, low frequency (LF: 0.04–0.15 Hz), high frequency (HF: 0.15–0.4 Hz) and total powers (<0.4 Hz) of heart rate (HRV) and blood pressure variabilities (BPV) were obtained from power spectral density of 5-min long waveforms using fast Fourier transformation. HF power and the ratio of LF to HF power (LF/HF) of HRV and LF power of BPV represent cardiac parasympathetic activity, cardiac sympathovagal balance, and sympathetic vasomotor control, respectively. Subsequently, hepatic hemodynamic parameters including blood flow of the portal and hepatic veins and hepatic artery per minute for 100 g liver weight were measured using spectral Doppler ultrasonography.
Results: A significant logarithmic regression model between HAF per minute for 100 g liver weight and LF/HF of HRV was observed (adjusted R2 = 0.131, $p = 0.026$: Figure 1). The area under the receiver operating characteristic curve and cut-off value of LF/HF of HRV to predict patients with the HAF less than its median (26.9 ml/min/100 g liver weight) were 0.742 (95% confidence interval [0.562 – 0.921], $p = 0.022$) and 0.83 (sensitivity = 56%, specificity = 87%), respectively.
Conclusion: A shift of cardiac sympathovagal balance toward sympathetic predominance reduces HAF during the neohepatic phase.



Clinical Kidney Cardiovascular complications

OS119 ARE WE OVER-INVESTIGATING LOW RISK KIDNEY TRANSPLANT CANDIDATES PRIOR TO LISTING?

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Introduction: As comorbidity in transplant candidates increases, so does the number of pre-listing investigations. We studied the work-up of low risk kidney transplant candidates in the UK as part of the national ATTOM study.
Methods: 1852 patients on the kidney transplant waiting list were recruited between 2011–13 from all 23 UK transplant centres. Low risk patients were defined as aged 18–40 years with no history of diabetes, cardiac disease or vascular disease at the time of listing for first kidney transplant. The proportion of low risk patients undergoing work-up investigations was analysed and compared between centres.
Results: 269 patients (14.5%) fulfilled the low risk criteria. of these, 61.3% underwent echocardiogram, 11.5% stress echocardiogram, 19.7% exercise tolerance test (ETT), 2.6% myocardial perfusion imaging (MPI), 1.1% coronary angiogram, 12.3% carotid doppler and 18.6% lower limb doppler. 88 patients (32.7%) were listed without any of the above cardiovascular investigations, however 43.1% underwent one investigation and 24.2% underwent at least two investigations. There was significant variability in the cardiovascular work-up of low risk patients between the 23 transplant centres (Table 1). The median number of investigations for low risk patients varied from 0 to 5 between centres.

Investigation	Centre variation range (% of low risk patients undergoing investigation)	*p*-value
Echocardiogram	0–100	<0.0001
ETT	0–96.2	<0.0001
Stress echocardiogram	0–100	<0.0001
Carotid doppler	0–92.3	<0.0001
Lower limb doppler	0–92.3	<0.0001

Conclusions: Despite the absence of cardiovascular comorbidity, a significant proportion of low risk patients undergo potentially unnecessary investigations, and this varies significantly between centres. A more restricted set of investigations agreed as the standard work-up for low risk patients in all centres may reduce costs, workload and facilitate more timely listing.

Clinical Kidney Metabolic complications

OS120 SHORT TERM SAFETY OF EMPAGLIFLOZIN IN LONG TERM STABLE RENAL TRANSPLANT RECIPIENTS WITH POST TRANSPLANTATION DIABETES MELLITUS

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Oslo University Hospital Rikshospitalet Department of Transplantation Medicine, Norway

Background: Development of post transplantation diabetes mellitus (PTDM) in renal transplant recipients (RTRs) is associated with increased cardiovascular risk and impaired patient survival. Sodium-glucose co-transporter 2

inhibitors (SGLT2i) are a novel drug class for the treatment of diabetes, and the SGLT2i empagliflozin improved both renal and cardiovascular outcomes in patients with type 2 diabetes and established cardiovascular disease. We aim to evaluate whether empagliflozin (Jardiance®) safely and effectively improves glucose metabolism in RTRs with PTDM.
Methods: This is a prospective, placebo controlled, double-blind, randomized study. A total of 50 RTRs diagnosed with PTDM is being included >1 year after transplantation and randomized 1 : 1 to empagliflozin 10 mg or placebo once daily for 24 weeks. Patients with eGFR <30 mL/min/1.73 m^2 will be excluded. Oral glucose tolerance test, 72 h continuous glucose monitoring (iPro™2), measurement of arterial stiffness, body composition (visceral fat), 24 h blood pressure and 24 h urinary glucose excretion will be performed at baseline and after 24 weeks in addition to standard safety measurements. Two safety visits will be performed at week 8 and 16.
Results: This is an ongoing trial and this abstract shows baseline and 8 weeks safety data. So far 20 patients are included, mean age 59.2 ± 11.0 years (14 males/6 females) studied 5.0 ± 4.5 years after transplantation. 10 patients are through the 8 week safety visit. No serious adverse events have been reported, but moderate hypoglycemia (plasma glucose between 2.0 and 3.9 mmol/l) is observed in one patient on concomitant sulphonylurea and dipeptidyl peptidase-4 inhibitor treatment. Since this study is double-blinded, there are currently no comparable results between groups. Preliminary results (mean ± standard deviation) are shown in Table 1.

	BASELINE (n = 20)	8 WEEKS (n = 10)	p value (n = 10)
BMI (kg/m^2)	30.7 ± 5.6	29.2 ± 5.2	0.12
Fasting plasma glucose (mmol/l)	8.0 ± 2.2	7.6 ± 1.1	0.09
Systolic blood pressure (mmHg)	137 ± 12	133 ± 16	0.21
Diastolic blood pressure (mmHg)	78 ± 7	80 ± 8	0.87
eGFR (ml/min/1.732) CKD-EPI formula	62.9 ± 11.9	62.2 ± 10.8	0.24
Through (C0) concentration of immunosuppressive drugs			
Tacrolimus (μg/l, n = 13)	5.8 ± 1.6	5.7 ± 1.6	0.49
Cyclosporine (μg/l, n = 5)	94 ± 18	111 ± 38	0.19
Everolimus (μg/l, n = 2)	8.1 ± 2.7	–	–
Mycophenolate (mg/l, n = 20)	1.8 ± 1.0	3.0 ± 3.8	0.26

Conclusion: Preliminary results indicate that the use of empagliflozin is safe in RTRs with PTDM.

Basic Others Ischemia-reperfusion and preservation

OS121 CYTOTOPIC THROMBIN INHIBITION ATTENUATES MICROVASCULAR ENDOTHELIAL ISCHAEMIA-REPERFUSION INJURY

Bynvant Sandhu[1], Josefin Ahnstroem[2], Jim Crawley[2], Maria Prendecki[2], Neil Galloway-Phillips[2], Justin Mason[2], Tony Dorling[3], Richard Smith[3], Charles Pusey[2], Vassilios Papalois[2]

[1]Imperial College - Hammersmith Hospital, United Kingdom; [2]Imperial College London, United Kingdom; [3]King's College London, United Kingdom

Background: Microvascular endothelial susceptibility to ischaemia- reperfusion (IR) injury affects outcomes in all solid organ transplants. Thrombin generation post-reperfusion of the ischaemic endothelium may be implicated in cellular activation and increased permeability due to cytoskeletal derangement, manifesting as cellular necrosis and enhanced endothelial permeability. We examined the effect of endothelial pre-treatment with a novel, cytotopic direct thrombin inhibitor (Thrombalexin) on cellular injury.
Methods: Thrombin inhibition efficacy by Thrombalexin was measure using a fluorogenic thrombin generation assay (Thrombinoscope B.V). Human microvascular endothelial cells (HMECs) were used in an *in vitro* model of ischaemia-reperfusion injury. Cellular apoptosis and necrosis were assessed using Annexin V/Propidium Iodide staining on flow cytometry. Endothelial permeability was assessed by measuring Fluorescein isothiocyanate-dextran passage through HMECs seeded on semi-permeable Transwell inserts.
Results: Thrombalexin (1 μM, 2 μM) treated plasma resulted in an increase in the lag time (clotting time) and a reduction in the endogenous thrombin potential compared to untreated plasma. 10 μM Thrombalexin treated plasma reduced thrombin generation to near zero. Pre-treatment with Thrombalexin prior to cold storage reduced the percentage of Annexin V/PI positive cells (p = 0.0287). Annexin V/PI negative cell percentages increased in Thrombalexin treated cells (0.47% to 14.4% respectively, p = 0.0007). IR injury resulted in a significant increase in endothelial permeability compared to resting conditions (119 vs. 36 Mean Relative Fluorescence Units respectively, p = <0.0001). Pre-treatment of the microvascular endothelium prior to cold ischaemia with Thrombalexin abrogated this effect (p = <0.0001).
Discussion: Pre-treatment with cytotopic thromboregulation effectively protects the microvascular endothelium from deleterious reperfusion injury.

Basic Liver Ischemia-reperfusion and preservation

OS122 HYDROGEN PERFUSION AFTER COLD STORAGE; A NEW, SIMPLE, AND NON-INVASIVE GRAFT CONDITIONING FOR AMELIORATING HEPATIC ISCHEMIA/REPERFUSION INJURY?

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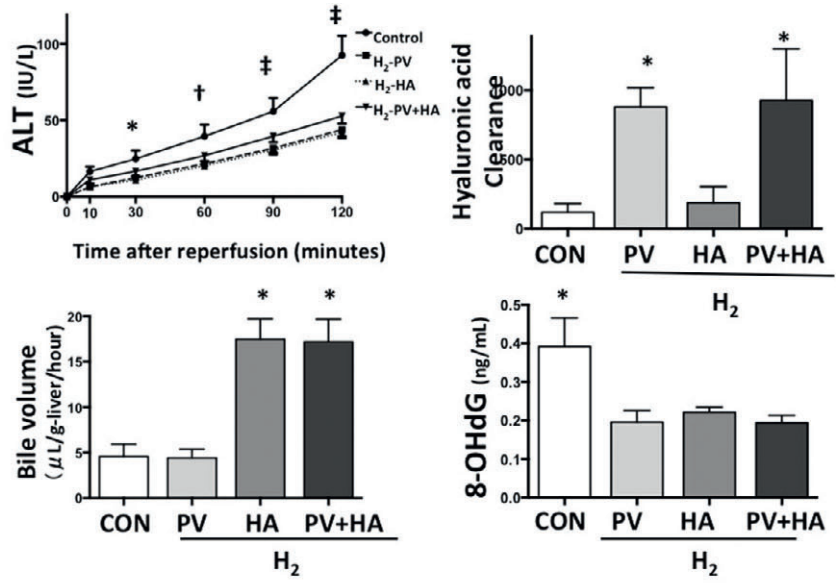
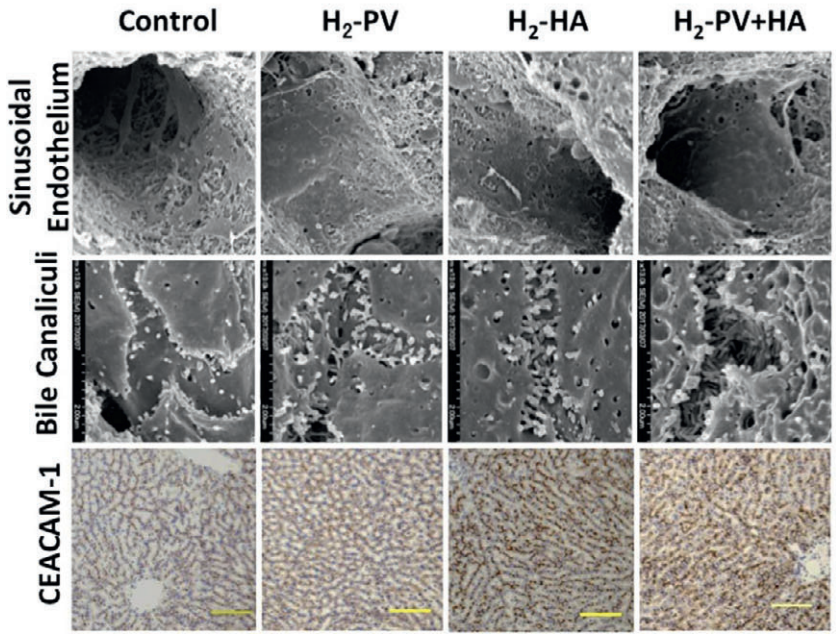
Background: Cold-ischemia/warm-reperfusion injury (IRI) has long been a critical issue in organ preservation. Hydrogen is ubiquitous gas having anti-oxidative properties, whereas its application in organ preservation has not yet been established.
Methods: Whole liver grafts were retrieved from male Wistar rats. After 24-h cold storage (CS), hydrogen solution (1.0 ppm, 40 ml) was simply perfused *ex vivo* via portal vein, or hepatic artery, or the both. Functional integrity of the livers was then evaluated by 2-h oxygenated reperfusion *ex vivo* at 37°C.
Results: Hydrogen perfusion after cold storage (HyPACS) significantly lowered transaminase (p < 0.01) and HMGB-1 (p < 0.0001) release than in vehicle-treated livers. Portal and arterial HyPACS both significantly reduced portal-venous pressure (p < 0.0001). of interest, portal HyPACS improved hyaluronic-acid clearance than in the others (p < 0.01), indicating the efficacy of HyPACS, as well as the superiority of portal-vein route to maintain sinusoidal endothelium. In contrast, arterial HyPACS significantly ameliorated bile production and LDH leakage therein (p < 0.01), reflecting the superiority of arterial route to preserve the integrity of biliary systems. Consistently, electron microscopy revealed that sinusoidal ultra-structures were well-maintained by portal HyPACS, while microvilli in bile canaliculi were well-preserved by arterial HyPACS. Immunohistochemistry for carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM-1) demonstrated significantly-maintained stainability of bile canaliculi (p < 0.001) by arterial HyPACS. Oxidative-stress markers, TBARS, 8-OHdG, and total glutathione, were all significantly attenuated by HyPACS (p < 0.01).
Conclusions: HyPACS protected liver grafts from IRI by alleviating oxidative damages, in the characteristic manner with its route of administration. Given its safety and simplicity, HyPACS may be a novel therapeutic treatment for alleviating preservation/reperfusion injury.





OS123

PROTECTIVE EFFECT OF CODIUM FRAGILE EXTRACT (FUCOIDAN) PRETREATMENT AGAINST HEPATIC ISCHEMIA-REPERFUSION INJURY IN MICE

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Background: Fucoidan is a complex of sulfated polysaccharides derived from marine brown seaweeds, One of marine algae is codium fragile (CF). Fucoidan demonstrated antiapoptotic as well as potential anti-inflammatory properties. Ischemia-reperfusion injury (IRI) is a major critical event that commonly occurs after liver transplantation and resection. In this study, we investigated whether CF protects against IR-induced acute liver injury in mice.
Materials and Methods: Partial (70%) hepatic IRI was induced in male C57BL/6 mice by portal triad pedicle occlusion for 45 min followed by reperfusion for 6 h. CF (500 mg/kg body weight [BW], oral) was administered 5 days before the IRI.
Results: Treatment with CF significantly decreased serum alanine aminotransferase (sALT), serum aspartate aminotransferase (sAST) and serum lactate dehydrogenase (LDH) as well as liver histological changes. CF also prevented hepatic glutathione (GSH) depletion and increased malondialdehyde (MDA) levels induced by IRI. Western blotting indicated that CF significantly increased the levels of Bcl-2, attenuated BAX, PRAP and caspase3 after IRI. The expression of the C-JUN, P38, iNOS and NFkB were significantly decreased in the CF treatment group.
Conclusion: CF improved the acute hepatic IRI by reducing oxidative damage, inflammation and apoptosis. These findings suggest that CF is a promising agent against acute IR-induced hepatic damage.

OS124

EFFECTS OF HUMAN LIVER STEM CELLS-DERIVED EXTRACELLULAR VESICLES ON HYPOXIC INJURY IN AN *EX VIVO* NORMOTHERMIC RAT LIVER PERFUSION MODEL

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Background: The gold standard for liver preservation is hypothermia induced by icy solutions. However, static cold storage is unable to fully protect the graft from ischemia/reperfusion injury. An emerging alternative is normothermic machine perfusion (NMP) which provides a basis for pharmaceutical interventions during the preservation phase. Human Liver Stem Cells (HLSC) are liver-resident pluripotent stem-like cells with regenerative and hepatoprotective properties, and Extracellular Vesicles (EV) derived from HLSC are able to mimic most of the HLSC effects, by transferring proteins, mRNAs and micro-RNAs.
Methods/Materials: To investigate the feasibility and efficacy of a protective strategy using HLSC-EV, we set up a murine model of NMP capable to maintain liver function in the presence of an ongoing hypoxic injury induced by a low hemoglobin content in the perfusate. Rat livers were perfused *ex vivo* via the NMP circuit for 4 h with (n = 9) or without (n = 10) HLSC-EV. Perfusate samples were collected every hour to measure cytolysis (AST, ALT, LDH), metabolic parameters (pH, pO2, pCO2) and bile production.
Results: During experiments, all livers were able to maintain homeostasis and produce bile. In the treated group, fluorescence microscopy confirmed the uptake of HLSC-EV within hepatic tissue by the end of perfusion. Compared with controls, livers perfused with HLSC-EV released significantly less cytolysis enzymes at 3 h (AST: 47 $\pm$ 7 U/l/g vs. 92 $\pm$ 14 U/l/g, p = 0.018; LDH: 340 $\pm$ 47 U/l/g vs. 619 $\pm$ 104 U/l/g, p = 0.032) and at 4 h (AST: 80 $\pm$ 14 U/l/g vs. 134 $\pm$ 20 U/l/g, p = 0.003). Tissue analyses demonstrated a significant reduction in necrosis (Suzuki score: 3.9 $\pm$ 0.4 vs. 5.7 $\pm$ 0.6, p = 0.030) and apoptosis (apoptosis index: 0.06 $\pm$ 0.01 vs. 0.14 $\pm$ 0.03, p = 0.049) in the treated group.
Conclusion: These preliminary data suggest that the association of HLSC-EV with NMP could represent a promising strategy for graft treatment before transplant surgery, deserving further investigations.

Clinical Liver Ischemia-reperfusion and preservation

OS125

36 HOURS OF *EX-VIVO* WARM CELLULAR PERFUSION OF SWINE LIVER USING THE ORGAN CARE SYSTEM (OCS™) LIVER WITH EXCELLENT FUNCTIONAL, METABOLIC AND HISTOLOGICAL OUTCOMES

Joseph Magliocca[1], James Markmann[2], Marwan Abouljoud[3], Mark Ghobrial[4], Anthony Demetris[5]

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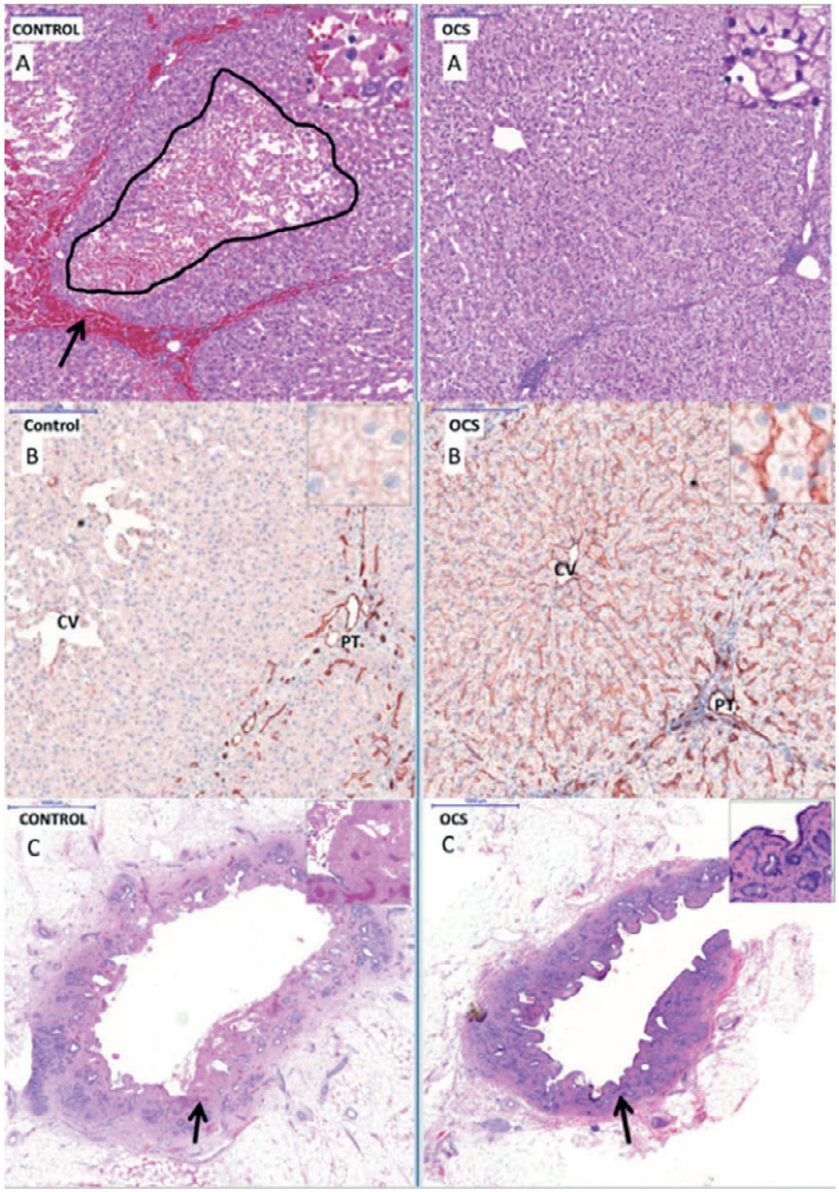
Cold storage preservation results in ischemia/reperfusion injury to the donor liver, it lacks any resuscitative or assessment capabilities. The OCS™ Liver maintains livers in a metabolically active and functioning state using warm, oxygenated, blood perfusion of both the hepatic artery and portal vein circulations.
Methods: We randomized 6 swine livers to 12 h of cold storage using Viaspan (Control) vs. 12 h of OCS Liver perfusion (OCS), followed by 1 h of cold flush and 24 h of simulated transplantation using OCS Liver perfusion primed with fresh whole blood from a different swine. We compared the metabolic, functional and histological outcomes between both groups.
Results: The mean cold ischemic time (CIT) for Control was 809 $\pm$ 1.5 min, and 106 $\pm$ 3.8 min for OCS. During the 24 hr simulated transplant phase the average peak AST level for Control was 1197 $\pm$ 597, and 94 $\pm$ 28 for OCS. Bile production was maintained at an average rate of 20 ml/h in both groups. Pathological assessment at the end of 24 hr simulated transplant showed moderate to mild hepatocyte necrosis in Control compared to minimal to none in OCS (Fig. 1A). CD31 stain to assess LSEC damage demonstrated intact sinusoidal endothelial cells in OCS compared to Control (Fig. 1B). Extra-hepatic bile duct assessment in Control demonstrated deeper and more extensive arterial thrombosis/necrosis and bile duct necrosis than OCS (Fig. 1C).
Conclusion: Livers maintained for 36 h *ex-vivo* perfusion on OCS had excellent post-transplant hepatocellular, hepatobiliary, metabolic and synthetic functions compared to cold storage in a 24 h of simulated transplantation swine model.



Clinical Others Ischemia-reperfusion and preservation

OS126

DYNAMIC TEMPERATURE RANGE MEASUREMENT OF THE ABDOMINAL ORGANS DURING DCD AND DBD PROCUREMENT IN COMBINATION WITH THORACIC ORGAN HARVESTING (REWARMING - WE ARE NOT EXPECTING THAT TO HAPPEN)

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Department of Abdominal Surgery And Transplantation Hopital Erasme Ulb, Belgium

Background: Donor organ procurement using low-temperature preservation is standard procedure in the use of organs from brain death donors (DBD) and donation after cardiac death (DCD). The normo-hypothermia during the procurement have well known shortcuts which affect the transplant organs. A fluctuation of the cooling and rewarming can be a negative factor. There is not much information about dynamic range of the organ temperature (T°) during organ procurements
Methods: The rectal donor T°(RDT), abdominal organ T°(AOT) and the T° of flash-out IGL-1 solution (FPST) were measured in DCD and DBD with/without thoracic organ harvesting. Thermal imaging of FLIR One and TESTO 885 cameras were acquired during procurements, back table preparations and packaging, visualized in real time and stored for analysis

Results: The violation of the cooling curves and rewarming were observed during all types of the procurements of all organs. At the end of the harvesting T° curves of all organs were increasing (tab.) Thoracic organ harvesting interferes the T° of the all abdominal organs enhancing rewarming. The cooling of the organs is not homogeneous. The liver strives to increase its T° faster than other organs. The constant declining of the abdominal organ T° was not observed in any donors. In DCD and DBD the mean RDT; and FPST was, respectively, 26.2 ± 4.4°C/19.8 ± 5.6°C and 22 ± 6.2/15.8°C
Conclusions: Common procurement technics have no control of the T° of the donor body and abdominal organs and required cooling equation

The abdominal organ T° remains much higher than presumed. Moreover, during all procurements the cycles of rewarming and cooling of the abdominal organs were registered supposing an adverse effect on transplant quality

Thoracic organ procurement depraves the hypothermic protection of abdominal organs because the first done

For adequate hypothermic protection, the T° control of the donor /abdominal organs is required to measure the exact volume of the cooling liquid and the ice splash

Translational Liver Ischemia-reperfusion and preservation

OS127 DNA METHYLATION PATTERN INFLUENCES SEVERITY OF ISCHEMIA-REPERFUSION INJURY AFTER LIVER TRANSPLANTATION

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Background: At transplantation, severity of graft injury depends on mechanisms and pathways, controlled in part by dynamic changes in epigenetic modifications that affect gene expression (GE) and response to the hypoxia. This study aimed to assess the effect of global DNA-methylation (DNAm) on GE changes leading to differential hepatic injury after liver transplantation (LT).
Method: Paired liver graft biopsies ($n = 74$) collected at pre- and post- LT were categorized based on graft response as severe (SI, AST/ALT >500 IU/l) and mild injury (MI, AST/ALT<500 IU/l) at 48 h post-LT. Simultaneous evaluation of DNAm and GE was done in the paired biopsies (Illumina Infinium 450K methylation arrays and GeneChip® HG-U133A v2.0, respectively). Raw data was analyzed using Bioconductor packages *minfi* (scanned DNAm arrays); oligo (scanned GE arrays) and Genome Runner for enrichment analysis. A FDR<10% was considered significant.
Result: Differentially methylated (Dme) mapped to 4641 and 448 CpG sites in MI and SI subgroup respectively. GE profiling of the same samples showed activation of 998 genes unique to SI group, mainly associated to hypoxia, angiogenesis, hepatic fibrosis, and inflammation, IL6 signaling; and 101 genes unique to MI involved in PXR\RXR activation, xenobiotic metabolism and cell-cell interaction. Integrated analysis of DNAm and GE data further differentiated MI vs. SI groups, with genes involved in cell-cycle progression and mechanism of cancer to SI profile and 218 unique genes involved anti apoptosis, immune response, early cellular stress response, ubiquitin proteasome system, and DNA repair in MI group. Predicted target mRNAs of several Dme micro-RNA genes also correlated to GE data in both SI and MI grafts.
Conclusion: Epigenetic changes appear to play a key role in governing pathways involved in mechanisms of IRI, mainly through activation or silencing of key genes and pathways such as anti-apoptosis, immune response, and early cellular stress response

OS128 IMPACT OF GRADED STEATOSIS ON THE *EX-VIVO* MACHINE PERFUSION PARAMETERS OF DONOR LIVERS USING A COMPREHENSIVE PROTOCOL OF PERFUSION TECHNIQUES

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Background: Steatosis is a common reason for donor livers declining due to diminished tolerance to ischemic reperfusion injury with high risk of primary non-function. Impaired microcirculation and low energy stores are mainly associated with this susceptibility in the literature. We aimed to study the behaviour of different grades of fatty steatosis during the *ex-vivo* machine perfusion.

Methods: Six discarded human donor livers were subjected to a protocol of 2 h dual vessel hypothermic oxygenated perfusion, 1 h of controlled oxygenated rewarming and then 3 h of normothermic machine perfusion using a bovine haemoglobin based oxygen carrier throughout. Livers were categorised as none/mild steatosis ($n = 2$), moderate steatosis ($n = 2$) or severe steatosis ($n = 2$) and perfusion parameters analysed in across groups using two-way ANOVA.
Results: Severely steatotic livers had a significantly higher hepatic arterial resistance over the course of the perfusion ($p < 0.001$), lower flows in both the hepatic artery ($p < 0.001$) and portal vein ($p < 0.001$). Additionally, oxygen consumption was higher in this last group along the perfusion ($p = 0.001$). Functional parameters on machine deteriorated according grading of steatosis; lactate clearance was delayed for moderate steatosis livers and kept increasing for severe fatty livers ($p < 0.001$) and similar patterns were seen for glucose consumption.
Conclusion: Steatosis was associated on the *ex-vivo* machine perfusion with higher vascular resistance, diminished flows and this was related to the degree of steatosis. These finds result in worsening of liver functional parameters accordingly and it brings evidence that fatty livers could benefit from additional therapeutic intervention during the perfusion process.

Clinical Kidney Other

OS129 TOWARD ESTABLISHING CORE OUTCOME DOMAINS FOR TRIALS IN KIDNEY TRANSPLANTATION: REPORT OF THE STANDARDIZED OUTCOMES IN NEPHROLOGY - KIDNEY TRANSPLANTATION (SONG-TX) CONSENSUS WORKSHOPS

Allison Tong[1], John Gill[2], Klemens Budde[3], Lorna Marson[4], Peter Reese[5], Lionel Rostaing[6], David Rosenbloom[7], Germaine Wong[1], Michelle Josephson[8], Timothy Pruett[9], Anthony Warrens[10], Jonathan Craig[1], Benedicte Sautenet[1], Nicole Evangelidis[1], Angelique Ralph[1], Camilla Hanson[1], Jenny Shen[11], Kirsten Howard[1], Klemens Meyer[12], Ronald Perrone[12], Daniel Weiner[12], Samuel Fung[13], Maggie Ma[14], Caren Rose[2], Jessica Ryan[15], Ling-Xin Chen[8], Martin Howell[1], Angela Ju[1], Siah Kim[1], Sobhana Thangaraju[16], Nicholas Larkins[1], Jeremy Chapman[17]
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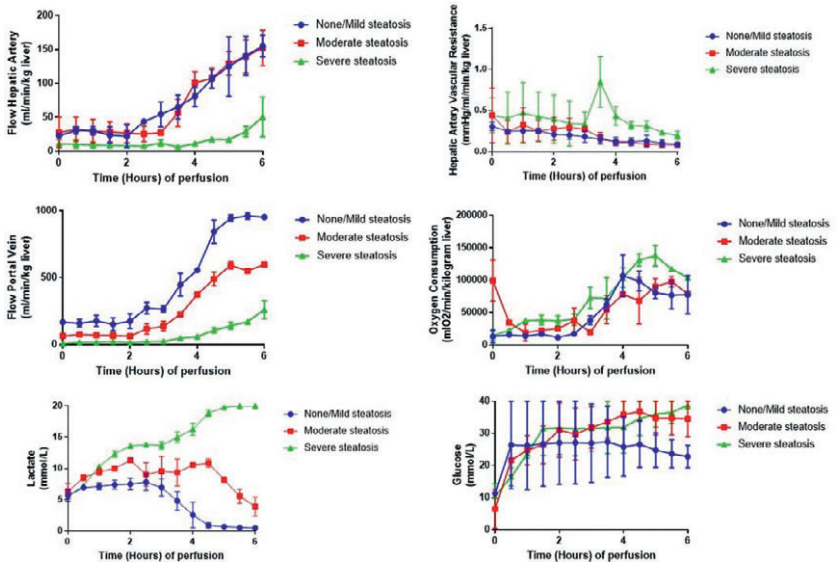
Background: Treatment decisions in kidney transplantation requires patients and clinicians to weigh the benefits and harms of a broad range of medical and



surgical interventions, but the heterogeneity and lack of patient-relevant outcomes across trials in transplantation makes these trade-offs uncertain; thus the need for a core outcome set that reflects stakeholder priorities.
Methods: We convened two international SONG-Kidney Transplantation stakeholder consensus workshops in Boston (17 patients/caregivers; 52 health professionals) and Hong Kong (10 patients/caregivers; 45 health professionals). In facilitated breakout groups, participants discussed the development and implementation of core outcomes for trials in kidney transplantation.
Results: Seven themes were identified. *Reinforcing the paramount importance of graft outcomes* encompassed the prevailing dread of dialysis, distilling the meaning of graft function, and acknowledging the terrifying and ambiguous terminology of rejection. *Reflecting critical trade-offs* between graft health and medical comorbidities was fundamental. *Contextualizing mortality* explained discrepancies in the prioritization of death among stakeholders – inevitability of death (patients), preventing premature death (clinicians), and ensuring safety (regulators). *Imperative to capture patient-reported outcomes* was driven by making explicit patient priorities, fulfilling regulatory requirements, and addressing life participation. *Specificity to transplant*; *feasibility and pragmatism* (long-term impacts and responsiveness to interventions); and *recognizing gradients of severity* within outcome domains were raised as considerations.
Conclusion: Stakeholders support the inclusion of graft health, mortality, cardiovascular disease, infection, cancer, and patient-reported outcomes (i.e. life participation) in a core outcomes set. Addressing ambiguous terminology and feasibility is needed in establishing these core outcome domains for trials i

Clinical Kidney Allocation

OS130 DECEASED DONOR KIDNEY TRANSPLANTATION IN ELDERLY RECIPIENTS. OUTCOMES AFTER LISTING AND TRANSPLANTATION IN PATIENTS AGED 70 YEARS AND OLDER

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Background: The number of patients aged ≥70 years receiving renal replacement therapy is increasing. There is uncertainty regarding whether listing for deceased donor kidney is appropriate in this age group, and if outcomes post-transplant are acceptable.
Methods: UK transplant registry data from Jan 2005 – Dec 2013 were analysed. Outcomes of patients aged ≥70 years at listing were compared with those aged 60–69. In a second analysis, post-transplant outcomes were compared in those aged ≥70 years at time of transplantation with those aged 60–69 years.
Results: During the study period 4739 patients aged ≥60 years were listed; 20.3% were ≥70 years old. By 2016, 42.1% of the older cohort had been transplanted but 50.3% had been removed or died on the list. Over the same period, 3261 patients aged ≥60 years underwent transplant; 22% of them were aged ≥70 years. Elderly recipients were more likely to receive a kidney from an older donor ($p < 0.001$), or a dual transplant (7.2% vs. 4.1%; $p < 0.001$). There were no significant differences in proportions of DCD donors, graft CIT, recipient ethnicity, or cRF. Graft outcomes were similar, with no significant differences in rates of PNF (2.9% vs. 3%), rejection within 3 months (9.1% vs. 7.9%), graft function at 1, 3, or 5 years, or death-censored graft survival up to 10 years ($p = 0.27$). Patient survival was worse in the elderly group ($p < 0.001$) and more had died with a functioning graft by the end of follow-up (20.6% vs. 15.2%; $p < 0.001$).
Conclusions: More than half of elderly patients listed for kidney transplant are removed or die on the list. Elderly recipients have similar graft function and death-censored graft survival post-transplant to those aged 60–69 years at transplantation. Patient survival is worse but higher proportion dies with a functioning graft. National organ allocation scheme should be altered to enable matching graft survival with recipient life expectancy

Clinical Kidney Other

OS131 CLINICAL VARIABLES ALONE ARE NOT ENOUGH TO RELIABLY PREDICT UNFAVOURABLE TRANSPLANT OUTCOME OTHER THAN DELAYED GRAFT FUNCTION

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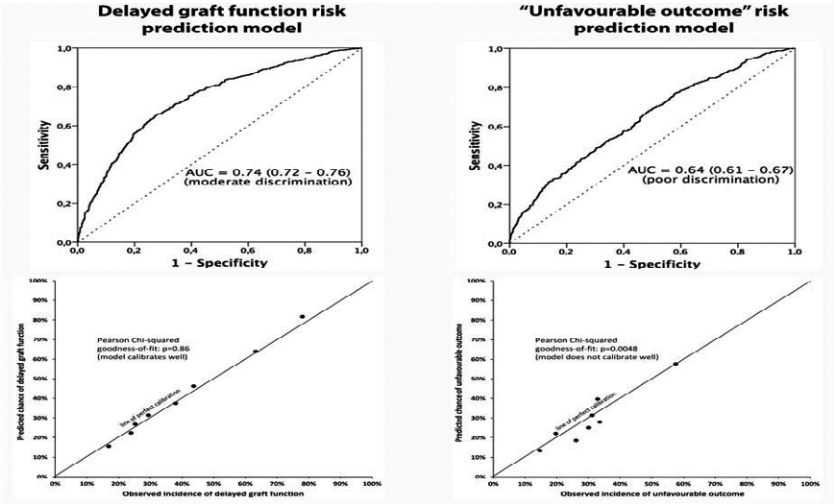
Introduction: With an ageing deceased donor pool and associated marginal renal grafts, objective tools to better predict post-transplant outcome are urgently needed. Current risk prediction models for delayed graft function (DGF) are notoriously unreliable, with c-statistics usually under 0.7 and poor calibration. In addition, DGF may not be the most relevant outcome measure to predict. We composed two new clinical risk prediction models for renal grafts recovered from aged deceased donors and studied their reliability.
Methods: Data from the Dutch Organ Transplantation Registry were used. We selected all renal transplants carried out between 01-01-2000 and 31-12-2015, from deceased donors aged ≥50 ($n = 3505$). Donors were either DBD ($n = 2052$) or controlled DCD ($n = 1453$). Half these data were used to construct prediction models (incorporating 21 donor and recipient variables) for the risk of DGF and the risk of "unfavourable outcome", defined as graft failure or death within 1 year, or an eGFR < 30 ml/min at 1 year post-transplant. With the other half of the data set, both models' discrimination was assessed by the area-under-the-receiver-operator-curve (c-statistic) and their calibration was assessed with the Hosmer–Lemeshow (HL) goodness-of-fit test and a calibration plot.
Results: The c-statistic for the DGF risk model was 0.74 (95% CI 0.72–0.76), indicating moderate discrimination. The calibration plot and HL-test ($p = 0.86$) showed good calibration. The c-statistic for the "unfavourable outcome" risk model was 0.64 (95% CI 0.61–0.67), indicating poor discrimination. The calibration plot and HL-test ($p = 0.0048$) showed poor calibration (see figure).
Conclusion: DGF could be predicted reasonably well for deceased 50 + donor kidneys, but other, more relevant unfavourable outcome could not be reliably predicted with clinical variables alone. Adding histology data, machine perfusion parameters and serum/urine biomarkers could be a strategy to improve predictivity of such models.



OS132 CAUSES AND PREDICTIVE FACTORS FOR KIDNEY GRAFT FAILURE AT ONE YEAR FOLLOWING RENAL TRANSPLANTATION: A MULTICENTER ANALYSIS ON 10 YEARS ON 179 CASES

Gauthier Flahaut[1], Pierre-François Westeel[1], Marc Hazzan[2], Christian Noël[2], Isabelle Etienne[3], Dominique Bertrand[3], Philippe De Sousa[1], Gabriel Choukroun[1]

[1]Amiens University Hospital, France; [2]Lille University Hospital, France; [3]Rouen University Hospital, France

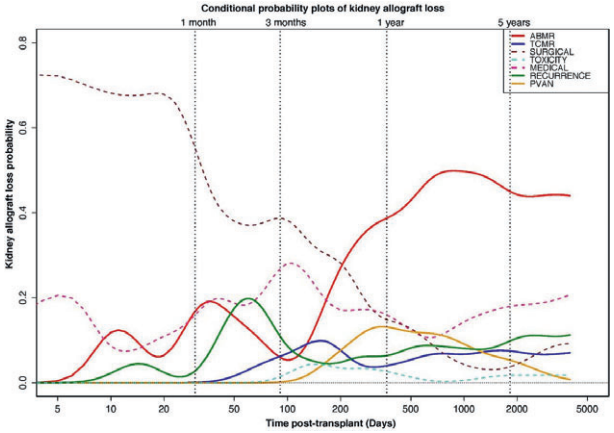
Background: Expanded criteria donors and older recipients have increased the risk of kidney transplantation failure at one year. The aim of this study was to describe the causes of graft failure and to determine predictive factors in a large population of kidney transplant recipients.
Patients and Methods: This case-control, multicenter study was conducted in 3 transplant centers between 2005 and 2014. All recipients of cadaveric kidney with a failed renal transplant during the first year were compared to a control population matched 1 : 1 for the time of transplantation and the center. Data were collected from the individual files of the patients. Predictive factors of graft failure were determined using a binary logistic regression model.
Results: During the time of the study, 144 returns to dialysis and 35 deaths occured during the first year of the transplantation. Returns to dialysis were mainly caused by vascular thrombosis (34%), acute rejection (23%), and primary non-function (9%). Half of the deaths were due to infection. The donor's data associated with an increased risk of failure, were death by hemorrhagic stroke (OR = 2.65, CI95% [1.54–4.57], $p = 0.01$) and body mass index >25 kg/m^2 (OR = 1.83, CI95% [1.05–3.19], $p = 0.03$). Recipients with a history of ischemic stroke were exposed to an increased risk of failure (OR = 4.78, CI95%[1.00–23.11] $p = 0.05$). After surgery, post-operative bleeding (OR = 3.94, CI95% [1.73–8.98], $p < 0.01$), urinary anastomotic leakage (OR = 4.48, CI95% [1.03–19.50], $p = 0.04$) predicted a higher risk of graft failure. The use of tacrolimus vs. cyclosporine appeared protective (OR = 0.34, CI95%[0.18–0.62], $p < 0.01$). The technic of dialysis prior of transplantation, cold ischemia and anastomotic times had no influence on the short-term prognosis.
Conclusion: Avoiding early failure after surgery remains an ongoing challenge. Identification of predictive factors may help to monitor high-risk cases and to improve short-term outcomes of renal transplantation.

OS133 DECIPHERING THE SPECIFIC CAUSES OF KIDNEY ALLOGRAFT LOSS: A POPULATION BASED STUDY

Charlotte Loheac[1], Olivier Aubert[1], Jean-Paul Duong Van Huyen[1], Nassim Kamar[2], Michel Delahousse[1], Denis Glotz[1], Christophe Legendre[1], Carmen Lefaucheur[1], Alexandre Loupy[1]

[1]Paris Translational Research Center For Organ Transplantation, France; [2]Toulouse Hospital, France

Background: Understanding the specific causes of kidney allograft loss are mandatory to improve the longevity of allografts. However, the current literature is limited by the low level of phenotyping, small series with selected populations or data from registries that lack precision diagnoses.
Methods: We conducted a multicentric prospective study including unselected kidney transplant recipients from 4 referral centers transplanted between 2004 and 2014. Donor, recipient, transplant parameters, clinical and biological post-transplant parameters as well as circulating anti-HLA DSA and allograft biopsies performed post-transplant were included. The main outcome was long-term kidney allograft survival and specific causes of graft loss.



Results: 4783 kidney recipients were included and 9959 kidney allograft biopsies were analyzed. During a median follow-up post-transplant of 4.51 years, 732 graft losses occurred. After inclusion of biopsy, clinical, biological, and anti-HLA DSA data, a primary cause of allograft loss was identified in 95% of cases. The causes were: immune related (31.7% of antibody-mediated rejection (ABMR), 4.8% of T-cell mediated rejection), surgical related (25.6% of thrombosis, 2.5% of urinary disease), medical related (tumoral, infectious or cardiac intercurrent disease (14.6%)), recurrence of primary disease (7.1%), virus related (BK or CMV associated nephropathy, 4.78%) and calcineurin inhibitor nephrotoxicity related (1.1%). ABMR was associated with the worse allograft survival (55% at 9 years). Conditional probability plots give the dynamic range of graft loss causes with time (Figure 1).
Conclusion: In this multicentric extensively phenotyped population of kidney transplant recipients, we identify the contemporary picture of specific causes of kidney allograft loss. Such effort highlights the current priorities to detect such complications to improve long-term allograft outcomes.

Translational Kidney Other

OS134 URINARY AND KIDNEY GRAFT PECS: NEW PROGNOSIS MARKER FOR GRAFT OUTCOME

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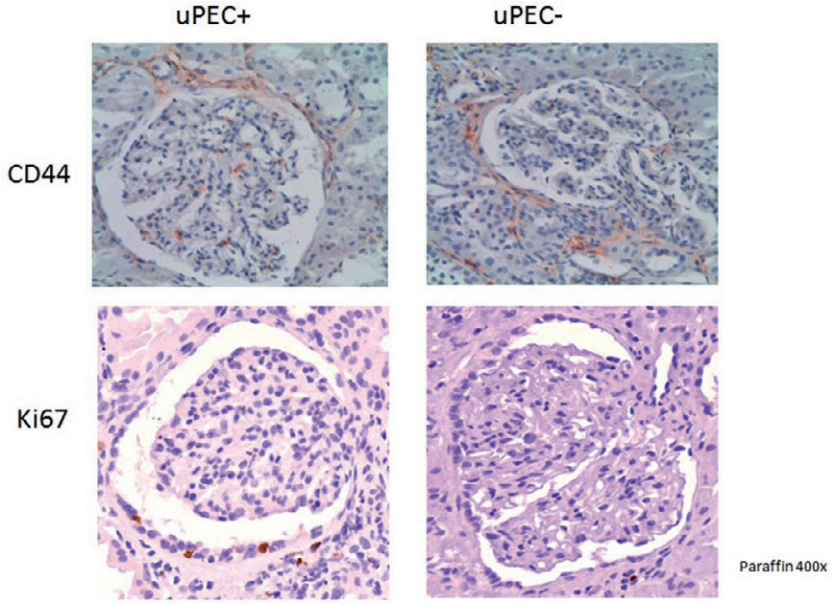
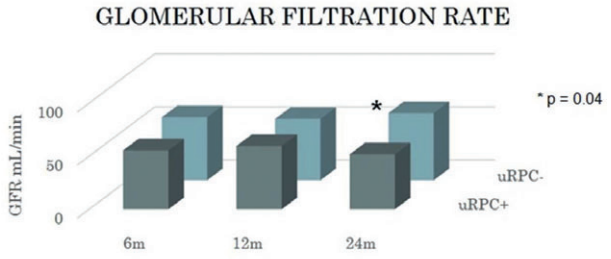
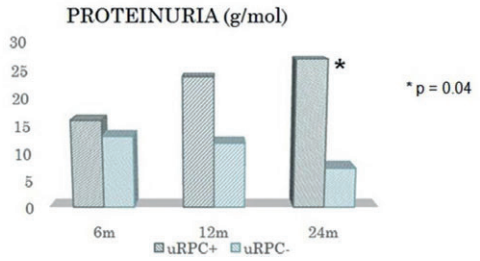
Background: Main knowledge of kidney allograft (KA) outcome is about graft injury mechanisms, while kidney reparative responses to intrinsic tissue damage have been set apart. Progenitor cells arise as a potential tool to evaluate graft capability to maintain its architecture and function, being Parietal Epithelial Cells (PEC) a kidney resident stem cell niche susceptible for analysis.
Methods: We included 66 recipients at the time of 6 month surveillance biopsy. PEC were isolated from urine and selected by FACs cell-sorting (CD24 + CD133 +). Clinical, demographics, analytical (GFR, proteinuria), treatment and immunological data (luminex, single antigen, ELISPOT, uCXCL9 and 10) were assessed. Kidney biopsies were evaluated according to Banff classification, and CD133, CD44 and Ki67 staining were performed. Follow up was 2 years.
Results: uPEC were isolated in 62.1% patients at the time of 6 m biopsy, and patients divided according to the presence/absence uPECs. Study groups were comparable regarding baseline characteristics, immunosuppression, DGF, acute rejection, GFR, proteinuria and immunological risk. Protocol biopsy was similar between groups, without differences for any particular Banff item, including C4d staining. Glomerular CD44 + staining showed no differences between groups, while Ki67 identified an increase of dividing PEC on Bowman's capsule in uPEC+ group (0.05 vs. 0.25 Ki67 + /glom, $p = 0.03$) (Fig 1).

No significant differences on GFR were found at 6 m nor 1 years, but GFR became significantly lower in the uPEC+ group at 2 years (52 vs. 63 mL/min) (Fig 2). Proteinuria was significantly higher in uPEC+ group at 2 years.

Conclusions: In stable KA recipients with similar effector mechanisms of damage, renal function and histology assessed by surveillance biopsy, the presence of CD24 + CD133 + progenitor cells in urine was associated with enhanced glomerular parietal epithelial cell proliferation and identifies a subgroup of patients at risk for subsequent GFR decline







Clinical Kidney Other

OS135

GFR DECLINE AS AN ENDPOINT FOR LONG TERM RENAL TRANSPLANT OUTCOME: COMPARISON BETWEEN INULIN-MEASURED AND CREATININE-ESTIMATED GFR

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[1]*Chu Nord Saint Etienne, France;* [2]*Chu De Nîmes, France*

Background: Doubling of serum creatinine (Scr) is deemed as a robust endpoint for CKD long term outcome. This increase in Scr (corresponding to a GFR decline ≥ 57%) is however a late and rare event. An alternative smaller GFR decline ≥30% has been recently validated both in patients with native kidneys and in renal transplant recipients (RTR). This novel threshold has only been evaluated from creatinine-estimated GFR (eGFR) declines which are known to underestimate –particularly in the transplant setting - the true decline obtained from direct measurements of GFR (mGFR). We sought to determine whether identification of renal transplant patients with a GFR change ≥30% determined with a reference methods of mGFR will improve the endpoint performance.
Methods: Retrospective analysis of RTR for whom GFR was measured by urinary clearance of inulin (mGFR) and estimated by the CKD-EPI equation (eGFR). Changes in mGFR and eGFR were calculated between 1 and 5 years post-tx. Association between mGFR and eGFR change ≥ 30% with graft failure and mortality was analyzed by a competing-risk Cox model. Respective performances to predict 16-years post-tx outcomes were compared by C-statistics.
Results: Out of the 417 patients, 116 lost their graft and 77 died with a functioning graft during the follow-up. Concordance between mGFR and eGFR to detect a GFR change ≥30% was 53%. Strength of the association between mGFR and eGFR decline and graft survival was similar (HR of 2.43[1.45–4.02] vs. 2.16[1.09–4.29] for inulin and CKD-EPI, respectively, NS). C-statistics for long term graft survival was not statistically different (0.59 vs. 0.63 for inulin and CKD-EPI, respectively, NS). Similar results were observed for mortality.
Conclusion: Despite a poor agreement between eGFR and mGFR decline, directly measuring rather than simply estimating GFR change does not provide better prediction for long term transplant outcome.

OS136

A MULTIDIMENSIONAL PROGNOSTIC SCORE AND NOMOGRAM TO PREDICT KIDNEY TRANSPLANT SURVIVAL: THE INTEGRATIVE BOX (IBOX) SYSTEM

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Background: The transplant field currently lacks of robust risk stratification models. The goal of this study was to generate an integrative scoring system that predicts kidney allograft loss.
Methods: This international study involved 8 European and 2 North American centers including 4806 kidney recipients transplanted between 2002 to 2014 and integrated the full spectrum of allograft parameters. The development cohort included 1540 patients. The prognostic ability of 80 parameters was evaluated using univariate and multivariate Cox regression analyses. Performance assessment and internal validation of the final model were done with Harrell's C-index, calibration plot and bootstrap sample procedures. Using the final model, a prognostic nomogram and a score were developed.
Results: Expanded criteria donor, allograft scarring (IFTA), allograft injury (g and ptc), allograft function (eGFR and proteinuria at 1 year post transplant), anti-HLA DSA status and level (MFI) were independently associated with 7-year post-transplant allograft survival. The model exhibited good calibration, excellent discrimination (C-statistic = 0.80; 95%CI = 0.76–0.84) and a nomogram for individual graft survival prediction was generated. Time dependent

ROC curves, Random survival forests survival analyzes confirmed the robustness of the iBox score. The performance of the score was confirmed in the external validation cohort from Europe (n = 2130, C-statistic = 0.81; 95% CI = 0.76–0.86) and North America (n = 1136, C-statistic = 0.83; 95% CI = 0.77–0.89). The capacity of the score to predict graft failure remained high in 1118 patients evaluated beyond 1-year post transplant (C-statistic = 0.80; 95%CI = 0.76–0.85).
Conclusion: The iBox prognostic score and nomogram precisely predict the individual long-term graft survival probability. The score demonstrates high performance, exportability across centers worldwide and adaptability beyond the first year post transplant evaluation.

Translational Liver Biomarkers and molecular changes

OS137 A PRETRANSPLANT GLYCOMIC SIGNATURE IN PERFUSATE IS PREDICTIVE OF PRIMARY NON FUNCTION AFTER LIVER TRANSPLANTATION

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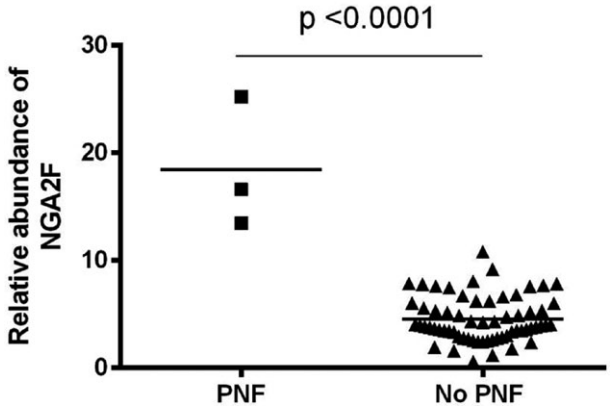
Background and Aims: Primary non function (PNF) is a rare but major complication after liver transplantation requiring urgent retransplantation. It is associated with the use of extended-criteria donors. The donor risk index is a clinical score that can guide the estimation of graft quality but lacks the power to predict PNF risk in individual patients. Perfusate analysis is an attractive tool for assessment of donor liver function before implantation. Glycomic assessment of serum has proven useful in the diagnosis of liver disease. Here, we performed a comprehensive analysis of perfusate in relation to the appearance of PNF.
Methods: In this prospective monocentric study 66 consecutive liver transplantations between October 2011 and July 2013 were included. Perfusate samples were collected after flushing of the hepatic veins before implantation of the liver graft. All donor grafts were transported using cold static storage. Based on an optimized DNA sequencer technology, we performed glycomic analysis of these perfusate samples and searched for glycomic alterations in PNF patients.
Results: One single glycan, an galactic core-alpha-1,6-fucosylated biantennary glycan (NGA2F) was significantly increased in the perfusate of the 3 patients who developed PNF after liver transplantation. It could identify PNF patients with 100% accuracy. This glycomarker was the only predictor of PNF in a multivariate analysis (logistic regression model) including donor risk index and perfusate AST/ALT levels ($p < 0.0001$).
Conclusions: In this cohort, patients who developed PNF after liver transplantation showed a specific glycomic signature in perfusate (before liver transplantation) that could distinguish them from non-PNF patients with 100% accuracy. This approach could guide the removal of donor grafts at risk for PNF from the donor pool, especially when the use of high-risk organs is considered.



OS138 STEATOTIC HUMAN LIVERS SHOW INFERIOR FUNCTION COMPARED TO NON-STEATOTIC LIVERS DURING *EX-SITU* VIABILITY ASSESSMENT BY OXYGENATED MACHINE PERFUSION

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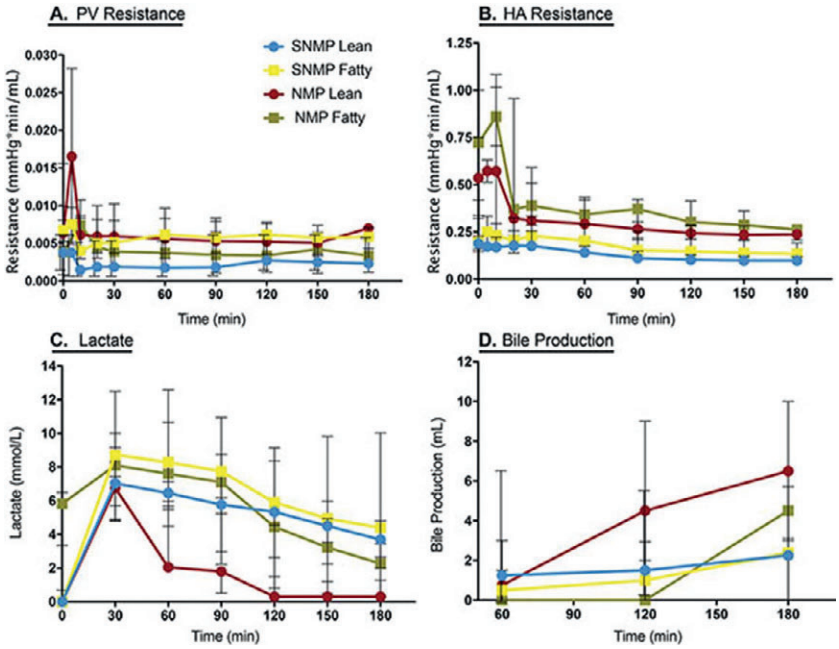
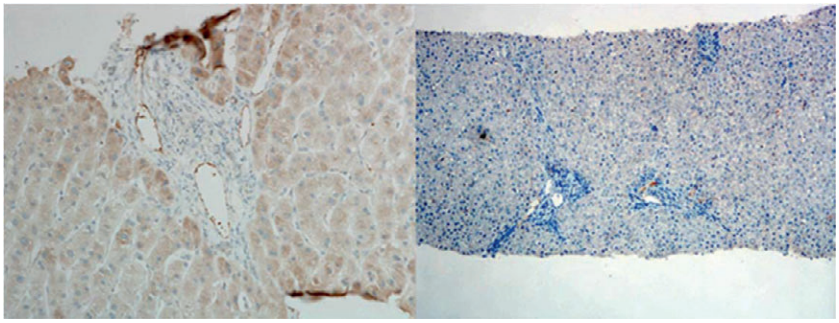
Background: Fatty livers are frequently declined for transplantation due to high risk of primary non-function. *Ex-situ* oxygenated machine perfusion (MP) has proven to be superior to static cold storage for fatty liver preservation. However, it is unknown whether simple perfusion alone is sufficient to render steatotic livers transplantable. We assessed the function of fatty livers compared to lean livers during subnormothermic (21°C) and normothermic (37°C) MP.





Methods: Twenty discarded human livers with research consent were included. Fatty livers were defined as >30% macrovesicular steatosis by histology. Three hours SNMP ($n = 4$ lean, $n = 10$ fatty) or NMP ($n = 3$ lean, $n = 3$ fatty) were performed.
Results: Portal venous resistance was relatively constant throughout the study period in all groups after the first 15 min (Fig. 1A). Hepatic arterial resistance decreased gradually over time in all groups, and tended to be higher in NMP than SNMP, and in fatty than lean livers (Fig. 1B). Lactate levels decreased over time, but more rapidly during NMP than SNMP (Fig. 1C). NMP fatty livers cleared lactate more slowly than NMP lean livers, resulting in >7-fold higher lactate levels by the end of perfusion. Both fatty and lean livers produced similar low amounts of bile on SNMP, however fatty livers produced markedly less bile at NMP than lean livers (Fig. 1D).
Conclusion: Although vascular resistance was similar in fatty and lean livers, functional differences were quite pronounced between fatty and lean livers at NMP that were not evident during SNMP. This suggests that the low metabolic activity of SNMP may not be sufficient to distinguish impaired function in fatty livers. In addition, either longer perfusion times or additional therapeutics will likely be necessary to restore transplantability in steatotic livers.

Clinical Liver Rejection

OS139

LIVER TNF-ALPHA EXPRESSION PREDICTS ACUTE ALLOGRAFT REJECTION AND GRAFT SURVIVAL

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Background: The part of cytokines in acute rejection (AR) after liver transplant is unclear. Previously some studies reported an association between proinflammatory cytokines and AR. We aimed to show the relationship of tumor necrosis factor-α (TNF-α) both with AR and graft survival.
Methods: Total 66 liver allograft included to the study. The inflammatory score, the presence and the number of AR episodes noted. Biopsies were immunostained with TNF-α. The expression of TNF-α investigated both in hepatocytes and inflammatory cells.
Results: Among 66 patients only 23 had AR at the date of study biopsy. Total 31 patients showed AR at least one time during follow-up. The mean number of AR was 0.8 ± 1.1. During follow-up, 18 (27.3%) patients developed recurrence and 7 (10.6%) developed cirrhosis. Total 22 (33.3%) patients died at a mean time of 20.3 ± 24.7 months. Both the degree of hepatocyte and inflammatory cell TNF-α expressions found to increased with increasing degree of inflammatory cell infiltration. Both hepatocyte and inflammatory cell TNF-α expressions showed association with the presence of AR at the date of biopsy, the presence of AR during follow-up and with the mean number of AR episodes ($p < 0.001$ for all). The development of recurrence and cirrhosis showed a significant association both with hepatocyte and inflammatory cell TNF-α expressions ($p < 0.01$). The overall 10-year survival was 94, 95, 31 for negative, mild and severe hepatocyte TNF-α expression respectively ($p < 0.001$). Overall 10-year survival was 96, 63, 36 for negative, mild and severe inflammatory cell TNF-α expression respectively ($p < 0.001$).
Conclusion: Our results suggest that increased liver TNF-α expression plays a significant role in the pathogenesis of AR. Also, we showed that TNF-α expression had significant association both with the development of recurrence and cirrhosis. Thus in addition to immunosuppression, combination of immunotherapy with monoclonal anti- TNF-α may increase graft survival.

OS140

SUCCESSFUL SERIES OF RITUXIMAB DESENSITIZATION FOR LIVER TRANSPLANTATION WITH PREFORMED DONOR SPECIFIC ANTIBODIES

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Backgrounds: Preformed donor-specific antibodies (DSA) are considered as a risk factor even after liver transplantation (LT). Strong DSA is associated with high mortality and increased risk of rejection.
Methods: Between October 2014 and March 2017, a total of 59 LTs were performed. Among them, 7 cases (11.9%) were identified with positive preformed DSA during the preoperative evaluations. A single dose of 500 mg rituximab was given to the DSA positive patients before LTs. No immunosuppressive agents were given preoperatively. Postoperative immunosuppression were triple regimens; tacrolimus, steroid, and mycophenolate mofetil. Postoperative DSA levels were checked, and liver biopsies were collected to rule out antibody mediated rejection (AMR).
Results: Seven patients identified with positive DSA were "class-I only" 2 cases, "class-II only" 3 cases, and "both class-I and II" 2 cases. Those DSA positive patients received LTs from living donors ($n = 6$) and deceased donor ($n = 1$). Rituximab was given to the LDLT recipients 1–21 (median 18) days before LTs, and to the DDLT recipient just before LT. DSA were checked at 1, 3, 6, 12, 24 months after each LT. MFI levels of DSA gradually declined in class-II, but rapidly disappeared in class-I. Liver biopsies obtained from "class-II only" DSA recipients early postoperative periods demonstrated positive C4d staining, but no signs of AMR. Those biopsies from late-postoperative periods turned negative C4d staining (figure), indicating that accommodation of preformed DSA was achieved by rituximab desensitization without causing AMR. In contrast, "class-I only" or both "class-I and II" recipients demonstrated negative C4d staining, even early postoperative periods.
Conclusions: Seven cases of LTs with preformed DSA were successfully managed by the rituximab desensitization. Further studies are required because the mechanism of DSA to AMR in LTs remains unclear, especially the difference between class-I and class-II DSA.

Clinical Liver Immunology

OS141

AN OPEN-LABEL PROOF-OF-PRINCIPLE PHASE 2A STUDY TO EVALUATE AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR ALLOGENEIC ORGAN TRANSPLANT TOLERANCE (ASCOTT)

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Background: Long-term survival of solid organ recipients is hampered by recurrent disease and immunosuppression-induced toxicity. Inducing a state of operational immune tolerance would be a major advance. Self-tolerance can be induced following autologous hematopoietic stem cell transplantation (aHSCT) for patients with autoimmune disease. We are examining whether aHSCT can induce tolerance in liver transplant recipients.
Methods: Eligibility in this Phase 2A trial is limited to liver transplant recipients for alcohol induced, genetic, or autoimmune liver disease who are >3 months post-transplant and 18 to 55 years old. Following baseline evaluation, hematopoietic stem cells are mobilized using cyclophosphamide (CTX) and filgrastim. Grafts are cryopreserved after auto- and allo-reactive lymphocytes are removed using CD34 cell selection. aHSCT follows a busulfan, CTX and α-

thymocyte globulin based regimen used to ablate auto- and allo-reactivity. Patients are removed from their immunosuppressive medication at the time of aHSCT. They receive 6 months of everolimus to expand regulatory T cells. Patients are followed for evidence of tolerance or rejection.
Results: 7 pts are enrolled (baseline testing $n = 1$, pre-HSCT work-up $n = 2$, post-HSCT $n = 3$). 1 pt did not receive aHSCT and instead underwent a second liver transplant. The median age is 39 (31–45) years. 4 pts received a deceased donor and 3 pts a living related donor transplant for PSC. All had recurrent PSC with moderate to severe ductopenia and fibrosis at enrolment. 6 of 7 pts have ulcerative colitis (UC). Median time from liver transplant to aHSCT was 9 years (4–20). Follow-up is 4, 7 & 9 months. Moderate to severe regimen toxicity was seen but pts recovered & are alive off immunosuppression without clinical rejection. Liver biopsies in the first two patients show normal histology. Symptoms have resolved in 2 pts with UC.
Conclusion: These results suggest that aHSCT may induce tolerance in liver transplant recipients.

OS142 EARLY TREATMENT WITH CMV-HYPERIMMUNOGLOBULIN ATTENUATES PRO-INFLAMMATORY AND PRO-IMMUNOLOGIC ACTIVATION IN CRITICALLY ILL HIGH MELD (≥30) LIVER RECIPIENTS

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Introduction: Liver transplantation (LT) in critically ill high model of end-stage liver disease (MELD) score patients is associated with an increased risk for early infectious and immunologic complications. Recently, specific immunoglobulins (Ig) were shown to provide beneficial immunomodulatory capabilities. The aim of this pilot trial was to analyse the immune-balancing impact of early post-LT application of cytomegalovirus (CMV) hyperimmunoglobulin (CMVIg) high MELD liver transplant recipients.
Material/Methods: Thirty-six liver transplant patients with a median MELD score of 38 (range: 30–40) were included. Based on donor/recipient CMV matching, 5000 IE CMVIg (Cytotect, Biotest, Germany) was administered daily for minimum one week post-LT. Its impact on serologic parameters of pro-inflammatory and pro-immunologic activation (C-reactive protein [CRP]; procalcitonin[PCT] and outcome was assessed.
Results: At LT, 23 patients were ICU-bound (63.9%), 14 received renal replacement therapy (38.9%), 17 patients were under ventilation (47.2%), and 20 patients needed catecholamine treatment (55.6%). 22 patients received CMVIg (61.1%) post-LT, whereas 14 patients did not. Mean post-transplant peak CRP (4.1 vs. 15.2 mg/dl) and PCT (10.5 vs. 73.3 ng/ml) were significantly lower in the CMVIg subset ($p < 0.001$). Rates of biopsy-proven rejections and CMV infections were significantly lower ($p < 0.05$) in the CMVIg subset. Overall survival rates at 3 and 6 months post-LT were 95.5% and 86.4% in patients receiving, but only 64.3% and 42.9% in those without CMVIg treatment (log rank < 0.001). In multivariate analysis, pre-LT CRP-level (HR = 7.8), ΔMELD (HR = 6.2), recipients' age (HR = 3.5) and CMVIg treatment (HR = 3.6) were identified as independent prognostic factors. Donor characteristics had no prognostic impact.
Conclusion: Early with CMVIg attenuates pro-inflammatory and pro-immunologic activity in critically ill liver transplant patients with MELD ≥ 30. Thus, the outcome may be

OS143 THE IMMUNOLOGICAL EFFECTS OF NORMOTHERMIC MACHINE PERFUSION OF THE LIVER

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Introduction: Normothermic machine perfusion of the liver (NMP-L) may enable reconditioning of marginal organs. NMP of lungs and hearts is known to reduce passenger leukocyte (LK) content; the effect on livers has not previously been assessed. We aimed to quantify major LK populations and cytokine profiles within the perfusate at serial time points to determine the immunological effects of NMP-L.
Methods: Donor type (DBD/DCD), level of steatosis ($n = 14$ none/mild vs. $n = 7$ moderate/severe), warm and cold ischaemic times (WIT/CIT), donor BMI, age and post-transplant peak-AST were recorded. Perfusate samples from 21 NMP-L were obtained prior to NMP and at 0.5, 1 and 4 hrs. LK populations were phenotyped and quantified using flow cytometry. Cytokine profile was characterised using Luminex assays.
Results: NMP-L induces significant migration of LK into the circuit within 30 min ($p < 0.05$ for B cells, T cells, NK cells, classical monocytes (CM), non-CM; $p = 0.08$ NKT cells). LK numbers reduce to marginally above baseline at 1 and 4 hrs. LK diapedesis is not altered by donor type ($p = 0.98$), WIT ($p = 0.47$), CIT ($p = 0.26$), BMI ($p = 0.32$) or age ($p = 0.29$) but does increase with steatosis severity ($p = 0.02$). Peak-AST is not affected by extent of LK migration ($p = 0.73$). There was a progressive increase in most inflammatory cytokines as the NMP progressed ($p < 0.05$ for IFNγ, IL-1β, IL-8, IL-10, MCP-1)
Discussion: NMP-L induces early diapedesis of passenger LKs into the circuit, an effect that is elevated in steatotic organs. The reduced LK count at 1 and 4 hrs suggests that these cells either adhere to the circuit or return to the organ. This provides insight into the immunological processes that occur following liver transplantation, and specifically the relationship between steatosis severity and ischaemia reperfusion injury. Incorporating a LK filter into the circuit may enable the removal of passenger LKs and prevent their transfer into the recipient, thereby modulating direct allorecognition.

Clinical Liver Histology

OS144 SIGNIFICANCE OF THE EARLY HEPATIC STELLATE CELL ACTIVATION ON THE FIBROTIC EVOLUTION OF LIVER ALLOGRAFTS: THE POSSIBLE BENEFIT OF ESTROGEN ON THIS PROCESS

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Background: HSCs in response to a various inflammatory stimulus, undergo phenotypic changes that express alpha-smooth-muscle actin (α-SMA). Reports suggest that the estrogen presents an antifibrogenic action through inhibiting the myofibroblastic transformation of HSCs. The aim of this study is twofold; first to understand the impact of early HSC activation on the liver fibrosis evolution, second to find out the impact of estrogen on this process.
Methods: Early taken liver allograft biopsies of 71 (M/F: 49/22) patients included in the study. Biopsies scored for liver fibrosis (LF) and immunostained with α-SMA and TGF-β. Activated HSCs determined by the expression of α-SMA. Only 50 patients had follow-up biopsies that taken within 18 months, and all 50 biopsies also scored for LF.
Results: Of 71 patients 35 (49.3%) had LF at the time of initial biopsy. Most of them had fibrosis score lower than 2 (68.6%). Among 50 patients with follow-up biopsies, 33 had LF in variable scores. Five patients developed new LF, while 19 patients fibrosis score (FS) did not change and nine patients FS progressed to a higher grade. The presence and the degree of LF both in initial and follow-up biopsies found to increase with increasing degree of α-SMA and TGF-β expression ($p < 0.001$). Also, α-SMA and TGF-β expression had shown association with the development of recurrence ($p < 0.01$) and cirrhosis ($p < 0.01$). The degree of the α-SMA expression found higher in males compared to females ($p < 0.05$). During 18 months the development of LF found higher in males ($p < 0.05$).
Conclusion: Early activation of HSC is an important sign of the progressive fibrosis and the development of hepatitis recurrence in liver allografts. Also, an increased number of HSCs may represent an unfavorable event related to cirrhotic evolution. We also suggested that lower progression of fibrosis in women may be due to the antifibrogenic action of estrogen.

Clinical Kidney Donation and donor types

OS145 CT-DERIVED SKELETAL MUSCLE INDEX CORRELATES WITH RESIDUAL GFR AFTER LIVE KIDNEY DONATION

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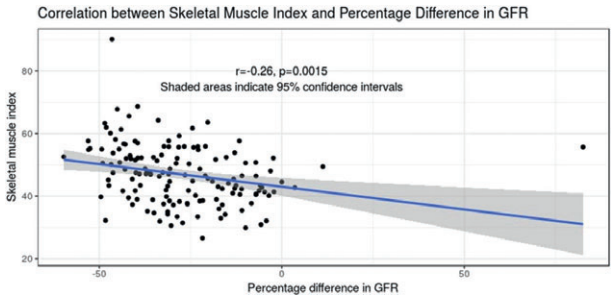
Background: Renal function in living kidney donors (LKD) falls after nephrectomy but recovers to near-normal over variable time. Skeletal muscle mass is proportional to urinary creatinine excretion. Skeletal muscle index (SMI) as a measure of muscle mass can be assessed by CT. We investigated the relationship between SMI and changes in estimated glomerular filtration rates (eGFR) postoperatively in living kidney donors.
Methods: All patients underwent CT scan as part of pre-donation work-up. Semi-automated body composition software (MatLab) was used to analyse CT scans at the 3rd lumbar vertebra level to calculate skeletal muscle index (SMI) [skeletal muscle area (cm^2) divided by height (m^2)]. Patients were stratified according to published body mass index (BMI) and SMI cut-points. eGFR was estimated using CKD-EPI calculation. R was used to investigate correlations between eGFR preoperatively and at discharge.



Results: From January 2009 to February 2017, 150 (M:F = 80 : 70) LKDs were studied. Median age was 50 years (range: 24–78). Median BMI was 26 kg/m^2 (range 18–34). 58 out of 150 patients (38.6%) had low SMI on CT according to sarcopenia definitions. Median preoperative eGFR was 98.86 ml/min (range: 58.2–127.8 ml/min) and dropped to 68.0 ml/min (36.1–121.1 ml/min) at discharge (3 days). SMI correlated with percentage difference in eGFR at discharge (Pearson r = −0.26, $p = 0.0015$).
Conclusions: A significant proportion of healthy individuals are sarcopenic by CT criteria developed in cancer patients. Interpretation in the LKD population should thus be done cautiously. SMI may help interpret renal function recovery after living kidney donation. Correlation with long-term outcomes needs further investigation.

OS146 KIDNEY FUNCTION AFTER LIVING DONATION IS HIGHLY PREDICTABLE FOR DONORS AND TO A LESSER DEGREE FOR RECIPIENTS

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Background: Safety is of highest priority for a living kidney donor. Kidney function after donation should be sufficient, reflect adaptive capacity of the remaining kidney and match recipient demand. Hence, assessment of expected post-donation kidney function is highly relevant.
Methods: Between 2014 and 2016 we measured pre- and post-donation kidney function in the living donor and corresponding recipient and compared it with the predicted function based on adaptive increase of 35%, age, gender and weight. In total, kidney function was analyzed in 47 donor-recipient pairs. In the donor baseline pre-donation serum creatinine (S-Crea) was compared to the lowest S-Crea during the first 3 months post-donation. In the recipient the lowest observed S-Crea during the first three post-transplant months was compared to the expected S-Crea based on a previously established formula: Expected recipient S-Crea post-transplant = ((140-recipient age)*recipient weight*recipient gender)/(((0.6*(140-donor age)*donor weight*donor gender)/predonation donor S-Crea)+8.7).
Results: The expected post-donation S-Crea in the donor was highly predictable, 89% of the observed values were measured within +/- 15% of the predicted values. Only 4 donors showed S-Creas outside the predicted range, all of the values lower than expected. In contrast the recipient S-Creas were less predictable. The mean difference between observed and predicted S-Crea was 11.5 umol/l, only 38% of all values were in the +/- 15% range. A lower adaptive increase in the remaining kidney in the living donor was associated with a lower adaptive increase in the mate kidney transplanted to the recipient. No age-dependent difference in adaptive increase could be detected.
Conclusion: Post-donation function in living donors can be predicted with a high accuracy, whereas post-transplant function in the recipient probably is impacted by multiple extra-factors not captured before transplantation.

OS147 ASSESSING GLOMERULAR FILTRATION RATE AFTER LIVING KIDNEY DONATION

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Introduction: Post-donation glomerular filtration rate (GFR) is a crucial measure because it might relate to long-term donor outcomes. The aims of the study were evaluating the changes in GFR after kidney donation and the risk factors related to post-donation GFR.
Materials and Methods: In this cross- sectional, descriptive study, the outcome of 312 living kidney donors (134 men vs. 178 women) were included from April 2010 to June 2016. Clinical and laboratory assessments were carried out at pre-donation and the first year, from 1 to 5 years, 5 to 10 years and after 10 years after donation.
Results: The GFR estimated by MDRD equation (eGFR) at the time of pre-donation, in the first year, from 1 to 5 years, 5 to 10 years and after 10 years of kidney donation were 89.9 ± 16.7; 61,5 ± 10.77; 63.12 ± 12.15; 63.12 ± 12.15 and 70.1 ± 13.6 ml/min/1.73 m^2, respectively. At the age of under 40, 40 to 50, 50 to 60 and above 60, the mean eGFR were 68.1 ± 12.6; 64.18 ± 15.15; 60.13 ± 11.1 and 57.59 ± 9.5 ml/min/1.73 m^2, respectively. Kidney donors under 50 years-old and male sex were significantly related to eGFR <60 ml/min/1.73 m^2 with OR = 0.411 (0.27–0.625), $\chi^2 = 17.485$, $p < 0.001$ and OR = 0.377 (0.246–0.579), $\chi 2 = 20.329$, $p < 0.001$, respectively; while pre-donation eGFR of <90 ml/min/1.73 m^2 was related to post-donation eGFR <60 ml/min/1.73 m^2 with OR = 4.726 (2.986–7.481) ($\chi 2 = 46.437$, $p < 0.001$).
Conclusion: Evaluating post- donation GFR is very important. We found that post-donation eGFR during the first year declined 31.6% compared to predonation-eGFR. However, there were no significant changes in eGFR after that. Besides, age, sex and pre-donation eGFR of kidney donors were related to the post-donation eGFR.
Key words: living kidney donors, pre-donation eGFR, post-donation eGFR.

OS148 QUANTIFYING POSTDONATION RISK OF ESRD IN LIVING KIDNEY DONORS

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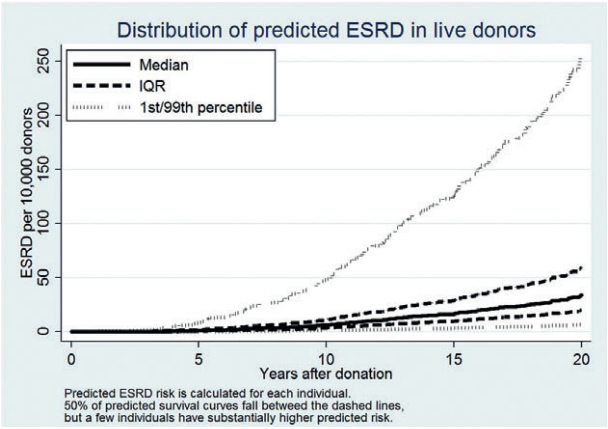
Background: Studies have estimated the average risk of postdonation ESRD for living kidney donors compared to healthy nondonors. Donors must understand the risk of donation in order to provide informed consent, but post-donation ESRD risk in individual donors is unknown.
Methods: We studied 133 824 living kidney donors from 1987 to 2015 in the United States, as reported to the Organ Procurement and Transplantation Network, with ESRD ascertainment via Centers for Medicare and Medicaid Services linkage, using Cox regression with late entries.
Results: Black race (HR = $_{2.25}$ 2.96 $_{3.89}$, $p < 0.001$) and male sex (HR = $_{1.50}$ 1.88 $_{2.35}$, $p < 0.001$) were associated with higher risk of ESRD in donors. Among nonblack donors, older age was associated with greater risk (HR per 10 years, $_{1.23}$ 1.40 $_{1.59}$, $p < 0.001$). Among black donors, older age was not significantly associated with risk (HR = 0.72 0.88 1.09, $p = 0.3$). Greater BMI was associated with higher risk (HR per 5 units, 1.29 1.61 2.00, $p < 0.001$). Donors who had a first-degree biologic relationship to the recipient had increased risk (HR = 1.24 1.70 2.34, $p < 0.01$). The C-statistic of the model was 0.71. Predicted 20-year risk of ESRD for the median donor was only 34 cases per 10 000 donors, but 1% of donors had predicted risk exceeding 256 cases per 10 000 donors. Online risk calculator at transplantmodels.com/donesrd.
Conclusions: Risk estimation is critical for appropriate informed consent and varies substantially across living kidney donors. Greater permissiveness may be warranted in older black candidate donors; young black candidates should be evaluated carefully.

Characteristic	HR (95% CI)	*p* value
Men (at age 40)	1.88 (1.50–2.35)	<0.001
Black race/ethnicity (at age 40)	2.96 (2.25–3.89)	<0.001
Age per 10y: non-black	1.40 (1.23–1.59)	<0.001
Age per 10y: black	0.88 (0.72–1.09)	0.3
BMI per 5 units	1.61 (1.29–2.00)	<0.001
First-degree biological relationship to recipient	1.70 (1.24–2.34)	<0.001



OS149 ASSOCIATION BETWEEN SHORT-TERM POST-DONATION RENAL FUNCTION AND LONG-TERM RISK OF END STAGE RENAL DISEASE IN LIVING KIDNEY DONORS

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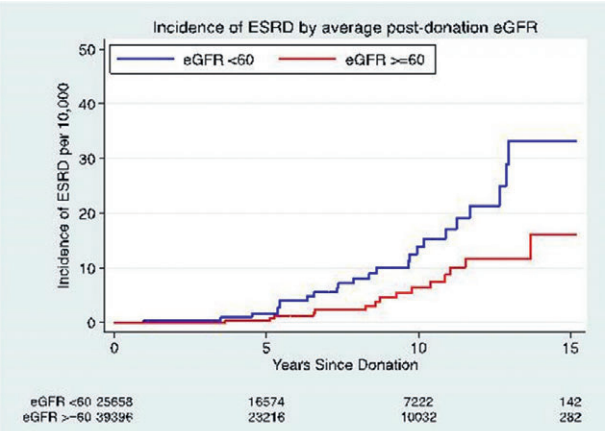
Background: Living Kidney Donors (LKD) are at an increased risk of long-term end stage renal disease (ESRD) compared to healthy non-donors. Changes in estimated glomerular filtration rate (eGFR) after donation may serve as an early screening tool for identifying donors at increased risk of ESRD.
Methods: Using national registry data from the United States, we studied eGFR in the first two years post-donation in 65 054 living kidney donors (LKDs) who donated between 1999 and 2014. We performed survival analysis to investigate the risk of ESRD using Cox regression and adjusting for donor age, sex, black race, and pre-donation eGFR.
Results: 39.4% of LKDs had post-donation eGFR below 60 mL/min/1.73 m^2. Donors with post-donation eGFR < 60 were at greater risk of eventually developing ESRD (logrank $p = 0.01$, Figure). After adjusting for donor demographics and pre-donation eGFR, a 10-unit decrease in post-donation eGFR in the first two years was associated with 68% higher long-term risk of ESRD (aHR = $_{1.20}$ 1.68 $_{2.36}$, $p < 0.01$).
Conclusions: Short-term post-donation eGFR is associated with long-term risk of ESRD in LKDs, even after adjusting for demographic characteristics. Post-donation follow-up is crucial for identifying donors at increased risk of ESRD.



OS150 MID-TERM EFFECTS OF HEMODYNAMIC CHANGES OF KIDNEY AND CARDIOVASCULAR SYSTEM AFTER NEPHRECTOMY IN LIVING KIDNEY DONORS

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Purpose: We aimed to find out mid-term effects of hemodynamic changes after donor nephrectomy to cardiovascular and renal system and figure out previously known increase in mortality in long term follow-up.
Material and Methods: We have analyzed retrospectively 123 living kidney donor (LKD)s who were undergone nephrectomy and were followed-up at least one year in between January 2010 to January 2015. Complete blood count, serum biochemistry, spot urine protein and creatinine levels were examined. Transthoracic echocardiography, FMD alteration of brachial artery and renal ultrasound were performed. Results were compared with preoperative values of donors and values of healthy individuals.
Results: Median age was 46 years, median follow-up period was 39 months and female to male ratio was 86/37 in LKDs. In LKDs, the last control serum creatinine level and CKD-EPI e-GFR were found as in order; 0.95 ± 0.92 mg/dl and 80.8 ± 16.72 ml/min/1.73 m^2 whereas pre-operative levels were in order; 0.72 ± 0.15 and 102.16 ± 15.2. Proteinuria was found to be 6.8% in LKDs. Compensated hypertrophy was revealed 24% in the remaining kidney. FMD alteration of brachial artery was found 12% and statistically significant lower than healthy individuals ($p = 0.016$). When comparing the last control transthoracic echocardiogram with pre-operative states, left ventricular end-diastolic and end-systolic dimensions were found lower, left ventricular back wall and septum thickness were in higher as statistically significant ($p = 0.002$–0.026). According the last control values 11.3% of LKDs were found to be phase 3 CKD through t-GFR levels.
Conclusion: Accelerated aterosclerosis, disrupted left ventricular elasticity and accelerated CKD process all might be presumed causes of mortality in super-selected, healthy LKDs. This study reveals that especially in younger LKDs, cardiovascular and renal dysfunctions that causes mortality in later stage after nephrectomy needed to have strict and long term surveillance.

OS151 END STAGE KIDNEY DISEASE RISK PROFILE IN LIVING KIDNEY DONORS FOR PAEDIATRIC VS. ADULT KIDNEY TRANSPLANT RECIPIENTS IN AUSTRALIA AND NEW ZEALAND

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Background: Living kidney donors (LKDs) to children have a high motivation to donate due to clear neurocognitive, growth, psychosocial, cardiovascular and survival benefits for paediatric kidney transplant recipients (KTRs) compared to dialysis. We hypothesised that younger LKDs with higher end stage kidney disease (ESKD) risk were more often accepted as donors for paediatric vs. adult KTRs.
Methods: ANZDATA registry data of LKDs were used to estimate baseline ESKD risk without donation using a risk calculator (Grams ME et al NEJM 2016) for paediatric vs. adult KTRs (2009–2014). Only 50 of 168 and 425 of 1835 LKDs for paediatric and adult KTRs respectively were included for analysis due to the unavailability of urine albumin/creatinine ratios.
Results: Compared with adult KTRs, LKDs for paediatric KTRs were significantly younger (median age 44 (IQR 36–50) vs. 53 (44–60); $p < 0.001$) and more likely to be the parents of KTRs (88% vs. 23%; $p < 0.001$). LKDs were younger when stratified for paediatric KTR age (≤10 vs. ≥11 years) (LKD age 37 (33–45) vs. 48 (41–52); $p < 0.001$). Baseline 15-year ESKD risk was lower (paediatric: 0.08% (0.05–0.10%) vs. adult: 0.11% (0.07–0.17%); $p = 0.001$) whereas lifetime ESKD risk was higher (0.42% (0.33–0.64%) vs. 0.37% (0.23–0.58%); $p < 0.05$). The 90th, 95th and 98th percentiles for lifetime ESKD risk estimates in LKDs for paediatric vs. adult KTRs were 1.38% vs. 0.93%, 1.71% vs. 1.22% and 2.12% vs. 1.85% respectively. The proportion of LKDs with lifetime ESKD risk threshold >1% (12% vs. 8%) and >2% (2% vs. 2%) was similar.
Conclusions: LKDs for paediatric KTRs have lower 15-year but higher lifetime baseline ESKD risk compared with adult KTRs, primarily driven by younger LKD parents. However, the absolute risk difference is minor. These data should improve informed consent for LKD candidates. The likely additional benefits to the parent LKD and family of a paediatric KTR candidates compared to remaining on dialysis merit further studies.

OS152 PREGNANCY OUTCOMES IN A DUTCH LIVING KIDNEY DONATION POPULATION

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Background: Female living kidney donors might have a future pregnancy wish. For these women it is of great importance to know if donating a kidney could have a possible negative effect on their future pregnancies. Literature is sparse on this subject. The aim of this study was to investigate if a kidney donation affects complications in pregnancies.
Methods: We conducted a single center retrospective study of living kidney donors between 1981 and July 2013. Women aged 45 years or younger at time of donation were interviewed about their pregnancies before and after kidney donation. Women who had been pregnant before donation were used as control group.
Results: 1462 living kidney donors donated their kidney at our hospital until july 2013. We could include 172/259 (66%) women in our study. Median age at donation was 38 yrs (18 - 45). 110/172 (68%) women had 292 pregnancies before donation at a median age at delivery of 27 yrs, compared to 25/172 (15%) women whom had 46 pregnancies after donation and median age at delivery of 33 yrs (p = 0.00). 37/172 (22%) had not been pregnant at all. Before donation women reported 38/292 (13%) miscarriages compared to 14/46 (30%) after donation (p = 0.01) and 11/292 (4%) abortions pre-donation compared to 1 (2%) post-donation (p = 1.00). Hypertension was reported in 19/243 (8%) of pre-donation pregnancies compared to 11/31 (35%) pregnancies after donation (p = 0.00). Pre-eclampsia before donation occurred in 4/243 (2%) of the pregnancies compared to 3/31 (10%) in post donation pregnancies (p = 0.03). HELLP syndrome was experienced in 2 pregnancies before donation (0.2%) compared to 1 (3%) in a post donation pregnancy (p = 0.30).
Conclusion: Pregnancies after kidney donation are significantly more complicated by hypertension and pre-eclampsia as compared to the pregnancies

before donation. Difference in age at delivery as well as the kidney donation may contribute to this finding. Further investigations are needed to confirm these outcomes.

Clinical Kidney Rejection

OS153 PROGNOSTIC IMPACT OF REJECTION IN BIOPSIES TAKEN DURING DELAYED GRAFT FUNCTION

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University Medical Center Groningen, The Netherlands

Background: Delayed graft function (DGF) is a frequent complication after deceased donor kidney transplantation (Tx). During DGF protocol biopsies are regularly performed and an increased incidence of rejection has been reported compared to non-DGF cases. However, as inflammatory changes may also result from ischemia-reperfusion damage we questioned the predictive importance of BANFF lesions in DGF biopsies.
Methods: We included 1170 deceased donor kidney transplantations performed between 2000 and 2015 at our center. DGF was defined as the need for dialysis in the first week after Tx. All biopsies were re-evaluated according to the BANFF '09 classification. Allograft survival was retrieved from our transplant database.
Results: DGF was identified in 381 cases (33%). After excluding cases without a biopsy ($n = 128$) and those who developed new rejection in repeat biopsies ($n = 51$), we included 202 cases (53%). Of which 95 cases *never had rejection* (NR), 37 *borderline rejection* (BR), 17 *interstitial rejection* (IR) and 53 *vascular rejection* (VR) in the first biopsy after Tx. Regarding death-censored graft survival, BR was associated with numerically better survival ($p = 0.09$), VR with numerically worse survival ($p = 0.06$) and IR had no impact on survival ($p = 0.69$) compared to NR. The impact of treatment was analyzed for the BR cases. Both in BR with treatment ($n = 19$, $p = 0.12$) and without treatment ($n = 18$, $p = 0.35$) death-censored graft survival was not different compared to NR. Moreover, no difference was observed between BR cases who were treated for rejection and those who were not ($p = 0.54$).
Conclusions: As both BR and IR had no negative impact on death-censored graft survival our findings suggest that the corresponding lesions may not always represent an alloimmune response. The finding that treatment of BR does not affect death-censored graft survival supports the concept that inflammatory lesions in early DGF biopsies may be in part attributed to ischemia-reperfusion damage.

OS154 THE VALUE OF REPEAT BIOPSIES IN KIDNEY ALLOGRAFT RECIPIENTS WITH DELAYED GRAFT FUNCTION

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University Medical Center Groningen, The Netherlands

Background: To exclude early rejection in patients with delayed graft function (DGF) kidney biopsies are frequently performed after transplantation (Tx). It is less clear whether biopsies should be repeated if DGF persists after 2 weeks. Hence, we evaluated the diagnostic value of repeat biopsies in patients with persistent DGF.
Methods: We included 1170 deceased donor kidney transplantations performed between 2000 and 2015 at our center. DGF was defined as the need for dialysis in the first week after Tx. All biopsy reports were re-evaluated in accordance to the BANFF '09 classification. The results of the repeat biopsies were compared with the previous biopsies.
Results: A total of 381 cases (33%) with DGF were identified, of which 116 cases (31%) underwent repeat biopsies during persistent DGF. The last day of dialysis was at a median of 19 days after Tx. The initial biopsy (B1), the second biopsy (B2) and the third biopsy (B3) were performed at a median of 10, 21 and 31 days after Tx, respectively. B1 revealed 40 cases with rejection and 54 cases without rejection. At B2 there was a 41% discovery rate of new rejection cases in patients who had no rejection at B1 ($p < 0.01$). Of the 40 cases that had rejection at B1, 15 cases (38%) showed resolution of rejection at B2 despite persisting DGF ($p < 0.01$). A total of 31 cases underwent a third biopsy, 12 of which had rejection at B2 and 19 did not. Of these 19 cases we observed 7 new rejection cases (37%) at B3 ($p < 0.01$). Of the 12 cases that had rejection at B2, 8 cases (67%) showed resolution of rejection at B3 ($p < 0.01$).
Conclusion: A significant number of new rejection cases were detected in patients with persistent DGF when a kidney biopsy was repeated at roughly 2 and 4 weeks after the first biopsy. Repeat biopsies during persisting DGF in patients with rejection at the initial biopsy and first repeat biopsy may also prevent unnecessary escalation of rejection treatment.

OS155 ACUTE CELLULAR REJECTION IS ASSOCIATED WITH INCREASED RISK OF EARLY AND LATE GRAFT FAILURE

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Background: The association between acute cellular rejection and subsequent early and late graft loss has not been well-quantified.
Methods: Using national registry data from the United States and Cox regression, we studied the association between acute rejection in the first six months (AR6) and death-censored graft failure (DCGF) among 83,008 deceased donor kidney transplant (DDKT) recipients 2005–2015 with ≥6 m graft survival, adjusting for recipient characteristics and KDPI; and among 48,399 living donor kidney transplant (LDKT) recipients, adjusting for recipient characteristics and living donor KDPI.
Results: Cumulative incidence of DCGF at 10y post-KT was higher for recipients with AR6 among both DDKT recipients (38.8% vs 20.7%) and LDKT recipients (27.3% vs 14.4%) (Figure). Among DDKT recipients, AR6 was associated with 4-fold higher risk of DCGF in the first year post-KT ($aHR = {}_{4.1}\,4.9\,{}_{5.6}$, $p < 0.001$); this association attenuated over time, but remained statistically significant >5 years post-KT ($aHR = {}_{1.3}\,1.5\,{}_{1.8}$, $p < 0.001$) (Table). Similarly, among LDKT recipients, AR6 was associated with 4-fold higher risk of DCGF in the first year post-KT ($aHR = {}_{3.4}\,4.6\,{}_{6.3}$, $p < 0.001$); this association also attenuated over time, but remained statistically significant >5 years post-KT ($aHR = {}_{1.3}\,1.6\,{}_{1.9}$, $p < 0.001$).
Conclusions: Acute rejection in the first six months is associated with substantially increased risk of early and late graft loss, with continued risk even beyond 5 years, both in deceased and live donor transplants. This persistent late risk of graft loss is consistent with mechanistic theories that acute cellular rejection primes the immune system for later development of de novo DSA and subsequent injury to the allograft.

	DDKT: aHR (95% CI)	LDKT: aHR (95% CI)
0.5-1y post-KT	4.9 (4.2–5.6)	4.6 (3.4–6.3)
1-3y post-KT	2.3 (2.1–2.6)	2.7 (2.3–3.1)
3–5y post-KT	1.8 (1.6–2.0)	1.6 (1.3–1.9)
>5y post-KT	1.5 (1.3–1.8)	1.6 (1.3–1.9)

OS156 META-ANALYSIS OF THE ASSOCIATION BETWEEN TRANSPLANT GLOMERULOPATHY AND GRAFT FAILURE AMONG PATIENTS UNDERGOING KIDNEY TRANSPLANTATION

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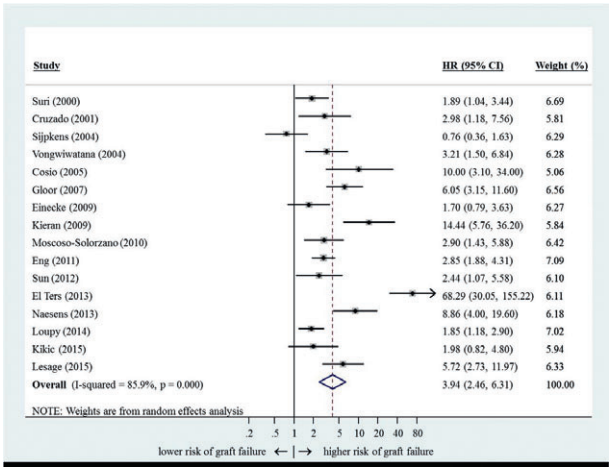
[1]Syreon Research Institute, Hungary; [2]Shire, United States; [3]Syreon Corporation and University Of British Columbia, Canada

Background: Transplant glomerulopathy (TG) is characterized by duplication of the glomerular basement membrane and can lead to irreversible kidney damage. TG is recognized as a surrogate marker for poor outcomes, including graft failure among patients undergoing kidney transplantation. There are currently no approved therapies to treat or prevent TG. The aim of this analysis was to synthesize published evidence to understand the relationship between TG and graft failure.
Methods: A systematic literature review evaluated published evidence on the association between TG and graft failure. A meta-analysis was undertaken to summarize the data using the hazard ratio (HR) and 95% corresponding confidence intervals (CIs) to measure survival. Sensitivity analyses evaluated this association within pre-specified sub-groups. Meta-regression was used to identify factors to explain observed heterogeneity, including mean time between transplantation and biopsy. The Egger-test and funnel plots assessed publication bias. Heterogeneity was assessed by I-squared (I^2) and the value of the heterogeneity chi-squared test.
Results: 16 publications, including 2,519 patients, were identified as eligible for data extraction, as they assessed the relationship between TG and graft failure among patients with and without TG. Of these studies (see Figure), which were highly heterogeneous ($I^2 = 85.9\%$), the combined HR was 3.94, (95% CI 2.46–6.31) indicating that TG had a significant negative effect on graft survival. There was no evidence of publication bias (Egger's $p = 0.152$). This finding was consistent in all subgroups. Furthermore, there was no association between time from transplantation to biopsy and graft failure.
Conclusion: The relationship between TG and graft failure is significant with the risk of graft failure nearly 4 times greater among patients who develop TG compared to those without TG. This meta-analysis supports the importance of TG as a surrogate measure of graft failure.



Clinical Kidney Histology

OS157

IDENTIFYING THE SPECIFIC CAUSES AND THE DETERMINANTS OF OUTCOME IN KIDNEY RECIPIENTS WITH TRANSPLANT GLOMERULOPATHY: A MULTICENTER STUDY

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[1]Paris Translational Research Center For Organ Transplantation, France; [2]7 Department Of Laboratory Medicine And Pathology, Canada

Background: Understanding the specific causes of Transplant Glomerulopathy (TG) and its long-term consequences is lacking.
Methods: This study includes all kidney allograft biopsies performed between 2004 and 2014 in three French referral centers and one Canadian center showing TG. All TG cases were extensively phenotyped and systematically assessed using light microscopy, immunohistochemistry, immunofluorescence, together with circulating anti-HLA-DSA at the time of biopsy.
Results: Among the 8207 post-transplant allograft biopsies performed during the inclusion period, 559 (6.8%) had double contours and corresponded to 392 patients. Three overlapping etiologies accounted for 467 (84%) cases. 417 biopsies showed alloantibodies-mediated injury (75%), 91 biopsies showed TMA (16%), 65 showed MPGN (12%), while 92 cases (17%) remained equivocal with no specific lesions identified by the pathologist (Figure 1). The median time to first cg lesion occurrence after transplantation was 32.7 months

Figure 1

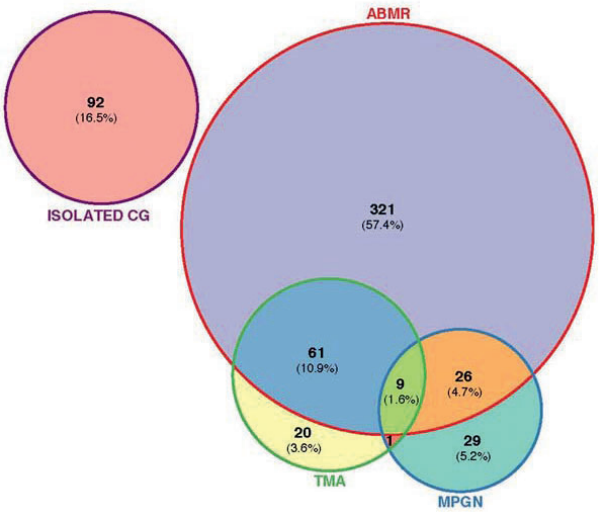
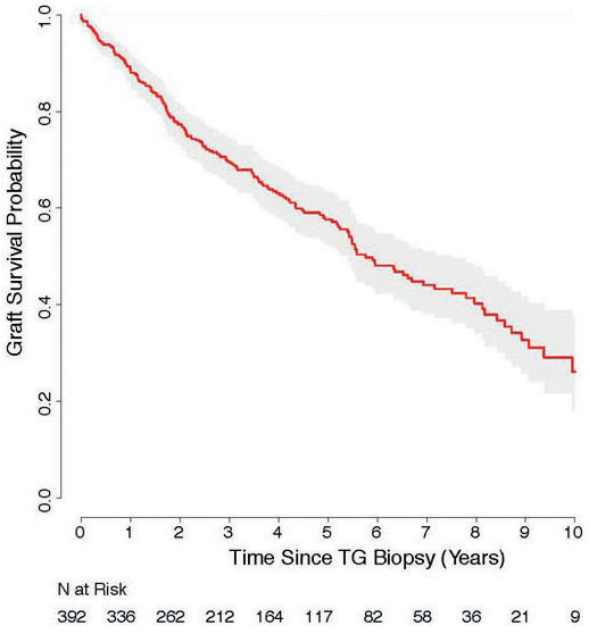


Figure 2



(IQR: 12.0–77.9). Kidney allograft survival after TG diagnosis was 59% at 5 years and 41% at 8 years (Figure 2). After adjusting for donor, recipient and transplant characteristics, immunological and histological parameters, we identified the following independent factors associated with long-term allograft survival in patients with TG: eGFR (HR:0.96; $p < 0.0001$) and proteinuria level (HR:2.17; $p < 0.0001$) at the time of biopsy, deceased donor (HR:1.64; $p = 0.0139$), delay between transplantation and TG diagnosis (HR:1.34p<0.0001) and endarteritis Banff scores (HR:1.82; $p = 0.0018$).
Conclusion: Using a large cohort of kidney recipients with a diagnosis of TG, we identify three overlapping pathways in TG: ABMR, TMA and MPGN. The identification of the main independent determinants of TG prognosis may help improving risk stratification and define specific causes and disease process in patients with TG.

OS158

THE PROGNOSTIC VALUE OF INDIVIDUAL HISTOPATHOLOGICAL LESIONS AND COMPOSITE SCORES IN 0-BIOPSIES FOR KIDNEY ALLOGRAFT SURVIVAL

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Background: We aimed to evaluate which acute and chronic lesions and composite scoring systems in 0-biopsies are best associated with kidney graft survival.
Methods/Materials: All recipients of cadaveric ($N = 101$) and living ($N = 29$) kidney transplanted in our center between 2005 and 2010, with adequate 0-biopsy and available follow-up data were included in this study. We investigated the association of individual histological lesions, acute, chronic and total Banff scores for indication biopsies (ind-Banff) and for 0-biopsies (0-Banff), Remuzzi score, donor damage score (DDS), chronic damage score (CDS), and chronic allograft damage index (CADI) with 5-year death-censored kidney graft loss.
Results: Sixteen patients (12.3%) lost their grafts during follow-up. Acute (hazard ratio (HR) = 1.66), chronic (HR=1.02), and total (HR=1.02) ind-Banff scores, chronic (HR=1.02) and total (HR=1.02) 0-Banff score, DDS (HR=1.20) and CDS (HR=1.41) significantly predicted death-censored graft loss. Chronic 0-Banff score demonstrated the highest AUC of 0.722 in ROC-analysis. Glomerulosclerosis (gs, >10%; HR=3.53), arteriolar hyalinosis (ah, Banff, >0; HR=4.28), interstitial fibrosis (if, Banff, >0; HR=4.67), and total inflammation (ti, Banff, 1-3; HR=3.52) individually significantly predicted graft loss. On the basis of these findings, we created the Donor Kidney Damage Index (DKDI): gs+ah+if+ti, which showed higher HR (2.69) than existing indexes, and also yielded the AUC of 0.763. After adjustment for clinical variables the DKDI showed significant independent association with graft loss (HR = 3.82). Then, a novel scoring system based on clinical variables (regraft, acute rejection, cold

ischemia time) and the DKDI was constructed by logistic regression, and it yielded an AUC of 0.853, indicating good value in predicting graft loss.
Conclusion: The new scoring system based on histological and clinical data have promise in the prediction of kidney graft loss.

OS159 INFLAMMATION IN SCARED AREAS IN THE KIDNEY ALLOGRAFT: MAJOR IMPACT OF T CELL-MEDIATED REJECTION AND UNDER-IMMUNOSUPPRESSION

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The important role of inflammation in scared areas in the kidney allograft (i-IF/TA) on transplant outcomes has been acknowledged by the 2015 Banff report, which has highlighted the need to clarify its significance. We investigated the determinants of i-IF/TA in a population-based study.

This observational, prospective cohort study included 1539 consecutive kidney recipients transplanted at Paris between 2004 and 2010, with systematic assessment of inflammation in allograft scarred area using the i-IF/TA Banff score on biopsies performed at 1 year post-transplantation. We considered donor and recipient baseline characteristics, transplant characteristics, immunosuppressive regimens, immunological parameters (HLA matching, anti-HLA DSA), infectious diseases (CMV, pyelonephritis, BK virus) and all the biopsy-proven diagnoses (TCMR, AMR, BK virus-associated nephropathy, CNI toxicity, acute tubular necrosis), recorded at the time of transplantation and in the first year after transplantation.

We identified 893 patients with IF/TA at 1 year post-transplant, among whom 194 (22%) showed severe i-IF/TA (≥2). The independent determinants for severe i-IF/TA were TCMR (OR, 2.7; 95%CI, 1.7–4.1), BK virus-associated nephropathy (OR, 3.5; 95%CI, 1.5–8.2), recipient age (OR, 0.9 95%CI, 0.9–0.9), CNI therapy (OR, 0.5; 95%CI, 0.2–0.9) and steroid therapy (OR, 0.5; 95% CI, 0.2–0.9). Patients with i-IF/TA showed a specific injury phenotype including increased inflammation in non-scarred areas ($p < 0.001$), total inflammation ($p < 0.001$) and tubulitis ($p < 0.001$). Patients with persisting severe i-IF/TA after TCMR treatment showed an accelerated progression of fibrosis over time ($p = 0.01$) and a decreased allograft survival ($p = 0.003$) as compared to those without persisting inflammation after TCMR treatment.

Inflammation in scared areas of the kidney allograft is mainly determined by previous TCMR and the level of immunosuppression, and is associated with poor kidney transplant outcomes.

Clinical Kidney Rejection

OS160 DIFFUSE EXTENT OF PERITUBULAR CAPILLARITIS IN LATE ANTIBODY MEDIATED REJECTION - ASSOCIATION WITH TRANSPLANT GLOMERULOPATHY AND MORE SEVERE CHRONIC ALLOGRAFT DAMAGE

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Introduction: Peritubular capillaritis (ptc) is a diagnostic criterion for antibody-mediated rejection (ABMR). Diffuse ptc extent (> 50% of the cortical renal tissue) has been identified as an independent risk factor
for inferior outcome.
Methods: This study assesses the clinical relevance of ptc subcharacterization (ptc score, extent and leukocytic subpopulation) in recipients with donor-specific antibody (DSA) and is a secondary analysis of a large prospective trial (BOsRTEJECT,-NCT01873157). It included 85 out of 741 stable transplant recipients subjected to cross-sectional antibody screening (≥6 months post transplantation). Based on DSA detection [mean fluorescence intensity (MFI) threshold >1,000], patients underwent protocol biopsy (scoring according Banff 2013 scheme). Outcomes were the presence of transplant glomerulopathy (TG) and the chronic lesion score (CLS), scoring was performed by one pathologist blinded for the outcome.
Results: Ptc ($n = 42$) scores 1, 2, and 3 were present in 36%, 55% and 9% while focal and diffuse ptc were found in 36% vs. 64%. Monocytes were the most prevalent leukocytic subpopulation (76%). Recipients with diffuse ptc were more frequently pre-sensitized, and presented with significantly higher post transplant DSA MFI sum (5172 (IQR: 3007–13783) vs. 2444 (IQR: 1355–7873), $p = 0.019$). TG and CLS scores were significantly higher in recipients with diffuse ptc extent (1.1 ± 1.1, $p = 0.002$ and 6.8 ± 2.2, $p = 0.01$, respectively) vs. no ptc (0.3 ± 0.6 and 5.2 ± 3.3). Ptc score 2 was only associated to TG (1.2 ± 1.0, $p < 0.001$) but not to CLS. In cox regression analysis diffuse ptc remained an independent risk factor for TG (OR: 4.22 (95%CI: 1.47–12.14, $p = 0.007$). and higher CLS (regression coefficient: 1.63 (95%CI 0.19–3.07) $p = 0.03$) while ptc score 2 lost its significant association.
Conclusions: Our results suggest diagnostic and prognostic relevance of reporting diffuse ptc extent and further emphasize its role as a risk factor for chronic damage in kidney allografts

Clinical Kidney Immunosuppressive agents

OS161 EARLY CONVERSION TO A CNI-FREE IMMUNOSUPPRESSION WITH SRL AFTER RENAL TX – LONGTERM DATA OF A MULTICENTER TRIAL

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Introduction: Early conversion to a CNI-free immunosuppression with SRL, MMF and steroids was associated with an improved 1- and 3- yr renal function as compared with a CsA-based regimen in the SMART study. Recently, there have been reports on increased occurrence of donor specific antibodies (*dn*DSA) under mTORis. This we evaluated in our controlled "SMART"- cohort.
Methods: We recruited patients from the core SMART study to primarily investigate the development of *dn*DSA in a controlled setting. Secondary outcome parameter were kidney function, overall and graft survival and development of malignancies, which were retrospectively documented for the whole SMART population.
Results: We were able to recruit 74 patients (53% of the core study population), 39 SRL and 35 CsA (ITT analysis) from 6 centers with an average exposition time of 3.7 years for SRL and 7.0 years for CsA. Blood samples for DSA analysis were collected with a mean of 8.7 years after Tx. No statistically significant difference between the therapeutic arms could be detected with respect to the development of *dn*DSA. Numerically, there were less *dn*DSA positive patients in the SRL arm (6/39, 15.4%) compared to the CsA arm (10/35, 28.6%). There was a significant benefit regarding GFR (Nankivell) under SRL with 64.37 ml/min/1.73 m2 vs. 53.19 ml/min/1.73 m2 ($p = 0.044$). Considering the whole SMART population ($N = 140$), patient survival does not differ between groups at 5 years or later on. Significantly more tumors occurred in the CsA arm (15/69 = 22.1%) compared to the SRL arm (4/71 = 5.8%, $p = 0.012$).
Conclusions: In this long term follow up multicenter trial on a controlled cohort, an early conversion to SRL did not result in an increased incidence of *dn*DSA nor increased risk for the graft or recipient. Furthermore, significant benefits remained under SRL regarding graft function and malignancy.

OS162 ELECTIVE CONVERSION TO SIROLIMUS VS. CONTINUED TACROLIMUS IN KIDNEY TRANSPLANTATION (THE 3C STUDY): RESULTS OF A RANDOMIZED TRIAL

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Background: Long-term outcomes after kidney transplantation have not improved in recent decades and calcineurin inhibitor (CNI) nephrotoxicity is considered to contribute to late graft loss. Sirolimus (SRL) may provide less nephrotoxic immunosuppression but has proved difficult to use in many patients: the use of potent lymphocyte-depleting antibody induction may facilitate the use of sirolimus.
Methods: The 3C Study is a randomized trial which recruited participants at the time of transplantation when they were randomized between alemtuzumab- and basiliximab-based induction therapy, both followed by TAC-based immunosuppression. Between 5–7 months after transplantation participants were randomly allocated to SRL- or tacrolimus (TAC)-based maintenance therapy. Participants were followed by clinic review, annual questionnaire and linkage to relevant national registries. The primary outcome was eGFR at 18 months after randomization.

Results: Of the 852 participants who entered the induction phase of the trial, 394 were subsequently randomized between SRL and TAC. Adherence to SRL and TAC was 48% and 94% at 18 months respectively. At 18 months, eGFR in the SRL group was 53.7 (SE 0.9) compared to 54.6 (0.9) mL/min/1.73 m2 in the TAC group ($p = 0.50$). Induction therapy assignment did not modify the effect of maintenance therapy allocation. Graft rejection was more common among participants allocated SRL (14.7% vs 3.0%; $p < 0.001$), but graft survival was similar (95.9% vs 98.0%; $p = 0.23$). Serious infections (opportunistic or requiring hospitalisation) were more common among those allocated SRL (42.6% vs 32.0%; $p = 0.02$), but cancer incidence was similar (8.6% vs 8.6%; $p = 0.99$).
Conclusions: SRL did not preserve graft function better than tacrolimus and was associated with significant increased risks of rejection and infection. Our results do not support elective conversion from TAC to SRL for the preservation of graft function, regardless of induction therapy.

OS163 MULTICENTER, RANDOMIZED, OPEN LABEL, PROSPECTIVE CLINICAL STUDY TO COMPARE THE EFFICACY AND SAFETY OF STEROID WITHDRAWAL ON DAY 5 IN A COMBINATION OF TACROLIMUS PLUS EVEROLIMUS VS TACROLIMUS PLUS MMF

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Aim of this multicenter, prospective, randomized, open label, 2-arm, parallel group clinical trial was to compare the safety and efficacy of early steroid withdrawal in renal transplant patients, receiving once a day tacrolimus in association with everolimus or mycophenolate mofetil.

The primary objective of this study was to compare in the two arms the 12-month composite endpoint including: incidence of clinical+BPAR acute rejection, graft survival, percentage of patients with creatinine >1.8 mg/ml, percentage of patients with failed steroid withdrawal, percentage of patients converted from the assigned therapy. The occurrence of at least one of these conditions was considered treatment failure.

Patients older than 18 years-old, receiving a deceased donor, first renal transplant were randomized on day 1 to the following treatment arms: Tacrolimus once-a-day + Everolimus (EVR) or MMF (MMF). In both groups Thymoglobuline (1 mg/kg/die) was administered preoperatively and on postop day 1, 2, and 3. Steroids were stopped in both groups on day 5.

A Data Safety Monitoring Board reviewed the safety of the study at regular intervals. After enrollment of 98 pts, the study was prematurely closed because the endpoint of the study was reached. Despite none of the single parameters included in the composite endpoint singularly reached statistical significance, the composite endpoint was highly statistical significant in favor of the MMF arm ($p < 0.002$). In the EVR group there were numerically more conversions, more steroid resumes and significantly more reports of serious adverse events related to everolimus by the investigators ($p < 0.0002$).

These results show the difficulties of conducting a multicenter study using the immunosuppressive combination of everolimus and tacrolimus together with early steroid withdrawal. Further evaluation in clinical trials is needed.

OS164 EVEROLIMUS ENABLES TACROLIMUS AND STEROID MINIMIZATION WITH REDUCED INCIDENCE OF CMV INFECTION AND PRESERVED GRAFT FUNCTION IN DE NOVO RENAL TRANSPLANT RECIPIENTS AT 12 AND 24 MONTHS POST-TRANSPLANT

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Introduction: CMV infection is associated with inferior long-term recipient and graft survival. Here we report the results from a 24-month (M), prospective, single centre, open-label study designed to compare the effects of 2 immunosuppressive regimens on the incidence of CMV infection in renal transplant recipients (RTxR).
Methods: Intention to treat population of 115 low immunological risk (PRA <50%) de novo RTxR were randomized (1:1) within 24 h post-Tx to either one of the two reduced tacrolimus (TAC, C0 4–7 ng/mL) regimens: (G1 = 59) everolimus (EVR, 1.5 mg bid, C0 3–8 ng/mL) or (G2 = 56) sodium mycophenolate (MPS, 720 mg bid). All patients received Thymoglobulin induction (6 mg/kg/day) and 90% were steroid-free after day-7. The primary outcome in this study was the incidence of CMV infection or disease during the first year of transplantation. None of the patients received CMV prophylaxis. CMV infection was monitored using a commercial quantitative CMV PCR assay for the first 6M.
Results: Both groups showed similar baseline characteristics mean age of 44 ± 14 years, 80% male and 97% RTxR from deceased donors (DD). Mean DD age was 31 ± 12 years and the mean cold ischemia time was 24 ± 8 h. CMV serum status D+/R- was seen in 10 patients in G1 and 3 patients in G2 ($p = 0.03$). CMV infection occurred in 11 (18.6%) patients in G1, 10 asymptomatic DNAemia and 1 syndrome, vs. 28 (50%) in G2, 25 asymptomatic DNAemia and 3 syndromes ($p = 0.001$). There was no case of CMV invasive disease. Death-censored 2-year graft survival was 99%, with 1 graft loss in G2. Biopsy proved acute rejection was seen in 2 cases in each group (3.4%). Estimated graft function (eGFR, mL/min/1.73 m2) using MDRD formula was similar at 12M (71.2 vs 76.6) and 24M (71.3 vs 70.8).
Conclusions: Two-Year analysis indicates that patients receiving EVR are at lower risk to develop CMV infection. These regimens also appear to provide comparable efficacy and similar renal function.

Clinical Liver Immunosuppressive agents

OS165 EVEROLIMUS WITH REDUCED TACROLIMUS DEMONSTRATES EFFICACY AND IMPROVED RENAL FUNCTION FOLLOWING LIVING-DONOR LIVER TRANSPLANTATION - 12 MONTHS RESULTS FROM THE PIVOTAL H2307 STUDY

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Background: Everolimus (EVR) with reduced-exposure tacrolimus (rTAC) has been shown to be effective after deceased-donor liver transplantation (LT) but trials in living-donor (LD) LT are lacking.
Methods: Study H2307 is an international, pivotal RCT (NCT01888432) conducted in adult LDLT patients randomized at Day 30 to either standard tacrolimus (TAC-Control) or EVR/rTAC. The primary objective was to demonstrate comparable efficacy at Month (M) 12 post LDLT.
Results: 284 patients were randomized (mean age 54 years; 72% male; 79% Asian; mean [SD] MELD 14 [5.5]; 42% hepatocellular carcinoma [HCC]; 30% hepatitis B). Mean estimated GFR (eGFR, MDRD4) at randomization (RDN) was 90 mL/min in both groups. The primary endpoint, a triple composite of treated biopsy-proven acute rejection (tBPAR), graft loss (GL), or death at M12 post LDLT, was similar between groups (Table) despite meaningful tacrolimus reduction >35% with EVR/rTAC. No GL occurred and patient survival was comparable. Although tBPAR rates were similar, only mild BPAR were observed with EVR/rTAC while moderate and severe episodes occurred only with TAC-Control. eGFR was significantly better at Month 6 and constantly higher throughout the study with EVR/rTAC. Mean change in eGFR from RDN to M12 was significantly better with EVR/rTAC *vs.* TAC-Control in patients who remained on study drug. HCC recurrence was seen only in TAC-Control patients. Serious adverse events/infections were comparable between EVR/rTAC and TAC-Control. Study drug discontinuations were very low and similar in both groups.
Conclusions: Early introduction of everolimus at Day 30 after LDLT allows meaningful tacrolimus reduction (>35%), provides similar efficacy and better renal function compared to standard tacrolimus at Month 12. No HCC recurrence was observed with everolimus, but occurred in 8.1% of TAC-Control patients.

Table. Outcomes at month 12 post-transplant

	EVR/rTAC (n=142)	TAC-Control (n=142)	Difference, % (90% CI)	*P* value for no difference
tBPAR, GL, or death; n (KM %)	7 (5.1)	8 (5.8)	−0.7 (−5.2; 3.7)	0.787*
GL; n (KM %)	0 (0.0)	0 (0.0)	–	–
Death; n (KM %)	4 (2.9)	3 (2.2)	0.7 (−2.5; 3.8)	0.728
tBPAR; n (KM%)	3 (2.2)	5 (3.6)	−1.4 (−4.7; 2.0)	0.501
Borderline	2 (1.4)	1 (0.7)		
Mild	1 (0.7)	1 (0.7)		
Moderate	0 (0.0)	2 (1.4)		
Severe	0 (0.0)	1 (0.7)		
Mean change in eGFR; mL/min				
All patients	−8.0	−12.1	4.2 (−0.1; 8.4)	0.108*
On-treatment	−8.0	−13.3	5.3 (0.9; 9.6)	0.046
Recurrent HCC; n/N (%)	0/56 (0.0)	5/62 (8.1)	−8.06 (−25.8, 10.2)	0.059
Any serious AE/infection; n (%)	70 (49.3)	61 (43.3)	–	–
Study drug discontinued; n (%)	22 (15.5)	25 (17.6)	–	–

*P<0.001 for non-inferiority

CI, confidence interval; EVR, everolimus; HCC, hepatocellular carcinoma; eGFR, estimated glomerular filtration rate; GL, graft loss; KM, Kaplan-Meier; rTAC, reduced tacrolimus; tBPAR, treated biopsy-proven acute rejection

OS166

EVEROLIMUS WITH REDUCED TACROLIMUS PROVIDES COMPARABLE EFFICACY VS. STANDARD TACROLIMUS FOLLOWING LIVING DONOR LIVER TRANSPLANTATION: A 12-MONTH SUBGROUP ANALYSIS FROM THE PIVOTAL H2307 STUDY

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Background: In the H2304 study, everolimus (EVR) plus reduced tacrolimus (rTAC) showed comparable efficacy to standard TAC (TAC-C) in deceased donor liver transplant recipients (LTR). H2307 (NCT01888432), the largest study i*n de novo* living donor LTR (LDLTR), compared the efficacy and safety of the EVR+rTAC and TAC-C arms in patients mainly from Asian countries. Here, we present the efficacy data of treatment arms among various subgroups.
Methods: In this 24-month, multicentre, controlled trial, adult primary LDLTR were randomised at day 30 ± 5 post-LT into two arms: EVR+rTAC (N = 142) and TAC-C (N = 142). Basiliximab induction was as per centre practice. The primary objective was to demonstrate comparable efficacy, as measured by the composite efficacy failure (CEF) of treated biopsy-proven acute rejection (tBPAR), graft loss, or death at month 12 post-LT. Efficacy outcomes were analysed in a variety of subgroups.
Results: Overall, 78.2% and 78.9% of patients were Asians in EVR+rTAC and TAC-C arms, respectively. Basiliximab induction was given to 50.7% and 64.8% of patients in EVR+rTAC and TAC-C arms, respectively. There was no significant difference in the incidence of CEF and efficacy components between arms (Table). No graft loss was observed in the study. Mortality rates were 2.9% vs 2.2% in EVR+rTAC and TAC-C arms, respectively. Efficacy outcomes were not significantly different between arms regardless of induction therapy, race, age, or HCC as reason for Tx. Importantly, no moderate or severe treated acute rejection episodes were observed in the EVR+rTAC arm.
Conclusions: In this largest study in LDLTR, the treatment with EVR+rTAC showed overall comparable efficacy vs TAC-C at month 12 across all subgroups, however in the patients who received EVR+rTAC, no moderate or severe rejection was seen.

Table: Efficacy outcomes at month 12

Parameters, n (%)	Treatment arms	CEF*	tBPAR	Death**
Overall	EVR+rTAC (N=142)	7 (5.1)†	3 (2.2)†	4 (2.9)†
	TAC-C (N=142)	8 (5.8)†	5 (3.6)†	3 (2.2)†
	Risk diff (90% CI)	−0.7 (−5.2,3.7)	−1.4 (−4.7,2.0)	0.7 (−2.5,3.8)
Basiliximab induction	EVR+rTAC (M=72)	5 (6.9)	2 (2.8)	3 (4.2)
	TAC-C (M=92)	7 (7.6)	4 (4.3)	3 (3.3)
	Risk diff (90% CI)	−0.7 (−13.6,12.2)	−1.6 (−14.5,11.4)	0.9 (−12.1,13.8)
Age (<60 years)	EVR+rTAC (M=101)	5 (5.0)	2 (2.0)	3 (3.0)
	TAC-C (M=105)	6 (5.7)	3 (2.9)	3 (2.9)
	Risk diff (90% CI)	−0.8 (−12.2,10.9)	−0.9 (−12.4,10.8)	0.1 (−11.4,11.7)
HCC+	EVR+rTAC (M=56)	4 (7.1)	2 (3.6)	2 (3.6)
	TAC-C (M=63)	3 (4.8)	1 (1.6)	2 (3.2)
	Risk diff (90% CI)	2.4 (−12.8,17.5)	2.0 (−13.2,17.0)	0.4 (−14.8,15.5)
HCV+	EVR+rTAC (M=24)	2 (8.3)	0 (0.0)	2 (8.3)
	TAC-C (M=26)	4 (15.4)	2 (7.7)	2 (7.7)
	Risk diff (90% CI)	−7.1 (−29.7,17.1)	−7.7 (−30.9,16.5)	0.6 (−22.7,24.5)
Asian race	EVR+rTAC (M=111)	6 (5.4)	3 (2.7)	3 (2.7)
	TAC-C (M=112)	6 (5.4)	5 (4.5)	1 (0.9)
	Risk diff (90% CI)	0.0 (−11.0,11.0)	−1.8 (−12.8,9.2)	1.8 (−9.2,12.8)
Caucasian race	EVR+rTAC (M=30)	1 (3.3)	0 (0.0)	1 (3.3)
	TAC-C (M=30)	2 (6.7)	0 (0.0)	2 (6.7)
	Risk diff (90% CI)	−3.3 (−25.7,19.3)	-	−3.3 (−25.7,19.3)

CEF, composite efficacy failure; CI, confidence interval; EVR, everolimus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; rTAC, reduced tacrolimus; TAC-C, tacrolimus control; tBPAR, treated biopsy-proven acute rejection
*tBPAR/graft loss/death;**No case of graft loss in both arms; †Kaplan-Meier incidence rates; n, the number of patients with events; M, the total number of patients within the subgroup level in the treatment group

OS167 EARLY TACROLIMUS WITHDRAWAL AFTER LIVER TRANSPLANTATION PROVIDES IMPROVEMENT OF RENAL FUNCTION VS. EVEROLIMUS-FACILITATED REDUCED-EXPOSURE TACROLIMUS: RESULTS OF A NATIONAL PILOT STUDY

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Background: The aim of this pilot study (REFLECT) is to assess efficacy and impact on renal function of early (from month 5 to 6) tacrolimus (TAC) withdrawal vs. reduced-exposure TAC (rTAC) in adult liver transplantation (LT).
Materials and methods: Primary, adult LT recipients were enrolled one month post-transplantation in a run-in period of EVR-facilitated rTAC (EVR trough 3–8 ng/mL; TAC trough 3–5 ng/mL). Eligible patients were randomized at month 5 to continue on rTAC (rTAC arm) or to eliminate TAC (WD-TAC arm) by month 6 with EVR trough 6–10 ng/mL. At transplantation, patients received triple or quadruple immunosuppression with TAC, antimetabolites, corticosteroids ± anti-CD25 as per local practice. Patients were followed up until 12 months for efficacy (treated and biopsy proven acute rejection (t/BPAR), graft loss or death) and renal function.
Results: Seventy-eight patients were enrolled in the run-in period, and 50 (mean age 54.5 ± 9.2; male 78%) were randomized (24 rTAC vs. 26 WD-TAC). The LS mean change in estimated GFR (eGFR, MDRD) from randomization (4 months) to endpoint (12 months) was +6.08 mL/min/1.73 m2 for WD-TAC vs. +3.19 for rTAC (difference LS mean (SE) 2.89 (4.21); p = 0.4973). Mean eGFR at 12 months post-tx was 93.44 ± 19.94 mL/min/1.73 m2 vs. 87.36 ± 18.78 mL/min/1.73 m2 for WD-TAC vs. rTAC (p = 0.3013). Treatment failure during 12 months was: 3 patients in WD-TAC, 1 patient in rTAC. No Graft Loss during the 18 months after transplantation has been detected. Five WD-TAC patients (20.8%) and 4 rTAC patients (15.4%) discontinued permanently study drug due to adverse events. No patient reported de novo hepatocellular carcinoma (HCC) during the study.
Conclusions: Early (between month 5 and 6) TAC withdrawal after a run-in period of EVR-facilitated TAC reduction appears feasible and associated with a benefit in renal function at 12 months vs. rTAC. Larger series are needed to confirm this pilot experience.

OS168 CONVERSION TO EVEROLIMUS (EVL) AFTER LIVER TRANSPLANTATION (LT) IN THE REAL LIFE: LONGTERM DATA FROM THE EVEROLIVER MULTICENTER OBSERVATIONAL FRENCH REGISTRY

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Conversion to EVL has been used mainly to optimize renal function. This multicenter study aims to analyze modalities of conversion and longterm renal outcome.
Patients and Methods: From 2006 till 2016, LT patients from 10 centers who were converted to EVL were recruited. Data were collected at baseline, at 1 month, every 3 months the 1st year then every 6 months. Indications of transplantation were mainly alcoholic (53.4%) and HCV cirrhosis (19.9%). HCC was present in 41% of the recipients.
Results: 930 adult recipients (74% male) had a mean age of 53.9 ± 10.4 years. EVL was introduced in 42.5% of the patients during the 1st year post-transplant. Main reasons of introduction of EVL were chronic renal failure (35.7%) treatment of recurrent HCC (6.8%) or de novo cancer (20.3%) and prevention of HCC recurrence (23.5%). Mean through levels of EVL were respectively 5.7 ± 4.4, 6.3 ± 3.1, 6.5 ± 2.6 ng/mL at M1, M36 and M60. CNI were withdrawn in 49.4% and 71% of the patients respectively at M3 and M12. In the group of patients with an eGFR at baseline ≥ 60 ml/mn/1.73 m2 (n = 438) mean eGFR from M3 till M60 didn't differ statistically from baseline. In the group of patients with at baseline a mean eGFR < 60 ml/mn/1.73 m2; n = 445), median time from transplant to conversion was 25.1 (0.1–352) months, mean eGFR improved statistically from 42.8 ± 10.5 at baseline to 51.4 ± 41.4 (p = 0.008) and 48.9 ± 16.8 (p = 0.027) ml/mn/1.73 m2 respectively at M36 and M60. Twenty patients (2.1%) developed a histologically proven acute rejection with a median delay of 4.3 months (extremes 1–30.8). Survival rates at 1 and 3 years were respectively 92% and 77%, and when excluding patients with cancer, survival was respectively 97% and 87%.
Conclusion: This real life registry showed that late conversion from CNI to EVL allowed a significant weaning of CNI and a significant improvement of GFR maintained at 5 years in patients with chronic renal failure with a very low risk of rejection.

Basic Kidney Ischemia-reperfusion and preservation

OS169 EXPOSURE TO ARGON AT EX VIVO STAGE PROTECTS RAT DCD RENAL ALLOGRAFT AGAINST ISCHEMIC-HYPOTHERMIC INJURY

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Background: Renal transplantation remains the only definitive treatment option for patients suffering from end-stage renal failure. To match the rising demand for organs, there has been an increasing use of suboptimal donors. Renoprotection mediated by noble gas could serve as a new strategy to protect renal grafts (1–3). This study assesses the protective role of argon (Ar)-saturated preserving solution against ischaemia reperfusion injury (IRI) in vitro, and evaluates the efficacy of argon in reducing ischaemic injury during ex vivo preservation.
Methods/Materials: *In vitro*, human kidney proximal tubular cells (HK-2) were challenged with hypothermia-hypoxia insults and exposed to 70% Argon gas. *In vivo*, the Fischer rat DCD renal graft (donor after cardiac death) was extracted and stored in 4°C preservative solution at 4°C, saturated with nitrogen (N_2) or Ar gas (70% Ar or N_2, with 5% CO_2 balanced with O_2) for 16 hours.
Results: Argon gas exposure enhanced the expression of Nuclear factor (erythroid-derived 2)-like 2(Nrf-2) and its downstream effector NAD(P)H dehydrogenase [quinone] 1 (NQO1) in cultured HK-2 cells and the renal cortex, HK-2 cell death after hypothermia-hypoxia insults was significantly reduced with argon treatment. In renal grafts, expression of calpain (necrosis marker), caspase-3 (apoptosis marker) and Mixed lineage kinase domain-like protein (MLKL, necroptosis marker) was reduced and renal morphology was preserved during cold storage compared to their N2 treated counterparts. In addition, argon-treated tissue exhibited a significant reduction in P2X7, RAGE, NLRP3 expression, indicating the inflammatory response was suppressed.
Conclusion: This study demonstrates that argon confers reno-protection for marginal donor grafts. The results of this study possess significant clinical implications. The use of argon during ex vivo preservation could potentially enhance the renal graft marginal pool by improving graft viability

OS170 PROTECTIVE EFFECT OF NITRIC OXIDE RELEASING NANOFIBER IN RAT MODEL OF RENAL ISCHEMIA-REPERFUSION INJURY

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Background: Ischemia-reperfusion injury (IRI) is a frequent and important event in transplantation. Nitric oxide (NO) is well known for having protective effects on cells during IRI. However, there was no way to properly deliver NO to the target organ. Recently, S-Nitrosothiol-modified silica/polymer hybrid nanofibers have been introduced as a NO storage and delivery nanoscaffold. The aim of this study was to investigate the effect of NO releasing nanofiber in rat model of renal IRI.
Methods: Fifteen male Sprague-Dawley rats were divided into three groups: (1) sham group (n = 5); (2) control group, renal IRI without any treatment (n = 4); and (3) NO group, renal IRI with wrapping the kidney using NO releasing-sheet (n = 6). Right nephrectomy was done one week before renal IRI. NO sheet was applied by wrapping left kidney one hour before clamp of renal artery. Renal ischemia was sustained during 55 minutes, followed by reperfusion. NO sheet was removed after 24 hours. The rats were sacrificed 48 hours after surgery.

Results: To determine the effect of NO on kidney function, we analyzed serum creatinine level. There were significant differences of creatinine between three groups: 0.48 ± 0.08, 4.67 ± 0.33, and 2.60 ± 1.0 respectively ($p = 0.002$). We also analyzed markers for inflammation, oxidative stress and apoptosis including ICAM-1, VCAM-1, TNF-α, IL-1b, 6, and 9, NFkb, cleaved caspase 3, Cox-2, iNOS, ED1, and BAX/Bcl-2 ratio in kidney tissue. Most of these markers increased significantly more in the control group as compared with the NO group ($p < 0.05$). We then, performed histopathological analysis of kidney tissue. NO group had significantly lower tubulointerstitial injury score than control group ($p < 0.05$).
Conclusions: In this study, we demonstrate the protective effect of exogenous NO in renal IRI. This new NO delivery system might be considered as a novel method for ameliorating IRI in renal transplantation.

Clinical Kidney Rejection

OS171 OLDER DCD KIDNEYS HAVE EXCELLENT OUTCOME MODIFIED BY THE USE OF MACHINE PERFUSION AND THE INCIDENCE OF REJECTION

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Introduction: We have previously shown that DCD kidneys have good outcome in the short term even when they are of the ECD variety. Most of those kidneys are offered to older recipients and therefore long term outcomes might not be so important.
Aim: To see if very old DCD kidneys have good outcome and define the factors that affect the outcome of kidneys of this donor age group
Results: 196 DCD kidneys were transplanted over 4 years in a single centre, 121 were categorized as ECD DCD, half of them were from donors over 63 years old, while in 48 of them the donor was over 70. The censored for death graft survival of those older DCD grafts was 98% and the patient survival for recipients over 60 did not differ whether they received a DCD kidney from a donor over 70 compared to younger DCD donors.

In DCD donor recipients there was a higher mismatch compared to DBD donors. The 3 years censored for death graft survival of DCD donors was 96% with 0 or 1 DR mismatch whereas it was 80% with 2 DR mismatches.

The eGFR at 1 and 3 years was dependent on the donor age ($p < 0.00010$), the rejection during the 1st year ($p = 0.037$) and the use of machine perfusion ($p = 0.039$). The use of machine perfusion resulted to a 3 years eGFR of 52 ml/min vs. 43 ml/min with cold storage. The rejection rate was correlated positively with the donor age ($p = 0.02$) and the use of Basiliximab vs. ATG or Campath ($p = 0.05$). The DR mismatch effect on rejection was restricted within the Basiliximab induced subgroup whereas its effect was obtunded when a more potent immunosuppression was used.
Conclusion: DCD kidneys from those selected older donors performed extremely well. They have an excellent censored for death graft survival therefore they can be offered to recipients over 60 without undue concern. The 3 years eGFR is still influenced by the donor age, the use of machine perfusion and the rejection rate. Rejection can be avoided by using more potent induction with the potential to improve outcomes.

Clinical Kidney Ischemia-reperfusion and preservation

OS172 PREDICTIVE FACTORS FOR NON-VIABLE RENAL GRAFTS FROM UNCONTROLLED DONORS AFTER CARDIAC DEATH

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Organs from uncontrolled donors after circulatory death (uDCD) sustain an inevitable period of warm ischemia after circulatory arrest (between cessation of cardiopulmonary function and preservation) which may have serious implications on short and long-term graft function. The main cause of uDCD graft loss is primary nonfunction, primarily due to thrombotic microangiopathy (TMA) secondary to warm ischemic injury.
Aim: o investigate which factors of uDCD can be predictive of graft loss due to TMA.
Methods: We compared data from 388 uDCDs that provided functional grafts vs. 21 donors in which both grafts were nonfunctional. These kidneys grafts were poorly perfused and required nephrectomy close to the surgical procedure, with histopathological study showing TMA without rejection. A logistic regression analysis was performed to predict the factors
Results: Univariate and multivariate logistic regression showed in uDCD, a strong relation between non viable donors lost due to TMA and a long warm ischemia time(Extrahospital cardiopulmonary resuscitation time in viable donors: 64.5 minutes, non viable donors: 73.0 minutes. p 0.027)

The multivariate logistic regression analysis showed the following predictors of TMA after transplantation from uDCD: death due to trauma (HR 2.78, 95% CI 0.84–9.19) or pulmonary embolism (HR 12.72, CI95% 2.71–59.69) and duration of cardiopulmonary resuscitation.

Donor kidney biopsy before transplantation did not show any data that could be indicative of future non-viability. There were no differences in cold ischemia time between transplant recipients from uDCD with or without TMA.
Conclusions: Both out-of-hospital and in-hospital teams involved in the transplantation process should strictly follow the established protocols in order to ensure an optimal organ protection and preservation. Patients whose cause of death is pulmonary embolism or trauma should be assessed in great detail and efforts should be made as far as possible to shorten warm ischemia time

OS173 RECONDITIONING AND EVALUATION OF ISCHEMICALLY DAMAGED COLD STORED KIDNEYS IN A PORCINE AUTOTRANSPLANT MODEL BY CONTROLLED OXYGENATED REWARMING (COR)

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Background: We have shown earlier that the concept of ex situ controlled oxygenated rewarming (COR) at the end of cold storage can be utilized to predict and improve renal function after reperfusion. COR was now assessed in a porcine autotransplant model.
Materials and Methods: After 20 minutes of warm ischemia porcine kidneys ($n = 6$) were preserved by cold storage (HTK, 4°C, 21 hours) and then gently warmed up to 20°C by ex vivo machine perfusion for 90 min with Custodiol-N, supplemented with 30 g/L of Dextran 40 (COR). Kidneys that were only cold stored for 21 h ($n = 6$) served as controls (CS). The remaining native kidney was removed during auto-transplantation. Second warm ischemia (implantation time) was similar in both groups (29.6 ± 2 vs. 29.4 ± 1 min; COR vs. CS). In vivo follow-up was one week.
Results: COR significantly improved cortical microcirculation (erythrocyte flux, by transit-time flowmetry) upon early reperfusion (92 ± 10% vs 51 ± 5% of baseline). Free radical mediated cell injury as assessed by systemic levels of lipo-peroxides at post-operative day 1 was significantly reduced (2.6 ± 0.1 vs 3.6 ± 0.2 nmol/ml; $p < 0.05$). Post-transplant kidney function was largely and significantly improved in comparison to the CS only group (peak levels of serum creatinine: 4.6 ± 0.6 vs. 9.9 ± 0.8 mg/dl and urea 42 ± 10 vs. 112 ± 24 mg/dl; $p < 0.05$).

Oxygen consumption as measured during machine perfusion at 20°C with a temperature-compensated fibre optic oxygen meter correlated well with post-transplant peak creatinine levels ($r2 = 0.81$).Only a weak inverse correlation was found between renal flow during COR and post-transplant peak creatinine ($r2 = 0.5$).
Conclusion: Gentle graft rewarming prior to transplantation by COR after CS can be safely applied and improves post-transplant graft function. COR may be a valuable tool in pre-transplant graft assessment.

Translational Kidney Donation and donor types

OS174 DOES SOLUTION VISCOSITY REALLY MATTER IN ORGAN PRESERVATION?

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Background: There is a perception that viscous solutions reduce the rate at which blood is washed out of organs during flush at retrieval, inhibit efficient cool-down and prohibit optimal cortical perfusion of donor organs. Actual data on this topic are scarce. To study perfusion characteristics we compared 4 hypothermic preservation solutions for abdominal organs i.e. UW SCS, HTK, IGL-1 and UW-MPS in a standard large animal model simulating DCD.
Methods: 70 kg pigs were terminated ($n = 6$ UW and HTK groups, $n = 4$ IGL-1 and UW-MPS groups) followed by aortic cold flush-out of abdominal organs after 40 min warm ischaemia. Companies' instructions for volumes were used. During wash-out perfusate samples were obtained for further analysis and to determine viscosity, whilst organ temperature and cortical perfusion of kidney and liver using contrast-enhanced ultrasound were measured. Biopsies were taken at start and end for histology including assessment of wash-out of blood.
Results: All solutions decreased temperature of liver and kidney not lower than 19°C and 15°C resp. No significant difference in end liver temperature was observed between different solutions with recommended volumes, however UW cooled the kidney significantly better than HTK (15°C vs. 19°C $p = 0.04$).

Cortical perfusion of livers was equally good between solutions (p = 0.28), although in kidneys UW and IGL-1 penetrated better compared to HTK (p = 0.02 and 0.03 resp.). No significant differences in kidneys were found with histology reflecting adequate wash-out.
Conclusions: This study contradicts a popular perception and provides evidence that increased viscosity of a preservation solution does not negatively affect cooling and quality of organ perfusion. In fact, we found that UW SCS may be better at perfusing and cooling the kidney. This study also provides interesting physiological data about the interaction between cold flush-out solutions and kidney and liver tissue at time of retrieval and start of preservation.

Clinical Liver Ischemia-reperfusion and preservation

OS175

COMPARISON OF 4 PRESERVATION SOLUTIONS IN LIVER TRANSPLANTATION. A MULTICENTER FRENCH REGISTRY STUDY

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Background: In the last years, the rate of marginal grafts used in liver transplantation (LT) dramatically increased. Preservation quality plays a key role in LT outcome: to date, static cold storage is the gold standard. Despite, data on the equivalence of preservation solutions (PS) are divergent. The aim of the study was to evaluate the prognostic role of 4 PS in LT.
Methods/Materials: A retrospective study of the prospective French Biomedicine Agency National Database was held from 2008 to 2013: From 6347 LT in 22 centers, 4928 LT were included. Exclusion criteria were mismatch or unknown solution and HTK solution (3%). Statistic calculation used survival analysis and linear models for the log-duration of stay in the intensive care unit (ICU).
Results: Solutions used were Celsior (n = 1452), IGL-1 (n = 2191), SCOT 15 (n = 477), UW (n = 808). Patient survival was 86%, 80% and 74% at 1, 3 and 5 year respectively, without difference between the 4 groups (p = 0.78). Graft survival was 82%, 75% and 69% at 1, 3 and 5 year respectively (p = 0.80). In multivariate analysis liver cancer was predator of patient survival. Retransplantation, recipient age and sex, dialysis, UNOS status, mechanical ventilation before LT, HCV positive antibody, HIV positive antibody were predictor of mortality and graft loss. The solution used was not an independent predictor of mortality (p = 0.23) or graft loss (p = 0.37) but was predictor of the stay in ICU at the multivariate analysis (p < 0.001): from the shortest to the longest stay we observed SCOT (median 6 days [3–12]) CELSIOR and UW (no statistical difference, median 7 days [4–14] and 7 days [3–13]) IGL1 (median 9 [6–17]). Protective factors associated with a shorter ICU stay were receiver's height (p < 0.001), presence of liver cancer (p = 0.022) donor's rescued cardiac arrest (p = 0.003).
Conclusion: Each solution was associated to different length of stay in ICU, but their use had no influence on patient or graft survival at 1, 3 and 5 years after LT.

Basic Others Ischemia-reperfusion and preservation

OS176

SUCCINATE ACCUMULATION DURING WARM ISCHAEMIA IS MUCH GREATER THAN COLD ISCHAEMIA IN MOUSE, PIG AND MAN: MECHANISTIC AND THERAPEUTIC IMPLICATIONS FOR TRANSPLANT ISCHAEMIA-REPERFUSION INJURY

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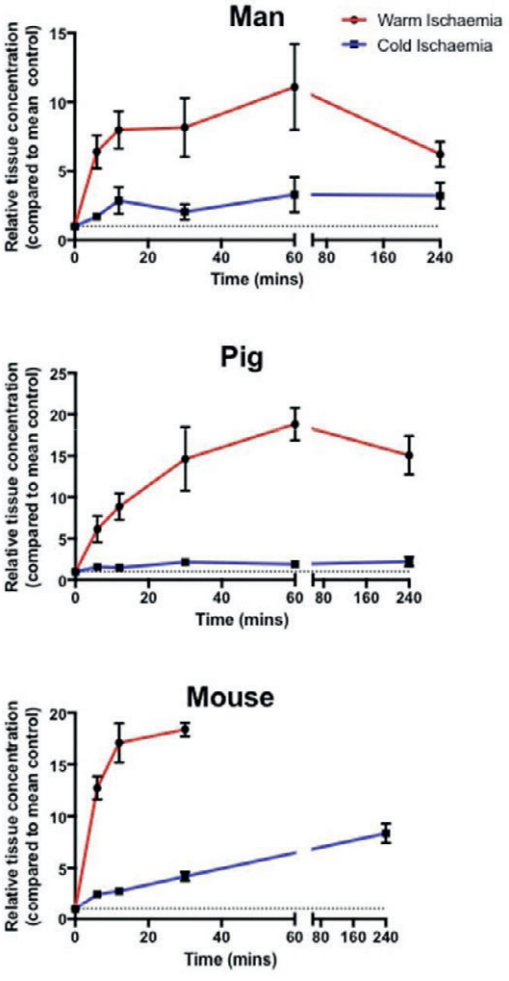
Introduction: Recent evidence from rodents suggests that the burst of reactive oxygen species associated with ischaemia-reperfusion (IR) injury is mediated through a specific metabolic pathway involving mitochondrial accumulation of the metabolite succinate. We hypothesized that succinate accumulation during ischaemia is a fundamental process shared by mouse, pig and man and may underlie the greater detrimental impact of warm ischaemia (WI) compared to cold ischaemia (CI).
Methods: Hearts from anaesthetized mice were exposed to varying periods of WI or CI (n = 5–8 per group). Porcine (n = 4) or human (n = 4) apical heart tissue was procured immediately after exsanguination (porcine) or following cross-clamp during donation after brainstem death (DBD) with appropriate ethical approval and informed consent. The apical tissue was rapidly divided into full-thickness myocardial sections and stored for variable periods of WI or



L: *Succinate accumulates during warm ischaemia in the mouse and pig heart during warm and cold ishaemia.*
ourse demonstrating relative succinate accumulation i ssue in warm and cold ischaemia. Similar findings repl and pig tissue.

CI. Metabolite concentrations were determined using mass spectrometry and compared to background levels in fully oxygenated tissue snap-frozen immediately upon removal.
Results: The metabolic changes during ischaemia were similar in mice, pigs and humans. Compared to CI, WI resulted in a much greater and more rapid increase in succinate levels. 6 min of WI resulted in 3–10 fold greater succinate accumulation than 240 mins of CI (Human; 6.384 ± 1.208 vs 1.705 ± 0.1648 [$n = 4$] p = 0.0086, pig; 3.955 ± 0.9330 vs 1.436 ± 0.2422 [$n = 4$] p = 0.0399, mouse; 12.75 ± 1.098 vs 8.366 ± 0.9447 [$n = 5$] p = 0.0165 (mean±SEM change compared to normoxic control).

Discussion: Greater succinate accumulation during WI may underlie worse IR injury and organ dysfunction following donation after circulatory death (DCD). Current dogma suggests that the metabolic processes underpinning IR injury are an inevitable consequence of ATP depletion however inhibiting the accumulation of succinate may be a novel promising therapeutic strategy to ameliorate IR injury in organ transplantation.

Clinical Kidney Other

OS177 PSYCHOSOCIAL LONG-TERM IMPACT OF DONATION ON KIDNEY LIVING DONORS - A COMPARATIVE STUDY OF TWO MAJOR EUROPEAN TRANSPLANT CENTRES

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Background: Kidney living donation appears to be a safe procedure that does not affect the health of the kidney living donors (KLDs). Although the medical outcomes are being widely studied information regarding the long-term psychological outcome of these healthy individuals is missing. In our study we assessed the postoperative psychosocial status of KLDs in two major European transplantation centres, in the Hospital Clinic of Barcelona and the Charité-University Hospital in Berlin.
Methods: All kidney living donors who underwent nephrectomy between 1998–2014 were contacted. Data from 767 donors were collected. The donors completed a battery of psychometric questionnaires (HADS, PHQ, SOC, SF-36, ACSA, life events, questions from the ELSA), as well as questions regarding satisfaction, decision to donate and the donor-recipient relationship in a total of 274 questions. In this preliminary study HAD, SOC, SF-36 were evaluated and the results of the two centers were statistically compared.
Results: Results regarding the long-term psychosocial wellbeing up to 16 years after kidney donor nephrectomy are presented and compared to the general population of the two countries. The results shows the KLDs in the studied centers are healthy adults with a QoL comparable to that of the general population for both countries. Anxiety and depression levels are low with a notable number of outliers explained. Group comparisons regarding age, gender, donor-recipient relationship, personality characteristics and recipient variables are made and multivariate analysis is performed to explain low psychosocial donor outcome.
Conclusion: The results and the differences between the two centers are critically discussed allowing conclusions regarding the donor evaluation practices and their postoperative care, as well as organizational and cultural differences.

OS178 PRESCRIBED MEDICATIONS, ADHERENCE AND SMARTPHONE USE IN KIDNEY TRANSPLANT RECIPIENTS: EVALUATING THE POTENTIAL OF A MOBILE APP TO ENHANCE MEDICATION ADHERENCE

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Background: Medication non-adherence is one of the leading problems causing poor long-term outcomes in kidney transplant recipients (KTR).
Methods: In August 2016 we initiated a randomized controlled trial. 142 KTR were 1:1 randomized to a smartphone-based application supporting adherence. In the baseline period medication, smartphone penetration, adherence (MMAS-8) and knowledge about the own medication were assessed.
Results: A total of 340 kidney transplant recipients (KTR) were screened. 191 (56%) KTR had a smartphone, of whom 159 (83%) were interested in using an app in the post-transplant aftercare. Baseline characteristics of 142 patients included in the randomized controlled trial are presented here. Medium age was 46 (12), medium time after transplantation 5.2 years (3.0–9.8). Medium number of prescribed medications was 8.2 (3.2), prescribed pills per day 11.8 (4.7). 39% of the prescribed medications (PM) could be recalled exactly (name, dosage, and schedule). 74% PM were remembered approximately (mistake in name, dosage, or schedule).

34% of patients quoted that they sometimes forget to take their medication. 48 (34%) patients had ≥10 different prescribed medications (median 12 drugs, 17 pills per day) of which only a median of 2 medications could be remembered exactly and 4 approximately (Fig. 1).

Direct correlation was found between the Morisky Adherence Score and both the time after transplantation (Spearman's rho of 0.18, p = 0.034) and age (rho 0.21, p = 0.012). A multiple regression model adjusted for gender, prescribed medications, time after transplantation and age confirmed the independent correlation of younger age and shorter time after transplantation with worse adherence. Smartphone penetration was very high among younger KTR (92% in KTR <50 years, Figure 1b).
Conclusions: Our data suggest that smartphone-based applications supporting adherence to medication may be of great value particularly in younger KTR.

OS179 TOTAL ONCE DAILY MEDICATION REGIMEN RESULTS IN LOW REJECTION AND TRANSPLANT FAILURE RATE IN HIGH RISK YOUNG ADULT KIDNEY TRANSPLANT RECIPIENTS

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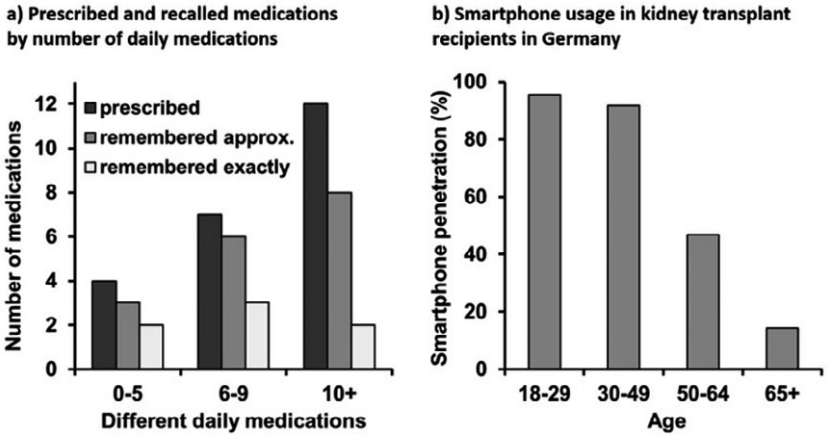
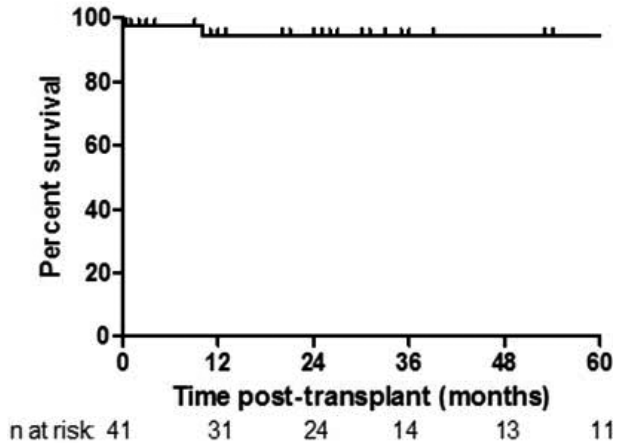
Introduction: Teenage and young adult kidney transplant recipients have a high incidence of non-adherence resulting in increased morbidity and up to 35% graft loss within 5 years. Young adulthood is a time of substantial life changes associated with increasing independence. Chaotic work and social lifestyle makes adherence to complex medication regimens difficult and unrealistic resulting in frequent omission or delay of evening immunosuppression doses. We aimed to improve outcomes by the introduction of a simplistic once daily regimen for all medications at the time of transplantation.
Methods: All young adult kidney transplant patients at a single centre aged 16–30 received a single dose of Alemtuzumab (30 mg iv) on day of transplant and Tacrolimus (Advagraf) 0.1 mg/kg and azathioprine 1 mg/kg immunosuppression (Young Adult / Non Adherence Protocol: YAP). All other medication

Figure 1.





was adjusted to a once daily dose including antihypertensives and CMV and PCP prophylaxis.
Results: 41 (31 m;10f) ESRD patients median age 23(17–59), 90% White; 10% Asian transplanted between May 2010 and March 2017 received the once daily YAP. (3 patients > age 30 at high risk of non-adherence were included). The kidney transplants comprised 25 LRD; 11 DBD; 1 DCD and 4 LURD including 2 altruistic donors. One DBD recipient had delayed graft function and early transplant failure due to renal vein thrombosis. Median serum creatinine at 3,6,12,24 and 60 months was: 122;117;119;128 and 129.5 umol/L respectively. Median tacrolimus levels at 3,6,12.24 and 60 months were 6.8; 7.5; 7.2;6.4 and 5.7 ng/dl. Median follow-up post-transplant was 26(1–81) months and 5 year graft survival is shown below in figure 1. One patient developed reversible polyomavirus nephropathy but there were no other significant infections.

Conclusions: Selective use of a total once daily medication regimen in newly transplanted young adult patients at high risk of non-adherence can result in excellent transplant survival.

OS180 THE DGF RISK SCORE HAS INSUFFICIENT PREDICTIVE VALUE FOR RENAL GRAFTS RECOVERED FROM OLDER DECEASED DONORS

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Introduction: In 2010, Irish and colleagues developed a risk prediction model for delayed graft function (DGF) in deceased donor kidney transplantation, based on a large retrospective cohort of transplants registered in the American UNOS/OPTN database.[1]This model remains the most widely used objective tool to assess DGF risk for any given donor/recipient combination. We studied whether it has satisfactory predictive value for typical North-Western European renal grafts these days: those recovered from older deceased donors.
Methods: Data from the Dutch Organ Transplantation Registry were used. We selected those renal transplants carried out between 01-01-2000 and 31-12-2015, from deceased donors aged 50 years and older, transplanted in any of the 8 transplant centres in The Netherlands (n = 3505). Donors were either DBD (n = 2052) or controlled DCD (n = 1453). The regression coefficients that Irish *et al* utilised were obtained from their 2010 paper[1] and the intercept was determined by means of extrapolation. DGF risk according to this model was calculated for each transplant. The model's discrimination was assessed by the area-under-the-receiver-operator-curve (c-statistic) and its calibration was assessed with the Hosmer–Lemeshow (HL) goodness-of-fit test and a calibration plot.
Results: Median donor age was 59 (range 50–86). The c-statistic for the Irish *et al* DGF risk model on these data was 0.70 (95% CI 0.67–0.73), indicating moderate discrimination. The calibration plot and associated HL-test ($p < 0.0001$) showed poor calibration (see figure).

Conclusion: The commonly used DGF risk model composed by Irish *et al* is not a reliable objective pre-transplant assessment tool to predict the chance of developing DGF for deceased 50 + donor kidneys in a typical North-Western European setting. A novel prediction model needs to be developed which better predicts DGF for such donor/recipient combinations.

1. Irish WD, Ilsley JN, Schnitzler MA *et al.* Am J Transplant 2010;10 (10):2279–86.

OS181 INTRA-OPERATIVE FLUID RESTRICTION IN KIDNEY TRANSPLANTATION IS AN INDEPENDENT RISK FACTOR FOR FUNCTIONAL DELAYED GRAFT FUNCTION IN LIVING DONOR KIDNEY TRANSPLANTATION

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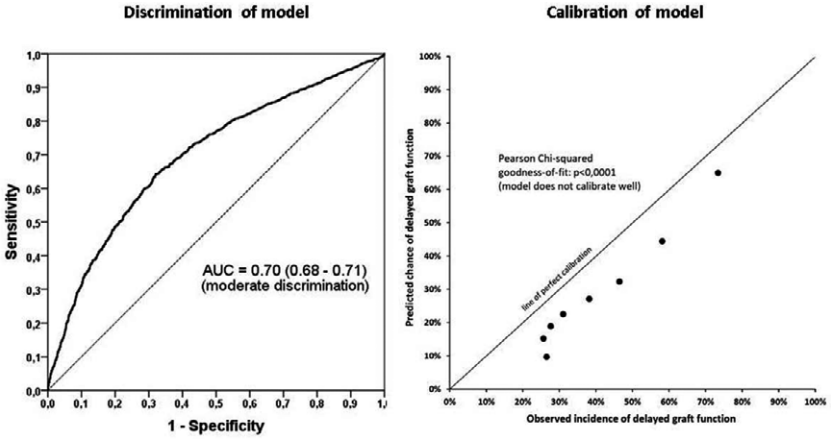
Background: To optimize individual fluid state during kidney transplantation we changed our intra-operative fluid regimen during 2015 from a standard 4–5 L balanced crystalloids to a goal directed fluid therapy (GDFT) approach. Goal was set to a stroke volume variation <10% at time of reperfusion. The first half of 2016 an increase in functional delayed graft function (fDGF) in our living donor kidney transplantation (LDKT) from 8.4%-8.9% in 2014–2015 to 26.4% in 2016 was noticed. We questioned whether the adjustment in fluid regimen was related to this increase.
Methods: A retrospective analysis of prospectively collected data was performed. Donor and recipient characteristics were obtained from hospital records. Intra-operative data were retrieved from our digital patient data monitoring system. From January 2014 to June 2016 214 LDKT were performed of which 26 patients developed fDGF and 188 did not.
Results: Univariate analysis detected various risk factors for fDGF. Donors of recipients developing fDGF were younger and taller. Recipients already on dialysis were more likely to develop fDGF compared to pre-emptively transplanted patients ($p < 0.001$). Furthermore, recipients developing fDGF received less fluid intra-operative, 34.3 (25.3–41.5) ml/kg vs 43.7 (34.2–53.6) ml/kg ($p = 0.006$) and were treated more frequently with noradrenaline, 79% vs 52% (P 0.010). Sacrifice of an artery occurred more frequently in fDGF (P 0.043). In the unadjusted analysis, the effect of the amount of fluid on developing fDGF was 0.962 (B-0,039, 95% CI 0.932–0.993 p = 0.016). When adjusted for dialysis, sacrifice of an artery and the use of noradrenaline, the amount of fluid remained independently associated with fDGF (OR=0.96, 95% CI 0.931–0.997, p = 0.032).
Conclusion: GDFT towards an SVV of 10% has led to reduced intra-operative fluid administration. This seems to be an independent risk factor for development of fDGF in LDKT.



OS182 PROSPECTIVE COMPARISON BETWEEN DCE-MR RENOGRAPHY AND 99MTC-DTPA SPECT RENOGRAPHY TO DETERMINE GFR IN TRANSPLANTED KIDNEY

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We investigated the accuracy of dynamic contrast-enhanced magnetic resonance (DCE-MR) and 99mTc-DTPA SPECT in measuring glomerular filtration rate (GFR) in renal allografts. DCE-MR and SPECT were used to measure the GFR of the kidneys of 70 kidney-transplant recipients. For MR image post-processing, the two tracer kinetic models BR and JZ2C were used. Results were compared with the reference GFR (rGFR). Bias, precision, Pearson correlation, and Bland–Altman agreement analysis were calculated for each modality compared with rGFR. For the 70 subjects, rGFR was 59.58 ± 23.72 ml·(min·1.73 m2)-1, and GFRs measured by BR, JZ2C, and SPECT were 36.78 ± 14.46, 48.99 ± 23.88, and 67.32 ± 18.44 ml·(min·1.73 m2)-1, respectively. GFR-JZ2C had the best overall performance with bias and precision of -10.58 and 14.61 ml·(min·1.73 m2)-1, respectively. Pearson correlation analysis showed that GFR-JZ2C was highly correlated with rGFR ($r = 0.81$, $p < 0.01$). Bland–Altman analysis showed a confidence interval of 57.2 ml·(min·1.73 m2)-1 for GFR-JZ2C. These findings indicated that DCE-MR can be used confidently to evaluate the renal function of transplanted kidney in the same time of determining anatomical information. DCE-MR renography was superior to SPECT renography to determine GFR in kidney transplant scenarios.

OS183 PROSPECTIVE COMPARISON OF EQUATIONS BASED ON CREATININE AND CYSTATIN C FOR THE GLOMERULAR FILTRATION RATE ESTIMATION IN CHINESE RENAL TRANSPLANT RECIPIENTS

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The First Affiliated Hospital Of Nanjing Medical University, China

Background: Currently, there is no dedicated equation to estimate glomerular filtration rate (GFR) for transplanted kidney. This study aimed to compare the performance of Scr- and CysC-based equations in Chinese renal transplant recipients.
Methods: A total of 252 stable renal transplant patients were enrolled in this study. The plasma clearance of ^{99m}Tc-DTPA (rGFR) was used as a reference standard. The Scr, CysC, and rGFR of the patients were measured on the same day. The bias, precision, accuracy (percentage of estimates within 10%, 30%, and 50% of rGFR), and agreements of 8 Scr and 5 CysC eGFR equations were assessed. The factors affecting the accuracy were also evaluated.
Results: Among the Scr-based equations, Japanese Society of Nephrology-Chronic Kidney Disease Initiatives (JSN-CKDI) equation had the best overall performance with a bias of –6.2 mL/min/1.73 m^2, and 96.1% of its estimates were within 30% of the rGFR. For the CysC-based equations, the Filler equation had the best performance with a bias of –3.9 mL/min/1.73 m^2, and 93.7% of its estimates were within 30% of the rGFR. In most cases, JSN-CKDI showed M of deviation (M was 3.47 mL/min/1.73 $m^{2)}$, which was similar to that of the Filler equation. In addition, the curve distribution (Rp5–p95 of 18.01 mL/min/1.73 $m^{2)}$ of the former were narrower compared with that of the latter. Overall, the CysC-based equations showed better performance than the Scr-based equations. In addition, significant differences were observed between bias and sex and between bias and rGFR value in some equations, whereas transplantation time and immunosuppressive regimens were not correlated with the bias.
Conclusion: The JSN-CKDI equation provides the best estimation of the GFR equations, and the CysC-based equations performed better than Scr-based equations in this population.

OS184 ESTIMATED GFR IN OLDER KIDNEY TRANSPLANT RECIPIENTS

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[1]Telemark Hospital Trust and Department Of Transplantation Medicine Oslo University Hospital, Norway; [2]Department of Transplantation Medicine, Oslo University Hospital, Norway

Background: Equations for estimation of glomerular filtration rate (eGFR) are not validated properly for kidney transplant recipients, especially not for older recipients. The primary aim of this study was to validate different creatinine based eGFR equations in kidney transplant recipients older than 70 years.
Methods: A single centre prospective study was conducted. GFR was measured by iohexol clearance at one year post transplant in consecutive kidney transplant recipients at our centre, transplanted in the period 2013 to 2015. Immunosuppression consisted of low-dose tacrolimus (C0 3–7 μg/L), mycophenolate mofetil and prednisolone. Measured GFR (mGFR) was calculated as iohexol clearance based on two samples; at 2 hours and, respectively, 5 or 8 hours after iohexol administration depending on if eGFR (CKD-EPI) was above or below 40 mL/min/1.73 m2. eGFR was calculated for a range of different creatinine based equations using information obtained at the time of iohexol clearance investigations. Bias (mean and median), precision (SD of bias and interquartile range) and accuracy (proportion within 30% (P30) and 15% (P15) of mGFR) were evaluated for each equation in patients older and younger than 70 years.
Results: A total of 486 kidney transplant recipients were included, 80 recipients (16%) were 70 years or older. Among recipients older than 70 the BIS1 and FAS equations had significantly lower bias ($p < 0.001$) and also slightly better precision and accuracy than the other equations (table 1). The MDRD equation showed significantly lower bias ($p < 0.001$) and better accuracy ($p < 0.001$) than all other equations in those younger than 70 (table 1).

Equation	Mean Bias	Median Bias	SD of Bias	Interquartile range	P30	P15
> 70 years						
BIS1	0.13	0.04	8.70	12.03	88.8	65.0
MDRD	3.88	1.62	10.39	11.58	85.0	62.5
FAS	-0.48	-1.35	9.02	11.93	88.8	66.3
CKD-EPI	3.87	1.63	10.78	13.86	82.5	61.3
Cockcroft-Gault	5.92	4.37	13.60	18.60	73.8	47.5
< 70 years						
BIS1	18.93	12.70	24.23	24.97	57.9	36.0
MDRD	1.40	0.20	12.24	15.03	88.7	58.6
FAS	6.87	5.82	12.74	14.85	80.3	55.4
CKD-EPI	6.99	5.31	13.28	16.53	79.3	52.0
Cockcroft-Gault	21.60	18.00	20.78	25.57	47.8	24.4

Conclusions: In elderly kidney transplant recipients all equations except the Cockcroft-Gault performed acceptably in predicting GFR, although FAS and BIS1 had significantly lower bias than MDRD and CKD-EPI. In patients younger than 70 years, the MDRD equation was superior to the other equations.

Clinical Liver Other

OS185 LANDSCAPE OF THE UNITED STATES LIVER TRANSPLANTATION

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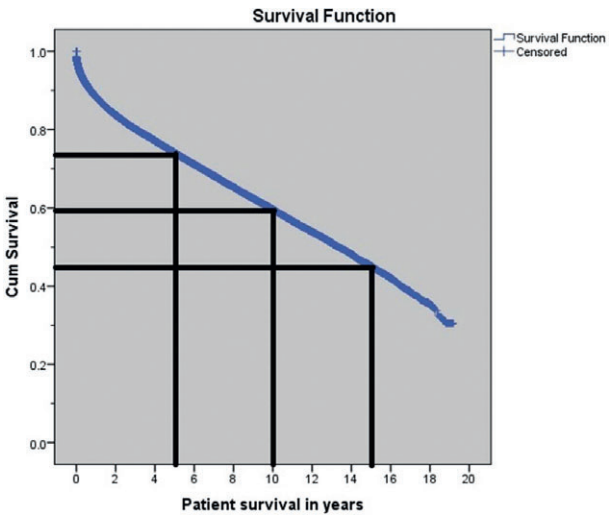
Background: SRTR database has a resourceful data on donor, recipient, and long-term liver transplantation outcomes in the United States. Primary objective was to carry on surveillance of SRTR database for donor/recipient characteristics and long-term patient survival. Secondary objectives were to analyze the functional and medical condition at listing and transplant



Methods: Surveillance of historical data from STAR files was performed from 1994–2013. Included in the study was first time whole organ cadaveric adult liver transplantation. Percentages, mean/median, and Kaplan-Meier curves were used to analyze donor/recipient demographic variables and long term patient survival.
Results: Of the 223,648 study population, 66,461 met the inclusion criteria with donor/recipient characteristics of mean age, percent male, median BMI of 39.89 ± 17.1, 60.2%, 25.4(7.4–73.2), and 53 ± 10, 66%, 27.38(10.76–72.86) respectively. Median cold (hours) and warm (minutes) ischemia time of 7(0–49.5) and 43(0–302) respectively, median MELD, waitlist and length of stay in days were 20(6–75), 101(0–6286), and 11(0–3045). Percent cum survival over 5, 10, 15 years are 75, 60, 45 respectively. Functional status at listing and transplant requiring total assistance were 15 to 24% respectively. Patients in ICU at the time of listing and transplant were 7.1 and 13.7% respectively.
Conclusion: From the time of listing to transplant there is a significant decline in the medical and functional status of the transplant candidates. Despite decline in medical and functional status, the long term median survival of liver transplant recipient has been good.

OS186 DESCRIPTION OF BODY WEIGHT PARAMETERS UP TO 3 YEARS AFTER SOLID ORGAN TRANSPLANTATION: THE PROSPECTIVE SWISS TRANSPLANT COHORT STUDY

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Background: Weight gain and obesity are serious concerns after organ transplantation (Tx). Due to diverse study methods, an unbiased comparison of body weight parameter across organ groups is lacking.
Methods: Based on the same methodology, we compared the evolution of weight parameters up to 3 years post-Tx using data from the prospective, nationwide Swiss Transplant Cohort Study. Changes in mean weight and body mass index (BMI) category were compared to reference value from 6 months post-Tx to account for potential pre- and early post-Tx fluid overload. Descriptive statistics were used to describe the data.
Results: We examined 1359 adult recipients, kidney (58.3%), liver (21.7%), lung (11.6%), and heart (8.4%), transplanted between 05/2008 and 05/2012. In all organ groups obesity increased over time. At all measurement points, kidney Tx patients had the highest prevalence of obesity (>19%), which is about twice the measure compared to the Swiss general population. Compared to the other organ groups at 3 years post-Tx, liver Tx recipients had the greatest weight gain (mean 4.8 ± 10.4 kg), the highest incidence of new onset obesity (38.1%) and the biggest proportion of patients (57.4%) gaining >5% body weight. Within organ groups, weight gain from 6 months to 3 years post-Tx differed between BMI categories: In liver Tx, those who were obese at 6 months post-Tx had the highest weight gain; while underweight kidney, lung and heart Tx patients gained most weight and accordingly, 41.2%, 53.8% and 100%, respectively, switched to the normal weight category.
Conclusion: Weight gain patterns differed across organ groups and BMI categories, yet the majority of our Swiss Tx recipients experienced lower post-Tx weight gain compared to international Tx data. Weight gain in kidney, lung and heart Tx patients who are underweight at 6 months seems to be favorable. However, liver Tx patients who are obese at 6 months post-Tx might benefit from interventions to prevent subsequent weight gain.

OS187 LOW SKELETAL MUSCLE MASS IS ASSOCIATED WITH INCREASED HOSPITAL COSTS IN PATIENTS WITH CIRRHOSIS LISTED FOR LIVER TRANSPLANTATION

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Ersamus Mc University Medical Center, The Netherlands

Background: Low skeletal muscle mass (sarcopenia) is associated with increased morbidity and mortality in liver transplant candidates. Our aim was to investigate the association between sarcopenia and hospital costs in patients listed for liver transplantation.
Methods: Consecutive patients with cirrhosis listed for liver transplantation between 2007–2014 in a Eurotransplant centre were identified. Patients listed with high urgency, for acute liver failure, re-, and multivisceral transplantation were excluded. Skeletal muscle mass was measured on computed tomography (skeletal muscle index [SMI], cm^2/m^2) performed within 90 days from waiting list placement. Sex-specific quartiles were created. The lowest quartile represented patients with sarcopenia.
Results: In total, 363 patients were listed during the study period, of which 225 were included. Median time on the waiting list was 169 (IQR 46–306) days and median MELD-score was 16 (IQR 11–20). The median total hospital costs in patients with sarcopenia were €11,294 (IQR 3,570–46,469) compared with €6,878 (IQR 1,305–20,683) in patients without sarcopenia (p = 0.008). In multivariable regression analysis an incremental skeletal muscle mass was significantly associated with a decrease in total costs (€458 per incremental SMI, 95%CI 14–902, p = 0.043), independent of the total time on the waiting list. Although costs during admission for transplantation did not significantly differ between patients with and without sarcopenia, a significant difference was found when these costs were added to the waiting list costs (€98,703 [IQR 75,909–121,071] vs. €81,982 [IQR 58,999–111,497], p = 0.037).
Conclusion: Sarcopenia is independently associated with higher costs during waiting list placement of liver transplant candidates, as well as with higher total hospital costs in patients undergoing liver transplantation. Optimizing patients' skeletal muscle mass may therefore lead to a decrease in hospital expenditure.

OS188 OUTCOME OF LIVER TRANSPLANTATION FOR HEPATITIS A VIRUS RELATED ACUTE LIVER FAILURE: COMPARATIVE STUDY WITH HEPATITIS B VIRUS RELATED ACUTE LIVER FAILURE IN ADULT RECIPIENTS

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Asan Medical Center University of Ulsan College Of Medicine, Korea

Background: Hepatitis A virus (HAV) infection can cause acute liver failure (ALF). This study intended to evaluate the results of liver transplantation (LT) for HAV-related ALF (HAV-ALF) and to compare the clinical profiles and outcomes between the patients undergone LT for HAV ALF and hepatitis B virus (HBV)-related ALF (HBV-ALF) in adult patients.
Methods: Between January 2005 and December 2014, 3616 cases of adult LTs were performed at Asan Medical Center. Among them, this study included adult recipients who underwent LT for HAV ALF (n = 29) that were compared with adult recipients underwent LT for HBV ALF (n = 34).
Results: HAV-ALF group included 18 males and 11 females with mean age of 33.1 years. The MELD score was 34.1. They underwent living-donor LT in 19 and deceased-donor LT in 10. Post-transplant HAV recurrence developed in 4 patients (13.8%). Causes of patient death after LT for HAV-ALF included sepsis from pancreatitis (n = 3), HAV recurrence (n = 3), graft infarction (n = 1), multiorgan failure (n = 1), and brain death (n = 1). Compared with HBV-ALF group, HAV-ALF group was associated with younger recipient age (p = 0.001), higher leucocyte count (p = 0.013), higher serum creatinine (p = 0.000), and explant liver weight-to-standard liver volume ratio (p = 0.000) Graft survival rates after LT for HAV- and HBV-ALF were 65.5% and 88.0% at 1 year and 65.5% and 84.0% at 5 years, respectively (p = 0.048). Patient survival rates after LT for HAV- and HBV-ALF were 69.0% and 88.0% at 1 year and 69.0% and 84.0% at 5 years, respectively (p = 0.093). Multivariate analyses demonstrated that acute pancreatitis and HAV recurrence were independent risk factors of graft and patient survival.
Conclusions: Post-transplant outcome was poorer in patients with HAV-ALF than in those with HBV-ALF due to higher occurrence rates of acute pancreatitis and viral reinfection. Special attention should be paid to prevention, detection, and treatment of these risk factors after LT for HAV-ALF.

OS189 FEMALE GENDER AND HYPERFILTRATION: INDEPENDENT PREDICTORS OF ACUTE KIDNEY INJURY AFTER LIVER TRANSPLANTATION

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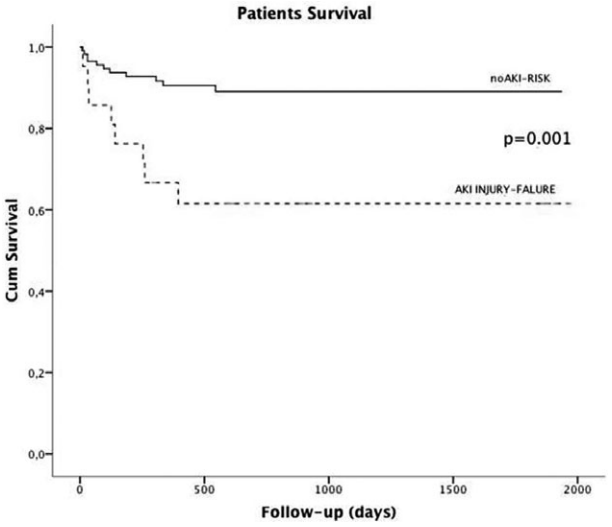
Sapienza University Of Rome, Italy

Background: Acute kidney injury (AKI) after liver transplantation (LT), in particular stages 2–3, has recently been recognized to be important predictor for worse post-LT outcome and increased mortality. Risk factors for post-LT AKI are multiple and include pre-LT renal dysfunction, lower pre-LT serum creatinine (sCr) levels, higher MELD score, HCV infection, diabetes, intraoperative haemodynamic instability, post-LT graft dysfunction and infections. Abnormally lower sCr values (<0.4 mg/dL) are frequent before LT, particularly in female, and are associated to hyperfiltration, not related to a better kidney function. Hyperfiltration has been recognized to be an important predictor of post-LT mortality. Aims of this study are to evaluate incidence and risk factors for AKI, its relation with hyperfiltration and its impact on patients' survival.
Methods: Retrospective single-centre study of 145 patients (117 M, 28 F) who underwent LT (January 2008–October 2015). We considered renal function from listing to transplant and within one week post-LT, functional recovery of the graft, intraoperative parameters. AKI defined and classified on the basis of KDIGO Guidelines (2012). Hyperfiltration defined as eGFR>120 ml/min/1,73 m2.



Results: 22 out of 145 patients (15%) experienced post-LT AKI stages 2–3 (13/117M, 11.1%; 9/28F, 32.1%). Survival was significantly lower in patients with AKI stages 2–3 (42% vs. 58%, p = 0.001) (see Figure 1).

The evaluation of risk factors on the univariate analysis evidenced female gender, lower pre-LT sCr, higher LAB-MELD and renal hyperfiltration as predictive factors for development of AKI stages 2–3. In the multivariable analysis, the independent predictors of development of AKI stages 2–3 were female gender (p = 0.020) and renal hyperfiltration (p = 0.045).
Conclusion: We showed a significant increased mortality in patient developing AKI post-LT. Female gender and renal hyperfiltration resulted independent predictors for development of AKI post-LT.

OS190 ASSESSMENT OF THE EFFICIENCY OF ALBUMIN DIALYSIS WITH THE "PROMETHEUS" SYSTEM IN THE TREATMENT OF PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE

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Department Of General Transplant And Liver Surgery, Poland

Background: At present, liver transplantation is the only recognised method of treatment patients with acute-on-chronic liver failure (AoCLF), which, however, is not widely applied due to the highly specialised nature of the procedure, its high costs, and most of all, a limited pool of organs for transplantation.
Aim: The aim of the thesis was to assess the use of the "Prometheus" - albumin dialysis non-biological liver support system (FPSA - Fractionated Plasma Separation and Adsorption) in the treatment of patients with AoCLF.
Material and method: A retrospective analysis was conducted on 134 patients treated in the Department between 2001 and 2012 for AoCLF. Patients were divided into a 31-person group that received standard therapy – the AoCLF-SMT group and a 103-person group of patients that additionally received albumin dialysis – the AoCLF-FPSA group. The groups were compared independently within each disease entity. Biochemical markers of liver function, kidney function, morphological parameters and vital functions were analysed and compared. The examination involved complications of both therapies.
Results: The survival of patients was compared across the following periods: a month, 12 months, and 144 months, showing respectively 50.5%, 38.8% and 37.9% survival rates in the AoCLF-FPSA group and 22.6%, 12.9% and 9.7% survival rates in the AoCLF-SMT group.
Conclusions: Albumin dialysis with the "Prometheus" system was found to be efficient in the treatment of patients with acute-on-chronic liver failure through decreasing the levels of total bilirubin concentration in patient's blood and significantly improving kidney function, as well as positively impacting the patients' central nervous system function through reducing the degree of encephalopathy. The use of albumin dialysis with the "Prometheus" system increases the survival of patients with acute-on-chronic liver failure with high degree of liver encephalopathy and high MELD scores.

OS191 THE PROGNOSTIC VALUES OF SCORING SYSTEMS FOLLOWING LIVER TRANSPLANTATION

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[2]Akdeniz University Hospital Anesthesiology Icu Department, Turkey;
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Introduction: The aim of the study was to evaluate the prognostic efficacy of various physiologic scoring systems recorded at early postoperative period following liver transplantation (LT) on prediction of ICU stay, mechanical ventilation (MV) duration and mortality.
Materials and methods: APACHE II, SOFA, MELD scores obtained at first day of ICU admission, ICU stay, MV duration and early mortality (28 days) of the patients who have undergone liver transplantation at Akdeniz University Anesthesia ICU between 2010 and 2016 were evaluated retrospectively. The patients under 12 years old (n = 39), suffering from fulminant hepatitis (n = 13) and undergone retransplantation were not included in the study. The study was improved by ethic committee.
Results: 213 patient records were evaluated. Median MV duration was 5 hours (1–186) and mean ICU stay was 35 hours (8–552). Mean APACHE II, SOFA and MELD scores were 9(2–29), 6(2–16) and 18(9–36) respectively. All scoring systems significantly predicted the patients whose ICU stay were higher than the mean value (p < 0.001). MELD score was insufficient to assume the patients with MV>5 hours while other were predictive. Early and 3 month survivals were 89% and 86%, respectively (SE: 0.03). ROC analysis results performed to identify the cut off values for predicting early mortality for APACHE and SOFA revealed 10.5 (AUC=0.853) and 6 (AUC=0.815), respectively (p < 0.001). Single and multi-variant Cox regression analysis revealed significant efficiency of APACHE and SOFA scoring systems at predicting early mortality.
Discussion: The patients with high APACHE II and SOFA scores following LT had high mortality, long ICU stay and MV duration in this study. MELD score was insufficient to predict these prognostic parameters. Studies including larger series of patients with various illness severities should be conducted to reveal the potential efficiency of scoring systems for predicting the prognosis of the patients undergoing LT.

OS192 HIGH SENSITIVITY AND SPECIFICITY OF PHOSPHATIDYLETHANOL FOR DETECTION OF ALCOHOL CONSUMPTION IN THE TRANSPLANT SETTING

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[1]University Hospital Hamburg Eppendorf, Germany; [2]University Hospital Hamburg Eppendorf, Germany; [3]University of Bern, Switzerland; [4]University Medical Center Heidelberg, Germany

Phosphatidylethanol (PEth) is a new, highly specific direct alcohol marker which can detect alcohol consumption dating back up to three weeks. The aim of this study was to assess its diagnostic value in the liver transplant setting.
Methods: In this prospective study the alcohol marker PEth, ethanol, methanol, carbohydrate deficient transferrin (CDT), ethylglucuronide in urine (uEtG) and hair (hEtG) were tested in pre- and post-transplant patients with underlying alcoholic liver disease. Results were compared with patients' statements in a written questionnaire.
Results: Altogether 51 pre- and 61 post-transplant patients were included. 28/112 (25%) patients tested positive for at least one alcohol marker. There was no difference between patients pre and post transplantation. PEth alone revealed alcohol consumption in 18% of patients. With respect to detection of alcohol intake in the preceding week, PEth showed a 100% sensitivity. PEth-testing was more sensitive than the determination of ethanol, methanol, CDT or uEtG alone (sensitivity 25% (confidence interval [CI] 95%, 7–52%), 25% (7–52%), 21% (6–45%), and 71% (41–91%), respectively), or these four markers applied in combination. Specificity of all markers was 92% or higher. Additional testing of hEtG revealed alcohol consumption in 7 patients, who were not positive for any other alcohol marker. This indicates that these patients had not consumed alcohol in the preceding month, but in a time period of 2–6 months prior to presentation.
Conclusions: PEth was found to be a highly specific and sensitive marker for detection of recent alcohol consumption in pre- and post-transplant patients. It is determined in a blood specimen which in contrast to testing EtG in the urine cannot be falsified by the patient. The additional determination of hEtG was useful in disclosing alcohol consumption 3–6 months retrospectively.

Clinical Kidney Donation and donor types

OS193 LESSONS LEARNED FROM THE CLINICAL USE OF NORMOTHERMIC REGIONAL PERFUSION (NRP) IN UNCONTROLLED DONATION AFTER CIRCULATORY DEATH (UDCD)

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The national protocol for the uDCD program restricts the donor age to < 55 y, the no flow period to <30 min and the total warm ischemia time (WIT) to <150 min. In situ kidney perfusion is realized by a double-balloon catheter (ISP) or by a nRP. Perfusion machine is systematic. Only non-immunized recipients for a 1st transplantation were eligible. 499 kidney transplantations (KTR) (period 2007–2014) were analyzed. In situ organs perfusion by nRP was performed in 50%, mean WIT was 135 min and mean cold ischemia times (CIT) was 14 hours.

Analysis risk factors of primary non function (PNF, $n = 37$) and graft failure (eGFR < 30 ml/min or graft loss at 1 year, $n = 66$) were performed by logistic regression.

PNF risk factor was donor age [OR = 0.95, p = 0.002] and a sensibility analysis shown a center effect.

Graft failure risk factors (excluding PNF) were donor BMI [OR = 1.2, p < 0.001] and ISP (compared to nRP) [OR = 1.2, p < 0.001]. No effect of donor age, no flow period, WIT or CIT was found in multivariate analysis.

Graft survival (period 2007–2015 endpoint 31 December 2016) was significantly different according to donor type with at 5 years 76% [71% - 79%] for uDCD, 68% [67% - 69%] for brain death extended criteria donors (DBD ECD) and 84% [84% - 85%] for optimal DBD. After adjustment by Cox model on recipient age, a significant increased risk of failure remains in uDCD recipients compared to optimal DBD [HR = 0.54, p < 0,001]. After the exclusion of failures of less than 2 months and adjustment by Cox model on recipient age, we observed a significant difference risk of failure between uDCD recipients compared to optimal DBD [HR = 0.63, p = 0.02] and DBD ECD [HR = 1.28, p = 0.03].

In conclusion, uDCD kidneys are an additional source of valuable transplants with a graft survival between those with optimal DBD and DBD ECD. The use of nRP seems to decrease graft failure, through restoration of oxygenated blood, acting as the first step of pre-reconditioning.

OS194 A PROLONGED AGONAL PHASE OF GREATER THAN 1 HOUR IN DONATION AFTER CARDIAC DEATH (DCD) KIDNEY TRANSPLANTATION DOES NOT IMPACT ON LONG-TERM DEATH CENSORED GRAFT SURVIVAL

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Background: Shortage of organs, and resulting long wait times have been a significant issue in transplantation. Within the UK, donation after cardiac death (DCD) has significantly increased the number of kidney transplants performed, and contributed to a reduction in average wait times. Transplantation centres have often stepped-down from organ retrieval if cardio-respiratory arrest has not occurred within 1 hour of controlled withdrawal of life-supporting treatment, due to concerns with prolonged organ ischaemia during the agonal phase. In this review we look at long-term outcomes of DCD kidney transplants with agonal phases >1 hour compared with those with agonal phases <1 hour.
Methods: Data from 2010 to 2016 was collected from the NHSBT database. 4493 DCD adult kidney transplant recipients were identified, 4035 received kidneys from donors with an agonal phase <1 hour and 448 received kidneys from donors with an agonal phase >1 hour. Patients receiving a first transplant, second transplant, and dual transplant were included. Those without complete data for withdrawal time, death censored graft survival, donor age, and HLA match were excluded.
Results: For agonal phase <1 hour, 1 year death censored graft survival was 93.3% and 3 year death censored graft survival was 90.1%. For agonal phase >1 hour, 1 year death censored graft survival was 95.5% and 3 year death censored graft survival was 93.4%. Risk adjustment (donor age, recipient age, cold ischaemic time (CIT), donor history of hypertension, machine perfusion, donor pre-mortem creatinine, HLA mismatch, recipient primary renal disease, transplant centre) demonstrated no difference in death censored graft survival up to 5 years post-transplant when the agonal phase was >1 hour, when compared to an agonal phase <1 hour (HR 0.69, 95% CI 0.46–1.02, p = 0.065).
Conclusion: This study has demonstrated that there is no significant impact of a prolonged agonal phase on the function and long-term outcome of kidneys from DCD donation.

OS195 WARM ISCHAEMIA TIME AFTER CARDIAC ARREST IS ASSOCIATED WITH GRAFT LOSS IN CIRCULATORY-DEAD DONOR KIDNEY TRANSPLANTATION: A EUROTRANSPLANT COHORT STUDY

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Background: Kidneys from circulatory-dead donors (DCD) are increasingly used for transplantation. Consensus reports state to limit the duration of warm ischaemia time in DCD donors, but it's effect on graft outcome has rarely been investigated.
Methods: We investigated death-censored graft survival in 18,065 adult recipients of single deceased-donor kidney transplants in the Eurotransplant region: 1,059 recipients of DCD kidneys and 17,006 recipients of brain-dead donor (DBD) kidneys. DCD warm ischaemia time was defined as the time between cardiac arrest and cold flush in the donor. Graft survival was analyzed by cox regression, both unadjusted as well as adjusted for donor, preservation, and recipient variables.
Results: Graft survival was worse in recipients of DCD kidneys compared to recipients of DBD kidneys (unadjusted HR 1.31, 95%CI 1.19–1.44, p = 0.00002; adjusted HR 1.28, 95%CI 1.10–1.46, p = 0.008). More specifically, the increased risk of graft loss in recipients of DCD kidneys was only evident compared to recipients of standard criteria DBD kidneys, with an almost two-fold increased risk of graft loss (HR 1.79, 95%CI 1.66–1.93, p < 0.00001), while there was no difference in graft survival in recipients of DCD kidneys vs. expanded criteria DBD kidneys (p = 0.80). Interestingly, DCD donation was no longer associated with increased graft loss when also adjusted for donor warm ischaemia time (p = 0.51), while donor warm ischaemia time was (p = 0.02). In recipients of DCD kidneys, the duration of donor warm ischaemia time increased the risk of graft loss (adjusted HR 1.02 per minute increase, 95% CI 1.00–1.04, p = 0.03). There was no signification interaction between donor warm ischaemia and donor age, cold ischaemia time, or the kidney donor risk index on graft loss.
Conclusion: This study on the Eurotransplant registry demonstrates that the duration of warm ischaemia time in DCD donors is associated with worse graft survival after kidney transplantation.

OS196 SUCCESSFUL LONG TERM RENAL FUNCTION IN KIDNEY TRANSPLANTS FROM DECEASED CARDIAC DONORS AFTER 20 MINUTES OF CIRCULATORY ARREST

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Background: The pool of kidneys currently available for transplantation could be expanded with the procurement of organs from the Donation after Circulatory Death (DCD). Italy differs from other countries for a legally required no touch period of 20 minutes.
Methods: Here, we report the long-term results of the first Italian experience in DCD kidney transplanted patients from September 2008 to January 2017.
Results: We performed 32 DCD kidney transplants. The mean age was 49.5 y+/- 7.61 years for donors and 52.72 ± 10.8 for recipients. Mean warm ischemia time was 46.6 ± 7.0 minutes while the total mean cold ischemia time was 17.3 ± 4.0 hours (cold storage + machine perfusion). The perfusion parameters were the following: mean perfusion flow 0.95 ± 0.27 ml/min and median renal resistance (RR) 0.21 (IQ 0.15 - 0.34). The median follow up was 54 months (range: 1–108 months). The post transplant complications were: Delayed Graft Function 100%, urinary leakage 6%, acute rejection 3%, pyelonephritis 3%, venous thrombosis 3%, Primary Non Function 3%. 1 year graft survival was 96.5% while 5 years graft survival was 93.1%.

4 patients died with a functioning graft. During the follow up period the median GFR was 45 ml/min/1.73 m2 (range: 40 – 80). GFR was inversely correlated with RR ($r = 0.89$, $p = 0.03$).
Conclusion: Our results show a long term good DCD graft function despite of an extended warm ischemia time required by the Italian law.

OS197 DE NOVO SINGLE KIDNEY TRANSPLANTATION FROM MAASTRICHT CATEGORY III DONATION AFTER CIRCULATORY DEATH DONORS AGED 60 YEARS OR OVER: IS IT SAFE?

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Background: Donation after cardiac death (DCD) donors represent a valuable source of organs. However, DCD kidneys transplants (KTx) have higher rates of primary non function (PNF), delayed graft function (DGF), and acute rejection compared to KTx from donation after brain death (DBD) donors. Due to an increased risk of premature graft loss, some authors have recently advised against the use of elderly DCD kidneys. Available data on this topic are scarce. We investigated the outcomes of single KTx from Maastricht category III DCD donors aged 60 years or over.
Methods: In this single centre prospective observational study we analyzed data from 113 consecutive de novo single kidney Tx from Maastricht category III DCD donors performed between 2007 and 2013. Only patients treated with the same immunosuppressive protocol and KTx performed using grafts preserved on static cold storage were included. KTx were divided in two groups: YOUNG (donor < 60 years) or OLD (donor ≥ 60 years). Outcomes were compared between groups at 3 years of follow up.
Results: Demographic and baseline characteristics are detailed in the table.

	OLD	YOUNG	P
Patients (#)	40	73	-
Follow up (years)	3.4 ± 2	3.6 ± 1.9	ns
Caucasian ethnicity (%)	40	36	ns
Afro-Caribbean ethnicity (%)	17.5	29	ns
De novo transplant (%)	100	100	ns
Recipient age (years)	58 ± 8	47 ± 11	<0.05
Donor age (years)	66 ± 5	40.5 ± 12	<0.05
HLA mismatch (#)	3.7 ± 1	3.4 ± 1	ns
Cold ischemia time (hours)	15 ± 4.5	15 ± 5	ns
Anti-thymocyte globulin induction (%)	72.5	81	ns
Cyclosporine-mycophenolate mofetil-steroid maintenance (%)	100	100	ns

After 3 years of follow up, OLD recipients showed significantly lower patient survival (75 vs 92%, $p < 0.05$), death-censored graft survival (75 vs 89%, $p < 0.05$), and calculated MDRD GFR (38 ± 5 vs 50 ± 6 mL/min, $p < 0.05$) compared to YOUNG. The incidence of DGF and renal vein thrombosis was significantly higher in OLD than YOUNG: 70 vs 47% ($p < 0.05$) and 10 vs 0% ($p < 0.05$), respectively. Cumulative rejection rates (YOUNG: 18 vs OLD: 12.5%), post-transplant diabetes, Polyomavirus infection and PTLD were comparable ($p = ns$).
Conclusions: Single KTx from Maastricht category III DCD donors aged 60 years or over are at increased risk of early graft loss and show inferior graft function compared to KTx from younger donors. Higher incidence of perioperative complications such as graft thrombosis and DGF should be expected with increased post-transplant mortality.

OS198 SIMILAR MIDTERM OUTCOMES FOR RECIPIENTS OF KIDNEYS FROM MAASTRICHT CATEGORY III DONATION AFTER CARDIAC DEATH DONORS AND DONATION AFTER BRAIN DEATH DONORS: A SINGLE CENTRE PAIR MATCHED ANALYSIS

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Background: Kidneys from donation after cardiac death donors (DCD) have been demonstrated to have higher rates of primary non function (PNF), delayed graft function (DGF), and acute rejection than kidneys from donation after brain death donors (DBD). Inferior graft survival and function have been recently reported.
Methods: In this single centre prospective observational study with 3 years of follow up, we performed a matched pair analysis of data collected from 296 consecutive deceased donor kidney transplants (113 Maastricht category III DCD and 183 DBD) executed between 2007 and 2013. Only de novo transplant recipients treated with cyclosporine, mycophenolate mofetil, and steroid were included. Dual kidney transplants and transplants from grafts preserved on hypothermic machine perfusion were not considered.
Results: Patient demographic and baseline characteristics are detailed in Table 1.

	DCD	DBD	P
Patients (#)	113	183	-
Caucasian ethnicity (%)	37	36	ns
Afro-Caribbean ethnicity (%)	25	16	ns
Recipient age (years)	50 ± 11	48.5 ± 12	ns
Donor age (years)	49 ± 16	50 ± 13	ns
HLA mismatch (#)	3.5 ± 1	3 ± 1	<0.05
Cold ischemia time (hours)	15 ± 5	16 ± 5	<0.05
Primary KTx (%)	100	100	ns
Cyclosporine-Mycophenolate mofetil-steroid maintenance (%)	100	100	ns
Follow up (years)	4 ± 2	3.5 ± 2	ns

Differences in HLA mismatch and cold ischemia time reflect different allocation policies between DBD and DCD organs in the United Kingdom. DCD and DBD transplants showed similar 1-year (89 vs 92%) and 3-year (84 vs 88%) patient survival rates ($p = ns$). One-year (93 vs 93%) and 3-year (82 vs 90%) death-censored graft survival rates were also comparable ($p = ns$). No statistically significant differences were observed between DCD and DBD in incidence of renal vein thrombosis (3.5 vs 1.6%), cumulative acute rejection rates (17 vs 24%), and calculated 3-year MDRD GFR (54 ± 10 vs 56 ± 11 mL/min). DCD recipients had higher incidences of PNF (7 vs 0.5%) and DGF (55 vs 26%) than DBD ($p < 0.05$). Multifactorial analysis showed that donor age was the most important risk factor for early graft loss after DCD transplantation.
Conclusions: Our data show similar midterm outcomes for Maastricht category III DCD and DBD primary kidney transplant recipients treated with cyclosporine, MMF and steroid. These findings further support the development of Maastricht category III DCD kidney transplant programs.

OS199 A CASE FOR THE USE OF DCD KIDNEYS IN PAEDIATRIC RECIPIENTS: A META-ANALYSIS

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Background: Donation after circulatory death (DCD) kidneys have been used extensively in the adult population with outcomes comparable to donation after brain death kidneys (DBD) observed. The paediatric population has not seen the same drive due to concerns over graft survival. This study assessed adult and paediatric outcomes of DCD as compared to DBD kidneys.
Methods: This review collected data from 3 databases: MEDLINE, Journals@OVID and Books@OVID. Re-transplants, bilateral and all kidney transplants were included; multiple organ transplantation was excluded. The primary outcome measure was the 1 year graft survival, secondary outcome measures were rates of delayed graft function (DGF), primary non-function (PNF) and acute rejection. Data synthesis was carried out using Revman Version 5. Relative risks (RR) were quoted for binary outcomes and mean difference (MD) for continuous outcomes. Mantel Haenszel testing was used to assess differences between the DBD and DCD groups using a fixed effects model.

Results: A total of 31,240 kidney transplants from 11 adult and 4 paediatric studies were reviewed. In both adult and paediatric populations 1-year graft survival was comparable in both DBD and DCD groups (RR 1.23 95% CI 0.78 - 1.92 for adults and RR 1.02 95% CI 0.96 - 1.08) in paediatrics). In the adult group the PNF rate was higher in the DCD group (RR 1.3 95% CI 1.06 - 1.6) but was equivalent in the paediatric group (RR 1.24 95% CI 0.63 - 2.46). Delayed graft function was higher in the DCD group in both adult (RR 1.94 95% CI 1.86 - 2.03) and paediatric recipients (RR 1.77 95% CI 1.34 - 2.34). Long term DCD and DBD graft function at 5 years was comparable in both adults (RR1.23 95% CI 0.78 - 1.92) and children (RR 1.26 95% CI 0.67 - 1.72).
Discussion: This meta-analysis supports the continued use of DCD kidneys in both the adult and children without detriment to graft survival. Further studies on this issue should collect and assess data on 10 year patient and graft survival.

OS200 KIDNEY TRANSPLANTATION FROM UNCONTROLLED DONORS AFTER CIRCULATORY DEATH: REAL-WORLD DATA FROM AN OBSERVATIONAL COHORT

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Kidney transplantation from controlled donors after circulatory death (DCD) has substantially increased in Europe and the USA in the last decade, allowing for an increase in the amount of kidney transplants performed, obtaining good long-term results. However, there is scarce information on the long-term results of kidney transplantation from uncontrolled DCD (uDCD) We report the largest single-center series of kidney transplants from uDCD.
Aim: To analyze the factors that can be predictive of graft loss due to TMA in uDCD.
Methods: Observational cohort study that included all kidney recipients from uDCD (n = 774) and from donors after brain death (DBD) (N = 613) performed in our center between 1996 and 2015. Recipients from DBD were divided into two groups: standard criteria brain death donors (SCBD) (n = 366), and expanded criteria brain death donors (ECBD) (n = 247). Clinical outcomes were compared.
Results: After the introduction of kidney transplantation from uDCD, the median waiting time on the kidney transplant list for patients in dialysis decreased from 25.1 months (IQR 13.0–54.9) to 12.9 months (IQR 5.6–24.8), and 107 patients were transplanted pre-emptively. One, 5 and 10-year graft survival rates for SCBD were 91.7%, 86.2% and 81.3% respectively vs. 86.0%, 75.7% and 61.3% for ECBD and 85.1%, 79.2% and 73.3% for uDCD ($p < 0.001$). Graft survival in transplants from uDCD donors was worse than those from SCBD ($p = 0.028$) but better than in those from ECBD ($p = 0.028$). The main cause of graft loss in uDCD was primary nonfunction, mainly due to thrombotic microangiopathy. Multivariate Cox regression analysis for graft loss (censored for death) showed an association between the presence of delayed graft function (DGF) and donor type. In presence of DGF, kidney transplant recipients from DBD had a higher risk of graft loss, both those from SCBD (HR 1.79 95% CI 1.08–2.99) and ECBD (HR 2.75.95% CI 1.67–4.51). In absence of DGF, recipients from ECBD had a higher risk of.

Clinical Kidney Rejection

OS201 DO WE KNOW HOW TO TREAT RESISTANT ANTIBODY-MEDIATED REJECTION EFFECTIVELY? A SINGLE CENTRE EXPERIENCE

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Background: The aim of this work was to analyze the efficacy and safety of administration of bortezomib (BTZ) and rituximab-based treatment of resistant antibody- mediated rejection (AMR).
Methods: We retrospectively analyzed documentation of 772 patients who underwent renal transplantation between 1/2012-6/2015. Novel therapeutic approach to resistant acute AMR in kidney transplant recipients was applied in 23 patients (3%) based on administration of BTZ [1 cycle of 4 doses of BTZ (1.3 mg/m2)], small doses of intravenous corticosteroids, plasmapheresis (PP) and a dose of rituximab (375 mg/m2). This protocol was administrated after conventional treatment had failed (PP+ intravenous immunoglobulin). Patients were followed for 12–48 months.
Results: Therapy of resistant acute AMR was administered to 23 patients after kidney transplantation with median peak PRA 52%, actual PRA 36%, mean HLA mismatch was 3, with median of 5.8 years on dialysis. 20 patients underwent for retransplantation. Immunosuppressive protocol consisted of induction with antithymocyte globulin (n = 22) or basiliximab (n = 1). Diagnosis of resistant acute AMR was made on 14.th POD (7–60 days). 15 patients received 1 cycle, 7 patients 2 cycles and 1 patient was treated with 3 cycles of BTZ. We observed delayed graft function in 26.1%. Using BTZ regimen in treating resistant acute AMR led to decrease in DSA quantity in HLA especially in class I ($p = 0.005$), class II ($p = 0.015$), but not in DQ ($p = 0.2$). No significant improvement of renal function was observed during the follow-up.
Conclusions: BTZ was effective against HLA I and II class antibodies, the problem with DQ antibodies is still unsolved. Bortezomib-related toxicities (thrombocytopenia and peripheral neuropathy) were all transient and responded to conservative management.

OS202 IMPACT OF ANTIBODY-MEDIATED VASCULAR REJECTION ON KIDNEY ALLOGRAFTS: HOW IMPORTANT IS PTC?

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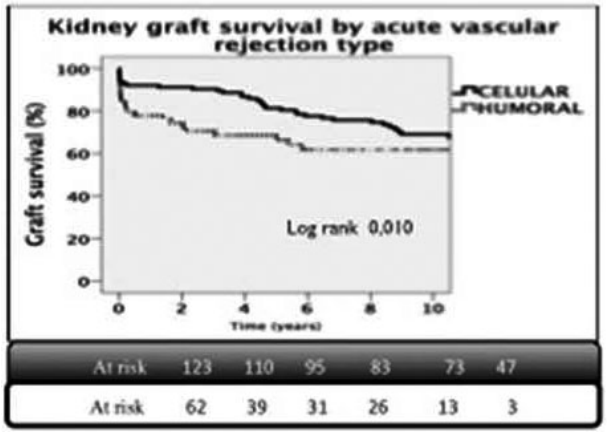
Introduction:
Athoughacute vascular rejection (AVR) is associated with a high risk of graft loss, it remains unclear whether AVR with accompanied cellular or humoral rejection (AHR) have dissimilar outcomes. The aim of this study is to examine the association between subtypes of AVR and graft loss.

We assessed patients who provided biopsy samples for acute allograft rejection, between 1998 and 2014. To investigate distinct rejection patterns, we retrospectively assessed rejection episodes with review of graft histology, as well as donor-specific anti- HLA antibodies when available.
Results: 1004 patients were biopsied and included in the main analyses, of which 259 (32.87%) had acute biopsy-proven rejection. We identified 3 patterns of graft rejection defined according to the presence of peritubular capillaritis (ptc): a) T cell-mediated acute vascular rejection (TAVR),if ptc-free; b) humoral-mediated acute vascular rejection (HAVR), if ptc>0 and c) T cell-mediated rejection (AVR-none), if vasculitis = 0 and ptc = 0 (148[57%], 70 [27%], 41[16%] respectively). At 5 years, graft survival was lower among

COX	OR	IC 95%	P
Age	1.03	0.99-1.06	0.059
Sex	0.69	0.28-1.68	0.408
t2-t3	0.67	0.26-1.74	0.409
i2-i3	3.27	1.45-7.57	0.006
v2- v3	2.73	1.20-6.17	0.016
ptc2-ptc3	2.84	1.23-6.58	0.014
g2- g3	2.87	1.19-6.96	0.019
DSAs	2.43	0.90-6.20	0.064



patient with ptc-vascular rejection than those with T cell vascular rejection (72.3%vs83.2% p0.010). T cell-mediated rejection without vasculitis had comparable survival than rejection absence (89.3%vs89.2% p0,698). Multivariate analysis adjusted by age and sex, showed that risk of graft loss was higher in biopsies with high scores of glomerulitis(g2-g3); vasculitis(v2-v3), capillaritis(ptc2-ptc3) or interstitial inflammation(i2-i3). However, tubulitis and C4d were not statically significant.
Conclusions: We conclude that the antibody-mediated acute vascular rejection involves a poor prognosis than the T-cell-mediated acute vascular rejection. The presence of tubulitis do not seem to determine a poor long term renal graft prognosis.

OS203 DEVELOPMENT OF TRANSPLANT GLOMERULOPATHY IN RECIPIENTS WITH ANTIBODY MEDIATED REJECTION: ACTIVATION OF INFLAMMATORY PATHWAY THROUGH RENAL POLY (ADP-RIBOSE) POLYMERASE (PARP)

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Background: Activation of PARP is a critical factor in the pathogenesis of various inflammatory process. Thus we aimed to show the integral of PARP in the inflammatory process of glomeruli and the development of transplant glomerulopathy (TG).
Methods: Total 82 patients with humoral rejection were included to study. PARP, α-SMA, and TNF-α, expression of glomeruli studied. The mean number of neutrophil, macrophage, and lymphocyte infiltration per glomerulus evaluated. The degree of the peritubular capillary (PTC) inflammation investigated. PTC C4d, PARP, and HLA-DR expression graded. The decreasing intensity of PTC-DR expression accepted as the increasing degree of the PTC destruction. Follow-up biopsies analyzed for the development of TG.
Results: Of 82 recipients only 40 showed TG. The time of the development of TG decreased with increasing degree of PTC neutrophil and macrophage infiltration, PTC inflammation, intraglomerular macrophage, and neutrophil infiltration ($p < 0.001$). TG development increased with increasing amount of C4d expression and with decreasing degree of PTC-DR expression ($p < 0.001$). TG was found earlier in recipients who had a higher degree of glomerular, and PTC PARP expression ($p < 0.001$). Patients with a greater degree of glomerular PARP expression showed a higher glomerular α-SMA and TNF-α expression. The intensity of the glomerular and PTC leukocyte infiltration increases with increasing glomerular and PTC PARP expression ($p < 0.001$). The 5-year graft survival was 78% and 15% for recipients with negative and positive glomerular PARP expression respectively ($p < 0.001$). The 5-year survival was 84%, 41% and %0 for patients with grade1, 2 and 3 PTC PARP expression respectively ($p < 0.001$).
Conclusion: Increased PARP activation both in glomeruli and PTCs leads to early TG and early graft loss. Thus it will be beneficial to use PARP inhibitor drugs in recipients with a high risk of TG.

Clinical Kidney Immunology

OS204 SUCCESSFUL KIDNEY TRANSPLANTATION IN RECIPIENTS WITH DONOR SPECIFIC HLA ANTIBODIES

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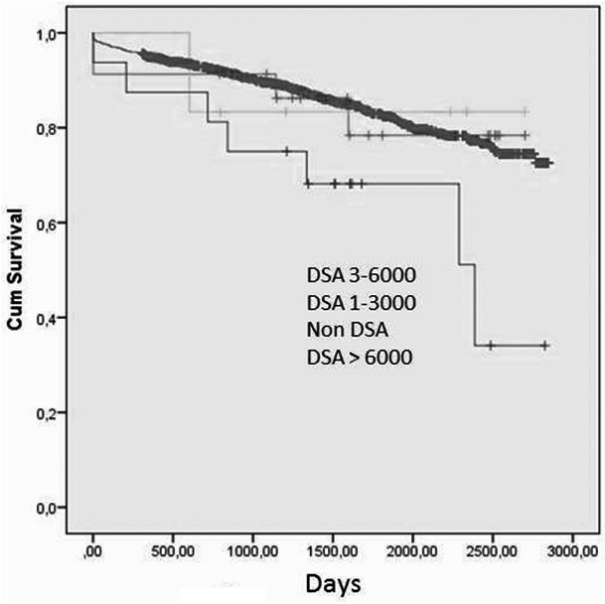
Introduction: HLA sensitized patients awaiting kidney transplantation face prolonged waiting times and reduced graft survival. We aimed to define a possible clinical cut-off level of donor specific antibodies (DSA) that results in outcomes similar to transplantation of standard immunological risk recipients.
Material/Methods: 1632 recipients transplanted at our center 2009–2014 were included. All were cytotoxic crossmatch negative. Recipient sera positive for HLA antibodies were tested on single antigen beads (Luminex platform). DSA positivity; MFI>1000, immunodominant DSA; highest MFI regardless of HLA class. All received basiliximab induction and maintenance tacrolimus (trough target standard risk: 3–7 μg/L, high-risk: 8–12 μg/L), mycophenolate (750 mg BID) and steroids. DSA positive patients also received rituximab 375 mg/m2 and IvIg 2 g/kg divided in 5 dosages.
Results: A total of 127 (8%) recipients were DSA positive before transplantation. There were more female recipients(61% vs. 29%) and more retransplantations (24 vs. 8%) in DSA positive groups. HR for non-censored graft loss was estimated by Cox regression entering recipient and donor age, recipient gender, deceased vs. living donor, first transplant vs. retransplant, HLA DR mismatches, dominant DSA MFI 1000–3000 ($n = 54$), 3000–6000 ($n = 24$) and >6000($N = 49$). Univariate Kaplan Meyer plot was used for graft survival.

Table 1 shows Cox regression analysis of risk of graft loss

	HR	p	CI 95%
DSA MFI 1–3000	1.062	0.863	0.540–2.089
DSA MFI 3–6000	1.126	0.816	0.413–3.068
DSA MFI > 6000	2.791	<0.001	1.695-4.595



Patient survival was not different between the groups (not shown).
Fig 1 shows graft survival according to level of dominant DSA
Conclusion: In this cohort of kidney recipients an immunodominant DSA with MFI < 6000 did not significantly impact patient- nor graft survival. With a consistent protocol of rituximab, IvIg, basiliximab induction and maintenance tacrolimus, mycophenolate and steroids, patients with the immunodominant DSA below MFI 6000 can be transplanted with acceptable results.

OS205 ACCELERATED KIDNEY ALLOGRAFT ARTERIOSCLEROSIS: MAJOR ROLE OF DONOR-SPECIFIC ANTI-HLA ANTIBODY STRENGTH AND COMPLEMENT-ACTIVATING CAPACITY

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The role of circulating anti-HLA DSAs in the development of accelerated arteriosclerosis has been recently reported in kidney recipients. This study investigated the characteristics of DSAs that are associated with the severity of allograft arteriosclerosis.

We included 744 kidney transplantation performed between 2004 and 2010 at Paris, France, with systematic assessment of injury phenotype and arteriosclerotic lesions using the vascular fibrous intimal thickening (cv) Banff score on allograft biopsies performed at one year after transplantation. We assessed circulating DSAs and their characteristics (specificity, HLA class, mean fluorescence intensity [MFI] and C1q-binding) at 6 months after transplantation.

We identified 281 patients with cv0 score, 213 patients with cv1 score, 189 patients with cv2 score and 61 patients with cv3 score. The distribution of DSAs according to cv score was: 47/281 (17%) in cv0 patients, 39/213 (18%) in cv1 patients, 63/189 (33%) in cv2 patients and 28/61 (46%) in cv3 patients. DSA MFI level was positively correlated with the severity of arteriosclerosis (rho = 0.23, $p = 0.002$), with a mean MFI of 3204 ± 3725 in cv0 patients, 3760 ± 3598 in cv1 patients, 4892 ± 4676 in cv2 patients and 5541 ± 3892 in cv3 patients. C1q-binding DSA prevalence increased with the severity of allograft arteriosclerosis: 8/281 (3%) in cv0 patients, 6/213 (3%) in cv1 patients, 25/189 (13%) in cv2 patients and 9/61 (15%) in cv3 patients ($p < 0.001$). Patients with C1q-binding DSA had a higher cv score compared with patients with non-C1q-binding DSA (1.7 ± 1.0 vs. 1.3 ± 1.1, respectively, $p = 0.01$). C1q-binding DSAs were associated with increased microvascular inflammation ($p < 0.001$) and C4d deposition in peritubular capillaries or arteries ($p < 0.001$).

There is a biological gradient between DSA level and the severity of allograft arteriosclerosis. Complement-activating DSAs are associated with an increased severity of arteriosclerosis and complement deposition in allograft.

Conclusion: Subclinical ABMR is associated with a distinct histo-molecular phenotype of kidney allograft rejection mainly driven by AKI and macrophages burden, which could explain the difference in terms of allograft survival.

Clinical Kidney Rejection

OS206 C3D-BINDING ANTI-DQ IS ASSOCIATED WITH HIGH RISK FOR ABMR AND GRAFT FAILURE IN STABLE KIDNEY TRANSPLANT RECIPIENTS

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Introduction: Donor specific anti-HLA antibodies (DSA) has been known as a risk factor for antibody-mediated rejection (ABMR) and poor graft outcome in kidney transplant recipients (KTR). Solid-phase assays are prevalent but it is too sensitive, evaluating the ability of DSAs to activate the complement cascade is important. Our study was to evaluate to impact of C3dDSA and SA (single antigen) DSA on ABMR and graft outcome.
Method: We examined 220 stable KTRs for development of DSAs from July 2013 to July 2016. We biopsied 24 recipients who were positive on Luminex PRA, subsequently tested SA-DSA and C3d-DSA on allograft kidney biopsy day.
Result: 10.9% (24 of 220) of stable KTRs had DSAs on Luminex PRA, Median timing of DSA occurring was 9.6(0.2–24) year of post-transplantation. 18 of 24 (75%) had DSAs on SA Luminex assays (Peak MFI, 5162 $\pm$ 1203). 11 of 24 (46%) had C3d-binding DSAs. (Peak MFI, 4567.7 $\pm$ 1820). 7 of 11 (63.6%) C3d-DSA (+) had ABMR, regardless of DSA status. Incidence of ABMR was significantly higher in C3d-DSA (+) than those in SA-DSA (+) (7 of 11, 63.3% vs. 7 of 18, 38.9%, $p = 0.03$). Among 9 had class2, C3d-DSA, 8 of them (88.9%) had DQ Antibody. Class2, C3d-DSA MFI is highly correlated with Class2 DSA MFI. ($r^2 = 0.796$, $p < 0.001$). ROC curve showed C3d-class2 is more accurate test to diagnose ABMR than class2-DSA ($p < 0.001$). Three recipients had graft failure at 2.6 (0.5–3) year after ABMR. Significant predictors of graft failure on multivariate analysis were high serum creatinine at the time of biopsy, ABMR, CABMR and Class2, C3d-DSA (+).Class2, C3d-binding DSA was associated with lower graft survival after ABMR (Fig 1 and 2).
Conclusion: We demonstrated that class2-DSA, especially class2, C3d-DSA of anti-DQ is associated with high risk for development of ABMR and graft failure. We suggested immune surveillance with C3d-DSA and subsequent allograft biopsy may be useful method to recognize development of ABMR and prevent graft failure in stable kidney transplant recipients.

Clinical Kidney Histology

OS208 CIRCULATING DONOR-SPECIFIC ANTI-HLA ANTIBODIES ACCELERATE THE PROGRESSION OF INTERSTITIAL FIBROSIS IN KIDNEY ALLOGRAFTS

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Addressing the causes of accelerated ageing of kidney allografts represents an important challenge to improve long-term transplant outcomes. We investigated the role of donor-specific anti-HLA antibodies (DSA) in the progression of kidney allograft interstitial fibrosis.

We prospectively enrolled 913 kidney recipients transplanted between 2004 and 2010. All patients were assessed for allograft interstitial fibrosis on biopsies performed at Day 0 and at 1 year after transplantation using the IF/TA Banff grade. We also integrated all the "for cause" biopsies performed in the first year post-transplant ($N = 1035$) and after the first year ($N = 784$, median time of biopsies 18.4 months; IQR, 13.3–40.4). All patients were screened for DSA by SAB at the time of transplantation (Day 0) and within the first year post-transplantation. The progression of IF/TA within the first year post-transplantation was evaluated by the difference between the 1-year and Day-0 IF/TA grades (ΔIF/TA). The progression of IF/TA over the long term was modelled using mixed-effect models.

The distribution of IF/TA on pre-implantatory biopsies ($N = 913$) was: 726 (80%) IF/TA0, 145 (15%) IF/TA1, 36 (4%) IF/TA2 and 6 (1%) IF/TA3 as compared to 325 (35%), 263 (29%), 173 (19%), and 152 (17%) on 1-year biopsies ($N = 913$) ($p < 0.001$). Over the first year, 507 (56%) patients presented progression of IF/TA (ΔIF/TA>0). Patients with Day-0 DSA ($N = 198$) showed increased progression of fibrosis within the first year (ΔIF/TA: 1.08 $\pm$ 1.15) as compared to those without Day-0 DSA ($N = 715$, 0.86 $\pm$ 1.12) ($p = 0.016$). Patients with post-transplant DSA (preformed or de novo) ($N = 236$) exhibited accelerated progression of IF/TA as compared to patients without post-transplant DSA ($N = 677$) ($p = 0.0078$) when integrating the biopsies performed at 1-year post-transplant and beyond.

Pre-transplant circulating DSA increase premature allograft fibrosis and post-transplant DSA accelerate the progression of allograft fibrosis over the long term.

Translational Kidney Rejection

OS207 GENE EXPRESSION SIGNATURE OF SUBCLINICAL ALLOGRAFT KIDNEY ABMR COMPARED TO CLINICAL ABMR

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Background: Antibody-mediated rejection occurs in clinically stable patients (sABMR) or in patients with allograft dysfunction (ABMR), but only little is known about the similitudes or discrepancies between the molecular landscape of sABMR and ABMR.
Methods: We used an integrative analysis strategy comprising a systematic assessment of clinical-biological parameters, transplant characteristics, histopathology, immunohistochemistry, type of treatment, circulating anti-HLA DSA assessment and gene expression.
Results: Among the 131 patients with ABMR, 99 had a clinical ABMR while 32 were sABMR. Clinical ABMR displayed a worse kidney allograft function (mean eGFR: 34.45 vs 48.24 mL/min/1.73 m2, $p < 0.001$) and an increased proteinuria rate (mean: 0.54 vs 0.31 g/g creatinine, $p = 0.041$) compared to sABMR. There was no difference for the highest anti-HLA DSA MFI at the time of ABMR between the two groups (Clinical ABMR: median MFI: 2779 (IQR: 1028–7573); sABMR: median MFI: 1842 (IQR: 1191–5391); $p = 0.356$). Allograft gene expression showed that patients with clinical ABMR exhibited significantly more injury-repair response transcripts ($p < 0.001$), more macrophage associated transcripts ($p = 0.003$) and a trend towards more IFNG production and inducing transcripts ($p = 0.066$). We compared the top 10 ABMR related transcripts with their corresponding fold change and p value (t-test) compared the sABMR. Five transcripts were AKI associated (LCN2, LTF, SERPINA3, SLPI and PTX3) and two were macrophages associated (CD163 and MSR1). A principal component analysis integrating the histological and molecular parameters identified a distinct histo-molecular allograft rejection phenotype in patients with clinical ABMR vs sABMR.

Clinical Kidney Immunosuppressive agents

OS209 IMPACT OF ANTIBODY INDUCTION THERAPY ON KIDNEY GRAFT SURVIVAL IN PATIENTS WITH DIFFERENT RISK FACTORS

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Background: The use of antibody induction therapy with ATG or IL-2RA in kidney transplantation is steadily increasing. We reported recently that only kidney graft recipients with an increased immunological risk profile benefit from antibody induction; a beneficial effect in 'normal-risk' transplants could not be demonstrated. Increased-risk was defined if one or more of the KDIGO high-risk parameters applied. We now analyzed to what degree the different risk factors are influenced by induction therapy.
Methods: More than 50,000 first deceased-donor kidney graft recipients transplanted between 2000-2016 in Europe and reported to the Collaborative Transplant Study were evaluated considering the pretransplant risk factors 5–6 HLA-A+B+DR mismatches (MM), advanced donor age ($\geq$60 years), young recipient (<30 years), panel reactive antibody (PRA) >5%, and cold ischemia time (ISC) (>24 hours) individually. 3-year death-censored graft survival was analyzed using the Kaplan Meier method and the log-rank test was applied. To achieve comparability of the different risk factors, Cox-regression analyses were performed.
Results: Since 2000, the proportion of European kidney graft recipients with induction therapy has increased from 29% to 71% while the percentage of high-risk patients has increased from 52% to 60%. Induction therapy decreased the risk of graft loss significantly in patients with PRA >5% (hazard ratio (HR) = 0.67, $p = 0.006$), 5–6 HLA MM (HR = 0.75, $p = 0.021$), donor age $\geq$60 (HR = 0.80, $p < 0.001$) or recipient age <30 (HR = 0.80, $p = 0.040$). The beneficial effect of induction became even more pronounced with further increasing donor age $\geq$70: HR = 0.73; $\geq$75: HR = 0.62. The impact on transplants with a > 24 h CIT did not reach statistical significance although HR for graft loss was reduced to 0.77 ($p = 0.11$).
Conclusion: Patients with PRA and high number of HLA MM benefit greatly from induction therapy. A strong beneficial effect can also be observed in recipients of organs from old donors.

OS210 MULTICENTER EVALUATION OF THE IMPACT OF LATE INTRA-PATIENT TACROLIMUS TROUGH LEVEL VARIABILITY ON KIDNEY GRAFT SURVIVAL – A COLLABORATIVE TRANSPLANT STUDY REPORT

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Background: Intra-patient variability of tacrolimus levels has been reported to be associated with poor graft and patient survival after kidney transplantation (TX). These findings were derived from single center analyses and restricted to outcome early after TX. We analyzed whether in patients with stable tacrolimus dosages and trough levels as well as good kidney function during the first 2 post-TX years, strong intra-patient fluctuations of tacrolimus during subsequent follow up were associated with impaired outcome.
Methods: More than 6,000 patients who received a deceased donor kidney transplant between 2000 and 2013 and who had a functioning graft for ≥3 years were studied. Tacrolimus dosages and trough levels at years 2 and 3 were analyzed using the Kaplan-Meier-Method for a possible influence on subsequent graft and patient survival during the post-TX years 4–6. The findings were substantiated by Cox-regression.
Results: The median of tacrolimus trough level decreased from 7.2 ng/mL at year 1 to 6.9 ng/mL at year 2 and 6.6 ng/mL at year 3. Tacrolimus trough level cut-off for subsequent inferior graft survival decreased from 5 ng/mL at year 1 to 4 ng/mL at year 3. When the 3-year trough level was compared with the 2-year-trough level, an increase as well as a decrease of 4 ng/mL or more was associated with significantly impaired graft survival beyond year 3 ($p = 0.001$ and $p < 0.001$, respectively). Patient survival was not impaired significantly ($p = 0.19$). An inferior outcome was observed in patients with strong fluctuation of trough levels despite a stable daily tacrolimus dosage and even when the trough level was above the critical cut-off of 4 ng/mL ($p < 0.001$). This applied also to patients with good graft function (serum creatinine <130 μmol/L) at 2 years post-TX ($p = 0.017$).
Conclusion: Even in patients with stable function during the first 2 years after TX, a fluctuating tacrolimus trough level is strongly associated with impaired graft survival beyond year 3.

OS211 CLINICAL PHARMACOLOGY STUDY OF A NOVEL PROLONGED-RELEASE FORMULATION OF TACROLIMUS IN COMPARISON TO THE STANDARD ONCE-DAILY FORMULATION IN DE-NOVO KIDNEY TRANSPLANT RECIPIENTS

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Background: LCPT (Envarsus®) is a prolonged release formulation of tacrolimus designed for once-daily administration. Although LCPT has already proven to have a greater bioavailability and flatter pharmacokinetic (PK) profile compared to the most commonly used twice daily immediate-release formulation, no study has so far compared the PK profile of LCPT to that of the standard once-daily prolonged-release formulation (PR-Tac, Advagraf®) in de-novo kidney transplant recipients.
Methods: Adult, Caucasian, renal transplant recipients were randomized to either LCPT or PR-Tac within 24 hours after surgery. The starting dose, respectively of 0.17 and 0.20 mg/Kg/day, was maintained constant until Day 3. Dose adjustments were allowed on Days 4, 8, 15 and 22, according to tacrolimus trough levels, targeting predefined ranges of 5–15 ng/mL from Day 2 to Day 15, and 5–10 ng/mL from Day 16 to Day 28. Thirteen blood samples for centralized tacrolimus determination were collected over 24 h on Days 1, 3, 7, 14. Concomitant immunosuppressive drugs were standardized to Basiliximab, MMF and corticosteroids.
Results: PK analysis set included 68 patients: 33 on LCPT and 35 on PR-Tac. Compared to PR-Tac, LCPT showed a consistently lower daily dose with a 40% dose reduction by Day 28. Accordingly, the bioavailability assessed as $AUC_{0\text{-}24\ h}$/Dose on Days 3, 7, 14 was on average 33% greater for LCPT in comparison to PR-Tac (Table 1). Mean peak concentrations were lower for LCTP leading to 30% lower fluctuation (C_{max}-C_{min}/$C_{average}$) (Table 1). LCPT had longer time to peak concentration in comparison to PR-Tac (6 h and 2 h, respectively). Finally, the safety profile of LCPT was comparable to that of PR-Tac, as was the improvement in renal graft function.
Conclusion: Compared to PR-Tac, LCPT has shown a significantly improved PK profile with greater bioavailability and lower fluctuation, characteristics that may improve tacrolimus tolerability and contribute to better transplantation outcomes

Table 1

	Estimated treatment effect ratio (%) LCPT/PR-Tac (90% confidence interval)	p value
Bioavailability on Day 3	131.89 (111.82–155.56)	0.007
Bioavailability on Day 7	124.73 (103.67–150.06)	0.051
Bioavailability on Day 14	142.57 (118.63–171.35)	0.002
Fluctuation on Day 3	70.17 (60.09–81.95)	<0.001
Fluctuation on Day 7	68.34 (58.21–80.23)	<0.001
Fluctuation on Day 14	72.60 (60.87–86.59)	0.004

OS212 LONG-TERM PROLONGED-RELEASE TACROLIMUS-BASED IMMUNOSUPPRESSION IN DE NOVO LIVER TRANSPLANT PATIENTS: 3-YEAR PROSPECTIVE FOLLOW-UP OF THE DIAMOND STUDY

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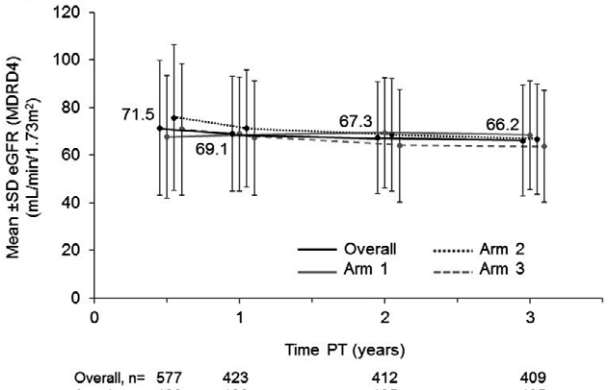
Background: DIAMOND was a multicentre, 24-week, randomised, controlled study of renal function with different initial prolonged-release tacrolimus (PR-T)-based immunosuppression regimens *in de novo* liver transplant patients. We present 3-year interim data from a prospective, 5-year follow up of DIAMOND (NCT02057484).
Methods: In DIAMOND, patients received: Arm 1: PR-T (initial dose 0.2 mg/kg/day); Arm 2: PR-T (0.15–0.175 mg/kg/day) + basiliximab; Arm 3: PR-T (0.2 mg/kg/day delayed to Day 5) + basiliximab. All patients had mycophenolate mofetil and one steroid bolus. Three-year follow-up endpoints included: estimated glomerular filtration rate (eGFR; Modified Diet in Renal Disease 4 (MDRD4)), graft survival, patient survival, acute rejection (AR), biopsy-confirmed AR (BCAR), and adverse events (AEs).
Results: Of 856 patients enrolled in DIAMOND, follow-up data were obtained for 578 (mean ± standard deviation age 54 ± 10 years). Baseline characteristics were similar between arms. Mean eGFR was similar at Year 1 and 3 post-transplant (PT) (69 and 66 mL/min/1.73 m^2), and between arms from 1 year PT (Figure). Kaplan–Meier (K–M) estimate of graft survival was 84% and 77% at 1 and 3 years PT, respectively, and comparable between arms (Table). Overall K–M estimate of patient survival was 86% and 80% at 1 and 3 years PT, respectively, and similar between arms (Table). Most ARs and BCARs occurred ≤6 months PT, with few additional events by Year 3 PT; AR- and BCAR-free survival at 3 years PT remained higher in Arm 2 vs. Arms 1 and 3 (Table). Fifteen (2.6%) patients had AEs during follow up that were considered possibly/probably treatment-related; one serious AE led to treatment discontinuation.

Figure.



Data labels on the graph are for the overall population. Data are not available for all patients at all time points. In the DIAMOND study*, mean eGFR at 6 months was significantly higher in Arms 2 and 3 compared with Arm 1 ($p=0.001$ and $p=0.047$, respectively); during follow-up, mean eGFR was similar between arms from Year 1. *Trunečka P, et al. Am J Transplant 2015;15(7):1843–54.

Table.

	Patients at risk of death, n*	Patient deaths, n	K–M estimate of patient survival, % (95% CI)	Patients at risk of graft loss, n*	Patients with graft loss, n	K–M estimate of graft survival, % (95% CI)	Patients at risk of AR, n*	Patients with AR episodes, n	K–M estimate of AR-free survival, % (95% CI)	Patients at risk of BCAR, n*	Patients with BCAR episodes, n	K–M estimate of BCAR-free survival, % (95% CI)
6 months post transplant												
Overall	**856**	**88**	**89.4 (87.3, 91.5)**	**856**	**105**	**87.5 (85.2, 89.7)**	**856**	**143**	**81.9 (79.2, 84.6)**	**856**	**121**	**84.7 (81.2, 87.2)**
Arm 1	288	31	88.7 (84.9, 92.5)	288	39	85.9 (81.8, 90.0)	288	54	79.7 (74.8, 84.6)	288	48	81.9 (77.3, 86.6)
Arm 2	291	31	89.1 (85.4, 92.7)	291	35	87.7 (83.9, 91.5)	291	36	86.4 (82.3, 90.5)	291	30	88.6 (84.8, 92.5)
Arm 3	277	26	90.5 (87.0, 94.0)	277	31	88.7 (85.0, 92.5)	277	53	79.5 (74.5, 84.5)	277	43	83.3 (78.7, 87.9)
1 year post transplant												
Overall	**510**	**105**	**86.4 (83.9, 88.9)**	**499**	**122**	**84.4 (81.8, 87.0)**	**363**	**145**	**81.4 (78.7, 84.2)**	**377**	**123**	**84.2 (81.6, 86.8)**
Arm 1	156	33	87.6 (83.5, 91.6)	150	41	84.8 (80.4, 89.1)	111	54	79.7 (74.8, 84.6)	115	48	81.9 (77.3, 86.6)
Arm 2	174	40	84.4 (79.8, 88.9)	171	44	83.0 (78.3, 87.7)	127	36	86.4 (82.3, 90.5)	131	30	88.6 (84.8, 92.5)
Arm 3	180	32	87.4 (83.3, 91.5)	178	37	85.6 (81.3, 90.0)	125	55	78.2 (73.0, 83.4)	131	45	82.0 (77.1, 86.9)
3 years post transplant												
Overall	**462**	**141**	**79.9 (76.9, 83.0)**	**449**	**162**	**77.3 (74.1, 80.4)**	**339**	**154**	**79.3 (76.3, 82.3)**	**354**	**131**	**82.3 (79.5, 85.2)**
Arm 1	147	44	81.2 (76.0, 86.4)	140	53	77.8 (72.3, 83.3)	106	58	76.8 (71.3, 82.3)	110	52	79.0 (73.7, 84.3)
Arm 2	152	54	77.1 (71.5, 82.6)	148	60	74.7 (68.9, 80.4)	119	39	84.3 (79.6, 89.0)	123	33	86.5 (82.1, 90.9)
Arm 3	163	43	81.7 (76.6, 86.8)	161	49	79.5 (74.2, 84.7)	117	57	76.8 (71.4, 82.3)	123	46	81.3 (76.3, 86.3)

*Number of patients at risk immediately before each time point.

Conclusion: Administration of PR-T-based immunosuppression for 3 years PT was associated with stable eGFR, and high long-term graft and patient survival rates irrespective of regimen. PR-T was generally well tolerated with no new safety issues after 3 years.

OS213

10-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL IN KIDNEY TRANSPLANTATION COMPARING 2 IMMUNOSUPPRESSIVE STRATEGIES: CYCLOSPORINE/AZATHIOPRINE VS. TACROLIMUS/ MYCOPHENOLATE MOFETIL

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Background: The Tacrolimus (Tac) and mycophenolate mofetil (MMF) superiority in benefit-risk ratio in renal transplantation is always debated. Few studies evaluate long term outcomes of this association compared to the cyclosporin A (CsA) and Azathioprine (Aza) one.
Methods: We analyzed the 10-years outcomes in terms of graft, censored or not by death (global) and, patient survivals, secondary events in a monocentric, prospective, randomized and controlled trial comparing CsA/Aza vs. Tac/MMF in 289 kidney transplant recipients treated with antithymocyte globulins and prednisone. Statistical analyses were performed in intention-to-treat.
Results: At 10-years of follow-up, the global survival was in the CsA/Aza arm and in the Tac/MMF arm 72.2% vs. 69.5%, respectively (p = 0.335). The graft survival was 83.3% vs. 78.9% (p = 0.61), and the patient survival was 86.7% vs. 88% (p = 0.738), respectively. The eGFR was 46.9 ± 1.8 mL/min/1.73 m2 in the CsA/Aza arm and 55.8 ± 2.2 mL/min/1.73 m2 in the Tac/MMF arm (p = 0.002). Acute graft rejections were more frequent in the CsA/Aza arm (17.8%) than in the Tac/MMF arm (9.1%) (p = 0.03). There were more opportunistic parasitic infections (5% v. 0%, p = 0,007) and digestive intolerance (11.2% v. 2.1%, p = 0,002) in the Tac/MMF arm. There were more *de novo* donor-specific antibody in the CsA/Aza arm (13.9% vs 2.9%, p = 0.001). However, there were 54.1% immunosuppressive treatment's modifications in the CsA/Aza arm vs. 25.5% in the Tac/MMF arm (p = 0.005). The cost of one year of treatment was more expensive with Tac/MMF than Csa/Aza.
Conclusions: In this study, we showed no long-term significant difference between CsA/Aza and Tac/MMF associations in case of induction with antithymocyte globulins, in graft, global and patient survivals. There were a higher eGFR, a lower rate of acute rejections but more non-lethal infectious complications and digestive intolerance in the Tac/MMF arm. In view of these results, an association CsA/Aza remains current.

Clinical Others Immunosuppressive agents

OS214

LOW DOSE OF ANTI-HUMAN T-LYMPHOCYTE GLOBULIN (ATG) WARRANT A GOOD GLOMERULAR FILTRATION RATE AFTER LIVER TRANSPLANT ON RECIPIENTS WITH PRE-TRANSPLANT RENAL DYSFUNCTION

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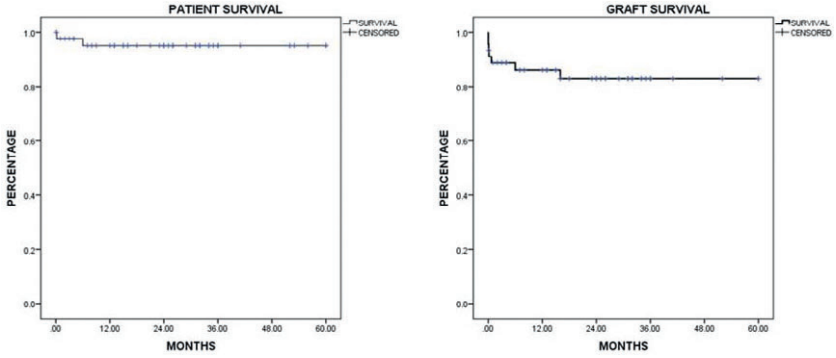
Anti-T-lymphocyte Globulin (ATG)-based immunosuppression induction has gained increasing use in liver transplantation (LT) in patients with pre-LT renal dysfunction. However, it has been historically associated with higher rate of infections.
Methods: A single-center cohort study which analyze prospectively those adult patients who received a primary LT between 2012 and 2016 from brain-dead donors, pre-LT renal dysfunction (eGFR < 60 mL/min/1.73 m2) and received ATG administered on day 1 and 3 at 1 mg/kg iv with dose adjustment according to CD2/CD3 levels (>20cel/μL) [*ATG group*]. This group was compared with a similar retrospective cohort with pre-LT renal dysfunction treated with basiliximab 20 mg iv administered at day 0 and 4 post-LT [*BAS group*] between 2005–2011. In both groups, low tacrolimus (TAC) dose <0.05 mg/Kg twice daily was introduced according to urine output.
Results: Twenty patients were included in each group with no differences in age, gender, indication for LT or MELD. The mean dose of ATG was 74 ± 10 mg at day-one and day-three post-LT. Whole blood trough levels of TAC were kept in the low level during the first week achieving values of 3(1–8) ng/dL in *ATG group* vs 5 (1–9)ng/dL (p = 0.29) in *BAS group*. Significant improvement in renal function was observed at day 7 post-LT compared to pre-LT in both groups (p = 0.036 in *ATG group* and p = 0.000 in *BAS group*). No severe adverse events were observed in those patients receiving ATG with similar incidence of acute rejection at one month post-LT in both groups (10% in *ATG group* vs 0%, p = 0.147). No significant differences were found in the incidence of overall infections (35% vs 47% in *BAS group*, p = 0.51) neither in 1-year renal function (59 ± 18 mL/min/1.73 m2 in *ATG group* vs 62 ± 16 mL/min/1.73 m2, p = 0.464).
Conclusions: Low doses of Anti-T-lymphocyte Globulin can be safely and effectively used as induction immunosuppressive agent. Further economical analyses should be performed to evaluate the best cost-effective strategy.

Figure 1. Patient and Graft Survival



Clinical Kidney Immunosuppressive agents

OS215

SUCCESSFUL KIDNEY TRANSPLANTATION OUTCOMES AFTER DESENSITIZATION WITH PLASMAPHERESIS, INTRAVENOUS IMMUNOGLOBULIN AND RITUXIMAB IN HIGHLY SENSITIZED LIVING DONOR KIDNEY TRANSPLANT PATIENTS: MULTICENTER

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Background: Highly sensitized kidney transplant candidates have few transplant opportunities. Herein, we describe our living donor kidney transplant experience in highly sensitized patients.
Methods: 44 highly sensitized living kidney transplant patients between 10/2011 and 11/2016 were analyzed. All patients underwent desensitization using pre-transplant plasmapheresis (three cycles as minimum), (PP) intravenous immunoglobulin (IVIG) with rituximab (thirty patients). Immunosuppression consisted of thymoglobulin, tacrolimus, mycophenolate mofetil / steroids. Demographics, immunologic characteristics of patients, acute rejection (AR) episodes, survival, allograft function and adverse events were evaluated.
Results: 44 patients were included (32 female 72.7%), mean age 33.6 $\pm$ 9.4 years, mean weight 58.2 $\pm$ 11.7 kg and 45.3 $\pm$ 47 months on dialysis. 18 patients were re-transplant (1 third transplant), mean HLA match was 3.2 $\pm$ 2.1 and mean PRA class I was 46.1 $\pm$ 32.7% and class II 44.2 $\pm$ 33.3% respectively. Three had one positive cross-match before desensitization. 32 patients (74%) received $\geq$ 18gr IVIG. Mean number of plasmapheresis sessions was 4.8 $\pm$ 1.3. Mean Rituximab dose was 343.7 $\pm$ 231.2 mg and thymoglobulin dose 5.95 $\pm$ 2.2 mg/kg. AR rejection rate was 20.5%. One & 5-year patient and graft survival was 95% (patient) and 86% & 82% (graft) is respectively (patient: 57.1 $\pm$ 1.9; graft 50.3 $\pm$ 3.3 months) (Figure 1). Glomerular filtration rate a 12 and 24 months was 58.9 $\pm$ 20 and 60.2 $\pm$ 27.9 ml/min/1.73m2BSA respectively. CMV infection rate was 6.8% (n = 3). Other infective episodes were .84 $\pm$ 1.21 events (n = 19) UTI's mostly (n = 20). One neoplasia (skin) have occurred during follow-up.
Conclusion: Good kidney transplant outcomes can be achieved with PP/IVIG with or without rituximab as desensitization regimen for positive cross-match and/or highly sensitized living donor renal transplant patients. Longer follow is warranted to evaluate further

OS216

IS IT REALLY NECESSARY TO REMOVE ANTI-A/B ANTIBODIES IN ABO-INCOMPATIBLE KIDNEY TRANSPLANTATION?

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Introduction: It is well known that blood type antigens cause humoral rejection in ABO-incompatible living-related kidney transplantation (ABO-ILKT) We compared recipients who had induction period immunosuppressive therapy with and without removing of anti-A/B antibodies
Methods: Thirty-two ABO-ILKT recipients were enrolled in our prospective study. ABO-I-NRA Group (ABO-I without removing anti-A/B antibodies) (n = 14) patients received desensitization without methods of removing anti-A/B antibodies during January, 2010 - July, 2013. ABO-I-RA Group (ABO-I with removing anti-A/B antibodies)(n = 18) was a control group. We also studied 18 ABO-ILKTx patients with DFPP/PEX/ Immune adsorption during February, 2009 - July, 2016.
Results: a)Patient (100% vs. 100%) and graft survival (100% vs. 100%) at 1 year were no different between the groups. b)Patients of ABO-I-NRA Group experienced less acute rejections than those in ABO-I-RA Group (7.1% vs. 38.8%, P = 0.053), the difference not significant. c)Two patients (2/18: 11.1%) in the RA group developed antibody-mediated rejection (AMR). There were no significant differences between the two groups with regards to other adverse events. d)There were no significant differences in the rates of change in anti-A/B antibody (IgG), anti-A antibody (IgM/IgG),or anti B-antibody (IgG) between 1 month pretransplant and at the time of transplant, or between 1 month pretransplant and 1 month post-transplant. e)On the other hand, a significantly higher rate of change (reduction rate) was seen in the RA group than in the NRA group with regards to anti-A/B antibody (IgM) and anti B-antibody (IgM).
Conclusions: We realized that the most important point in our therapeutic strategy was the inhibition of antibody formation through pretransplant desensitization therapy. Pretransplant desensitization therapy to suppress host B cell immunity against ABO-histo blood group antigens would be the most effective treatment to ensure the successful outcome.

Clinical Kidney Donation and donor types

OS217

WILL THEY DONATE? PREDICTORS OF NON-DONATION AND WITHDRAWAL IN A UK MULTICENTRE PROSPECTIVE COHORT STUDY OF POTENTIAL LIVING KIDNEY DONORS

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Background: For individuals who have volunteered for living kidney donation, little is known about what sociodemographic factors influence progression to donation or withdrawal. Identifying predictors may identify people who would benefit from further support.
Methods: This UK multicentre prospective cohort study collected data on all individuals who started living kidney donor assessment at seven renal units from 1/8/14 to 31/1/16. Multivariable logistic regression models were used to explore the relationship between sociodemographic variables and likelihood of kidney donation.
Results: 805 individuals presented for directed donation. 735 potential donors completed work-up; 84.8% did not donate. 24.8% did not donate because an alternative donor for the same recipient was selected to proceed. 17.8% were deemed clinically unfit. 15.0% withdrew. Potential donors for female recipients were less likely to donate than those for men (Odds Ratio (OR) 0.60 (95% CI 0.38–0.94) p = 0.03). Individuals were less likely to donate if they were intending to donate to a friend rather than relative (OR 0.18 (0.05–0.60)

p = 0.01), or to a recipient with renal failure due to a systemic disease (OR 0.41 (0.21–0.80) p = 0.01). Those in the greatest socioeconomic deprivation quintile were less likely to donate than those in the least deprived group (OR 0.49 (0.24–1.00) p = 0.05), but the trend with deprivation was consistent with chance (p = 0.12). Higher BMI was associated with a lower odds of donation (OR per +1 kg/m^2 0.92 (0.88–0.96) p < 0.001). Younger potential donors (OR per +1 year 0.97 (0.95–0.98) p < 0.001), those of non-white ethnicity (OR 2.98 (1.05–8.44) p = 0.04) and friends (OR 2.43 (1.31–4.51) p = 0.01) were more likely to drop out of work-up.
Conclusion: This is the first study of potential living kidney donors to describe predictors of non-donation. Qualitative work with those who withdraw might identify possible ways to support those who wish to donate but experience difficulties doing so.

Clinical Kidney Allocation

OS218 PAIRED LIVING KIDNEY DONATION IN THE UK

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Introduction: A national programme for kidney paired donation (KPD) started in the UK in 2007. Matching is carried out 3-monthly, identifying all possible exchanges involving two or three donor-recipient pairs and, since 2012, identifying altruistic donor chains (ADC) which facilitate one or two transplants for patients in the KPD pool and one transplant for a patient on the deceased donor waiting list. Compatible pairs have been included since 2011.
Methods: Data on enrolled and transplanted pairs are summarised.
Results: By the end of 2016, 1553 patients (1717 pairs) had enrolled for KPD: 62% of pairs were HLA incompatible [HLAi] (including 15% who were also ABO incompatible [ABOi]), 34% were ABOi only and the remaining 3% were compatible pairs. Half of all pairs were spouses/partners. Compatible pairs generally enter the scheme to gain a better HLA match or age match.

Recent matching runs have included up to 284 possible recipients and identified 30 - 72 possible transplants. About half of all patients enrolled have HLA antibodies to ≥85% of the deceased donor pool. Despite this, 1000 possible transplants have been identified, with 658 proceeding: 29% were 2-way exchanges, 39% 3-way exchanges and 32% through ADC. Ten transplants were in children (<18 years). 29 transplants were for compatible pairs (44% of those registered), enabling 48 other patients to be transplanted.
Conclusions: KPD is very successful in the UK, allowing two- and three-way exchanges and ADC. Last year, 14% of all living donor kidney transplants in the UK were identified through the KPD programme, with particular impact on immunologically complex recipients who wait a long time for transplant. A reduction in antibody incompatible transplantation in the UK has been seen in recent years. The inclusion of compatible pairs in the KPD programme increases transplant opportunities for all patients in the pool and the aim is to encourage more compatible couples to register to develop the KPD programme in future.

OS219 EXPANDED TRANSPLANT OPTIONS FOR PATIENTS REGISTERED IN KIDNEY PAIRED DONATION PROGRAM

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Introduction: Kidney Paired Donation (KPD) arranges transplants (Tx) by exchanging live donors for incompatible donor/recipient pairs. We reviewed outcomes of 1121 patients registered in the Alliance for Paired Donation (APD-KPD) during a 6-year period.
Methods/Results: Of all registered patients, 712 (64%) were transplanted: 409 (37%) by KPD (223 by APD-KPD and 186 by KPD outside the APD), 110 (10%) by donors from compatible live donors (APD-LD), and 193 (17%) by Tx from deceased donors (APD-DD). Those transplanted by APD-KPD required 522 offers with 1431 1-way proposed Tx: 127 offers were accepted (24.3% success rate) with 272 completed Tx (19% success rate): 87 Tx were done through 2-, 3-, 4- and 6-way simultaneous exchanges (cycles) and 141 Tx through non-simultaneous 1-, 2-, 3-, 4-, 5-, 6- and 7-chains: chains were 1.6-fold more successful than cycles. Chains used 36 non-directed donors (NDDs) and 41 bridge donors (BDs). Among APD patients 41% were highly sensitized (HS; cPRA 80–100%) with 30% very HS (VHS; cPRA 95–100%). Since only 22% of APD-KPD Tx were in HS with 11% VHS patients, this accumulated HS/VHS patients in the waiting pool. The death-censored 4-year Tx survival was 98.2% in APD-KPD (n = 168) in comparison to 91.4% in all KPD programs in USA (n = 2,579; p < 0.05). A 6-year up-to-date graft survival was 95.0% in APD-KPD, 92.5% in APD-other-KPD, 92% for APD-LD and 82% for APD-DD. Detail analysis showed that APD-KPD had an excellent 6-year up-to-date Tx survival in non-sensitized (94.8%; cPRA 0–19%; n = 115), as well as in HS (93.9%; cPRA=80–100%; n = 49) and VHS (96%; cPRA 95–100%; n = 25) patients.
Conclusions: 1) APD-registered patients utilized different options to receive Tx significantly expanding the pool of donors for HS/VHS patients; 2) APD-KPD Tx had excellent survival results which may be attributed to the frequent use of potent induction therapy and excellent donor/recipient matching.

OS220 POTENTIAL GAIN OF UTILIZING KIDNEYS FROM DECEASED DONORS TO INITIATE "CHAIN" KIDNEY PAIRED DONATIONS: QUANTIFICATION OF BENEFIT THROUGH A REAL-WORLD RETROSPECTIVE ANALYSIS

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Background: The option to utilize kidneys from deceased donors to initiate chains of living donor kidney paired exchanges (KPE) has been recently proposed: the gain of this practice needs to be quantified. We have measured with a mathematical algorithm the gain of implementing KPE transplantations, using retrospective data on the pool of donor/recipient incompatible pairs at a single centre; to maximize the number of transplants using deceased donor chains and to minimize the number of transplants performed by desensitization
Methods: From January 2012-December 2014 at our Centre 358 single kidney transplants (KT) were performed. 251 KT with grafts from deceased donors and 107 from living donors (77 AB0-compatible pairs, 22 AB0 incompatible pairs, 8 recipients with donor-specific antibodies DSA). 16 incompatible pairs were evaluated and enrolled in the KPE program and/or listed for deceased donor kidney transplantation and could not be transplanted within the three-year period. We checked whether any KPE could be performed among pairs in this pool, and non compatible transplant was feasible. To compute the number of patients who could receive a compatible kidney within a KPE program initiated by a deceased donor organ, we consider the sequence of organs from standard deceased donors that were allocated at our centre from January 2012-December 2014, and transplanted to patients in the deceased donor waiting list.
Results: The experiments showed that with 69 kidneys from deceased donors and 16 couples in the KPE program, in 3 years is possible to transplant 9 incompatible pairs(56%). Moreover including 30 desensitized couples for AB0 incompatibility or low DSA, it is possible to perform 10 transplants on incompatible pairs(62%), avoiding desensitization for 10 recipients(45%).
Conclusions: These findings on a real small donor/recipient population suggest a remarkable potential benefit from the utilization of deceased donor kidneys to initiate living donor chains.

Clinical Kidney Donation and donor types

OS221 UNSPECIFIED KIDNEY DONATION RATES IN THE UK ARE PLATEAUING – ARE TRANSPLANT PROFESSIONALS AT FAULT?

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Introduction: Unspecified (non-directed altruistic) donation has been legal for over 10 years in the UK. Nevertheless, it remains a rare practice internationally and qualitative data suggests that unspecified kidney donors (UKD) encounter variations in practice, as well mixed responses from transplant professionals (TPs). Furthermore, national unspecified donation (UD) rates in the UK have recently plateaued. This study aims to identify whether the attitudes and current practice of TPs are negatively impacting on UD in the UK.

Methods: Focus groups and semi-structured interviews were conducted to identify key themes relevant to UD using thematic analysis. These informed the development of a questionnaire that was piloted, validated and distributed nationally to TPs caring for UKD in all 23 UK transplant centres. The study recruited nephrologists, nurses, transplant coordinators, independent assessors and transplant surgeons.
Results: 152 TPs were recruited representing all professional subgroups. Altruistic behaviour patterns were highly prevalent: 151 reported at least 1 out of 5 listed behaviours (99%;median 3). TP expressed a strong interest in becoming either deceased (150, 99%) or specified donors (152, 100%). Furthermore, the majority reported actively considering being UKD themselves (113, 74%). Significantly fewer TPs were comfortable with the idea of being unspecified compared to specified (22% vs. 87%, $t = 121.7$, $p < 0.001$) or deceased (22% vs. 94%, $t = 112.9$, $p < 0.001$) donors. Nevertheless, TPs believed that UKD's had genuinely altruistic motivations for donating (mean 0.7, SD 0.7, where range is 0 = "strongly agree" to 4 "strongly disagree") and that they made balanced decisions (mean 1.2, SD 0.8).
Discussion: The study doesn't find evidence to suggest that the attitudes and practice of TPs are preventing UD. Some TPs remain uncomfortable with the concept of UD and further research is needed to determine whether service users also perceive TPs' practice as being supportive.

OS222 ASSESSMENT OF THE RISK INDEX FOR LIVING DONOR KIDNEY TRANSPLANTATION (LKDPI) IN A EUROPEAN COHORT

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Introduction: Recently, a risk index for living donor kidney transplantation (LKDPI) was proposed (Massie et al. AJT 2016) to compare living donor kidneys (LDK) to each other and to deceased donor kidneys. Until now, the LKDPI has not been validated externally.
Methods: This retrospective analysis included 1305 consecutive adult kidney transplant recipients (889 deceased donor kidneys, 416 LDK), transplanted 2000–2016. Outcome was followed over a median of 6.5 years.
Results: The median LKDPI was 17, while the median KDPI was 69 with a high proportion of donor kidneys with a high KDPI (40% KDPI ≥80) (Fig. 1a). LDK showed a significant better death censored graft survival (Fig. 1b). Categorization of LDK into LKDPI subgroups (LDKPI<0, 0–20, 20–40 and >40) revealed no significant difference in death censored graft survival (after 10 years 84% vs. 85% vs. 89% vs. 67%, respectively, $p = 0.323$). Without reaching statistically significance, there was a tendency for poorer graft survival for kidneys with LKDPI>40 (Fig. 1c). Analyzing the all cause graft loss showed similar results (Fig. 1d). Comparing corresponding subgroups of LKDPI and KDPI (LKDPI/KDPI 0-20 or 20-40) showed comparable graft survival (Fig. 1e). In Cox regression models KDPI (HR 1.15; $p < 0.001$) and age of the living kidney donor (HR1.03; $p = 0.046$), but not LKDPI (HR 1.11; $p = 0.100$) were significantly associated with the risk of graft loss. A multivariate model adjusted for recipient characteristics assessed by the EPTS score revealed KDPI (HR 1.17; $p < 0.001$) but not LKDPI (HR 1.11; $p = 0.135$) as a significant independent predictor of graft loss. ROC analyses for graft survival demonstrated lower predictive discrimination of the LKDPI (AUC 0.55) compared to the KDPI (AUC 0.66) (Fig. 1f).
Conclusion: These results provide some evidence for the comparability of LKDPI to KDPI regarding post-transplant outcome, but our data suggest limited benefit of the LKDPI for the prognosis of graft survival in this European cohort.

OS223 P-LKDPI: A DONOR RISK INDEX FOR PEDIATRIC RECIPIENTS OF LIVING DONOR KIDNEY TRANSPLANTATION

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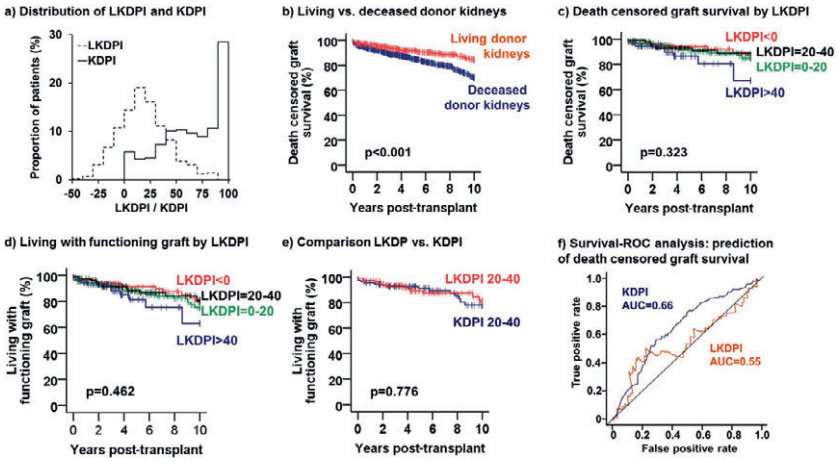
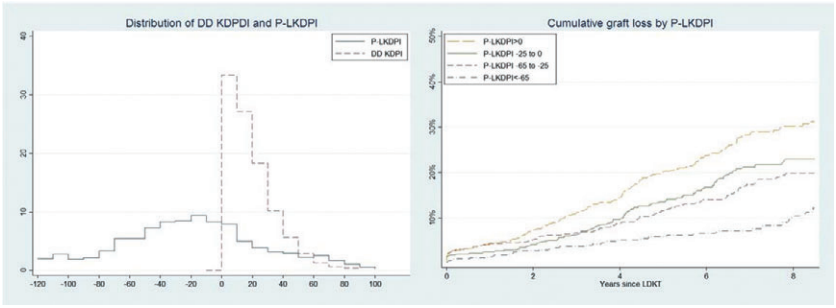
Background: The Living Kidney Donor Profile Index (LKDPI) measures risk of live donor kidneys for adult recipients, on the same scale as the KDPI. It is unlikely that this index can be used for pediatric recipients, given differences in the mechanism of allograft loss in this population.
Methods: We analyzed national registry data on 7,069 pediatric deceased-donor kidney transplant (DDKT) and live-donor kidney transplant (LDKT) recipients in the United States 2004–2013. We modeled risk of all-cause graft loss as a function of KDPI (DDKT recipients) and LD characteristics (LDKT recipients) in a single Cox regression model, adjusting for recipient characteristics (Table). The vector of coefficients for LD characteristics, multiplied by a vector of characteristics for a specific donor and divided by the coefficient for KDPI, yields a donor-specific risk score ("P-LKDPI") on the same scale as the deceased donor KDPI.
Results: Median (IQR) P-LKDPI score for LD kidneys was -21 (-55 to 9), compared to KDPI of 15 (7 to 27) for DD kidneys. 68.8% of LD kidneys had LKDPI<0, indicating less predicted risk than all DD kidneys (Figure, left panel). LDKT recipients with higher P-LKDPI scores had poorer graft survival (Figure, right panel). The C statistic of P-LKDPI was 0.60, compared to 0.53 for the deceased donor KDPI.
Conclusions: LD kidneys with higher LKDPI have poorer graft survival. The P-LKDPI may help with choosing between multiple live donor candidates; since it is on the same scale as the KDPI, the P-LKDPI may also help with choosing between a DD offer when a LD is available.

Donor characteristic	aHR (95% CI)
DD: KDPI (per 10 units)	1.06 (1.02–1.10)
LD: baseline	0.38 (0.15–0.95)
LD: age per 10y (past age 50) if recipient age<12	2.98 (1.15–7.74)
LD: systolic blood pressure (per 10 units)	1.10 (1.02–1.19)
LD: donor/recipient weight ratio (max 4)	0.87 (0.79–0.97)
LD: 2 HLA-B mismatches	1.50 (1.17–1.09)





OS224 THE CLINICAL UTILITY OF CT BASED ANTHROPOMETRIC MEASURES OF ADIPOSITY IN A LIVING KIDNEY DONOR POPULATION

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Background: Donor nephrectomy operative complexity and postoperative outcomes remain subject to large degrees of unexplained heterogeneity. Although obesity is generally linked to adverse outcomes and to challenging surgery, previous data presented to this conference has shown BMI to be a poor predictor.
Aims / Methods: This study sought to assess the clinical correlation of intraabdominal and perinephric fat content using 3 different fat calculation methods in 500 patients undergoing donor nephrectomy who had CT angiography performed as part of their routine preoperative work up. Analysis of association of each fat measure was carried out with spearman rank correlations for continuous parameters and t test and ANOVA performed for grouped variables.
Results: The mean age of the cohort was 44.1 yrs and mean BMI 26.1. 17% were obese and 51% female. All patients had minimum one year postoperative follow up. The cases were performed between 2005 and 2014. All fat measures correlated positively with BMI and Age. The strongest correlation was with total abdominal 3D visceral fat content (R^2=0.62 p = 0.0001).Total abdominal 3D visceral fat content also correlated strongly with operating time (R^2 = 0.14 p = 0.0019), all infections (102 mm^2 v 92 mm^2 p = 0.04), surgical site infections (SSIs) (122 v 105 mm^2 p = 0.02) and greater percentage loss of GFR at one year (r^2 = 0.1326, p = 0.03). Anterior perinephric fat measures also exhibited strong positive associations with length of surgery (r^2 = 0.16 p = 0.001) and minor complications (18 v 9 mm p = 0.02) and SSIs (18 v 8 mm p < 0.001). 3D perinephric fat (40 v 31% p = 0.02) and umbilical fat ratio 42 v 31% p = 0.002) were both associated with lower GFR (<45) at one year. 3D perinephric fat was associated with incisional herniation (225v162 mm p = 0.04).
Conclusions: CT anthropometric measures of living donors are useful clinical correlates of short and longterm postoperative outcomes and inform operative complexity of individual cases allowing pre-emptive planning.

Clinical Kidney Surgical technique

OS225 WHAT APPROACH FOR HAND ASSISTED LAPAROSCOPIC DONOR NEPHRECTOMY; TRANS- OR RETRO-PERITONEAL?

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Introductions: Hand Assisted Laparoscopic Donor Nephrectomy (HALDN) was introduced in our centre in June 2008.

Since then we perform Trans Peritoneal (TP) and Retroperitoneal Approach (RP) routinely on all our Living Donors.

The open approach has never been used since the HALDN program was established.

In this study we have reviewed the outcomes of HALDN and compared the two different approaches also analysing the recipients outcome.
Results: We reviewed our database and identified 339 HALDN performed between June 2008 and March 2016.

The TP approach was used in 255 (75.2%) donors.

The operation time, Warm Ischemia Time and days of hospitalisation showed no difference between TP and RP approach.

In the LD analysis the readmission rate of TP was 9.4% Vs 12.4% in the RP group (p NS).

There was also no difference in the complications observed except for the wound infections; TP 2.5% and RP 9.75% (p 0.0003).

Graft failures rate was 2.1% in TP group and 2.5% in the RP group; Similar rates of Ureteric complications were observed in the two groups.
Conclusion: The use of both approach TP and RP in the same unit is safe and there were no differences in outcomes of both donors and recipients.

There was only one conversion to open procedure. The operation time in both groups was 90 minutes in average. The overall WIT was 2 minute.

Both TP and RP are safe approaches and in our experience the only difference was observed in wound infections rates.

Hospitalisation and readmission rates were statistically non significant.

Implementing in the same unit different approaches and techniques can only enhance the quality of the service and better respond to different challenges presented by potential donors.

There were no graft failures or organ damages differences the TP and RP groups.

Although this remains a single centre study, this series shows that there is no disadvantages in any of the two approaches.

OS226 COMPARISON OF THREE APPROACHES FOR LAPAROSCOPIC DONOR NEPHRECTOMY: TRANSVAGINAL, TRANSUMBILICAL SINGLE SITE AND RETROPERITONEAL

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Objectives: Reduction of burdens to live kidney donors are important. The aim of this study was to compare the surgical outcomes of 3 approaches we have been using for live-kidney donors: Transvaginal (TV), transumbilical single site (TUSS) and retroperitoneal with Pfannenstiel extraction (RPE).
Methods: 64 cases of live donor nephrectomy by a single surgeon were included in the study. The followings were compared among TV (n = 13), TUSS (n = 35) and RPE (n = 16): operation time, blood loss, scar length sum, recipient serum creatinine at discharge (sCr), number of pain killer pills, visual analogue scale of postoperative pain (VAS) at day 1, 2, 3, 6 and the day of full meal recovery, the length of post-operative hospital stay and the frequency of complication (Clavien-Dindo classification >1).
Results: Operation time was longer in RPE than TV or TUSS (266, 226, 216 min). WIT was longer in RPE (5.6, 4.0, 3.5 min). The number of pain killer pills was less in TV than RPE or TUSS (2,4, 4.4, 4.5 pills). The day of full meal recovery was earlier in TV (1.6, 2.1, 2.4 days). The length of hospital stay was shorter in TV (6.1, 8.6, 8.3 days). Scar length sum was the shortest in TV (2.0, 10.2, 3.7 cm). There were no difference among the approaches in blood loss, sCr and the frequency of complications. VAS (1.0, 1.4, 0.2, 0 vs 4.1, 2.8, 2.0, 0.5) were less in TV than TUSS.

Conclusions: Transvaginal approach provided not only faster recovery but better postoperative pain and appearance compared to TUSS or RPE without compromising surgical outcomes.

OS227 OUTCOME OF TRANS-UMBILICAL LAPAROENDOSCOPIC SINGLE-SITE DONOR NEPHRECTOMY, FIRST 160 CASES IN SAUDI TERTIARY HOSPITAL

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Less DN has the advantage over conventional laparoscopy of using a single small incision concealed in the umbilical scar and no extraumblical ports. LESS DN can improve donor satisfaction with better cosmetic results. We report our experience with trans-umbilical LESS DN.
Methods: retrospective study of data from *160* Consecutive left LESS DN donors and their recipients. Standard laparoscopic instruments were used in all patients. Right nephrectomies were excluded as additional 5- mm port needed.

Results: From 05/2015 to 02/2017, 160 LESS DN were performed by three surgeons. The mean operative time was 175.9 ± 24.9 minutes and the mean warm ischemia time was 5.2 ± 1.02 mins. Mean body mass index was 24.8 ± 4.5 kg/m2. Multiple vessels and complex vascular anatomy were found in 52 patients. LESS-DN was successfully completed in 133 patients (84.5%). Due to technical difficulties, additional 1 or 2, 5- mm port(s) were added in 17 and 10 cases respectively. 70% of extra port/s was required only during first three months after starting LESS DN. There was no conversion to open surgery. Two negative exploration were performed in the first post-operative week for picture of small bowel obstruction. We had port site hernia in 1 donor, superficial wound infection in 3 donors and blood transfusion was required in one donor in the multiport group. Basiliximab was used as induction immunosuppression in 128 patients while Thymoglobulin was used in 32 high immunologically risk recipients. 144 recipients(90%) had immediate graft function postoperatively, 14 patients(8.8%) had SGF, and 2 patients(1.2%) had DGF. The mean serum creatinine levels were 1.3 ± 0.93 mg/dl, 1.1 ± 0.33 mg/dl, 1.05 ± 0.29 mg/dl and 1.05 ± 0.25 at 7, 30, 90 and 365 days after transplantation, respectively. *One recipient died of cardiac event on post day 3 with creatinine 2.0 mg/dl. 3 recipients required reoperation; for large subcapsular hematoma evacuation, postoperative bleeding control and open dra*

OS228 LAPAROSCOPIC VS. FINGER ASSISTED OPEN DONOR NEPHRECTOMY TECHNIQUES: WHERE DO THEY STAND?

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Introduction: Widespread use of laparoscopic technique is a standard of care for donor nephrectomy. However, progress has also occurred with open techniques. The aim of the study was to compare an innovative finger assisted open donor nephrectomy (FAODN) technique vs. standard laparoscopic living donor nephrectomy (LDN).
Materials and methods: Laparoscopic hand assisted technique was used for comparison. Retrospective data was collected for donor age, gender, race, surgical parameter, hospital length of stay, and 1 year donor renal function (serum creatinine and GFR) using two different institution's electronic databases (UVA and ICL), The analyses included 95 donors in each group during a similar period of time. Collected variables were compared using Fishers Exact Test for 2x2 tables.
Results: The FAODN group had more males donors (48.4% vs. 51.6% $p = 0.03$), while the LDN group had a statistically significantly larger number of females donors (70.5% vs. 29.5%, $p = 0.003$). Median body mass index (BMI) was similar between groups (28 vs. 26, $p = 0.032$). Left nephrectomy was overall preferred in both groups. Overall frequency of minor postoperative complications was significantly lower in the FAODN group as compared to the LDN group (14.7% vs. 31.6%, $p = 0.0094$). LDN group demonstrated a significantly higher creatinine (1.1 vs. 0.9 mg/dl, $p < 0.001$), and a significantly lower donor GRF at 1 year (60 vs. 89 *ml/min*/1.73 m2, *p*-value<0.001) post donation. Surgical parameters demonstrated a significant longer surgery time (3.5 vs 1.2 hrs, $p < 0.001$), a longer combined length of incision (6 vs. 5 cm, $p = 0.001$)and higher cost in LDN group, while demonstrating a statistically significantly shorter median hospital length of stay (3 vs. 4 days, $p < 0.001$).
Conclusion: Our study demonstrates that FAODN is a successful alternative to laparoscopic techniques. It appears to provide renal donors a favorable outcome in terms of complication, surgery duration, and renal function at 1 year post donation.

OS229 OUTCOMES OF ALLOGRAFTS WITH MULTIPLE VESSELS PROCURED BY TOTALLY LAPAROSCOPIC DONOR NEPHRECTOMY: AN ANALYSIS OF MEDICAL, VASCULAR AND UROLOGICAL COMPLICATIONS

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Background: In the majority of patients with end-stage renal failure, renal transplantation remains the preferred treatment option due to improved quality of life and overall survival. Totally laparoscopic donor nephrectomy (TLDN) in the presence of multiple renal arteries (MRA) is technically challenging. Furthermore, MRA grafts have traditionally been associated with a higher complication rate. We report our experience of using MRA grafts procured by TLDN.
Materials/Methods: Patients undergoing TLDN at our centre(2003–2014) were identified. Patients were divided into either single renal artery (SRA) or MRA groups for analysis. The postoperative complications analysed were vascular, urological and acute rejection. Graft survival rates were compared using Kaplan Meier (KM) analysis.
Results: 465 patients were included. 23% of patients had MRA. Both groups were reasonably matched with regards to demographic data. There were six vascular complications (1.7%) in the SRA group; two graft artery stenoses, one arterial intimal dissection, and three laparotomies for postoperative anastomotic bleeding. There were two vascular complications (1.8%) in the MRA group which were both laparotomies for postoperative anastomotic bleeding. There were eight ureteric complications (4%) requiring subsequent intervention (re-implantation or long-term ureteric stenting) in the SRA group compared to three (3%) in the MRA group ($p = 0.45$). Acute rejection following renal transplant was seen in 12% of the SRA group compared to 9% in the MRA group ($p = 0.23$). One year, five year and ten year graft survival were 98.2%, 91.3% and 89.8% in the MRA group vs. 98.0%, 90.4% and 77.5% in the SRA group (log rank $p = 0.13$)
Conclusions: The use of MRA grafts procured by TLDN in renal transplantation is a safe procedure with comparable complication rates to SRA grafts. The presence of MRA in a donor graft should not preclude its selection for renal transplantation.

OS230 ROBOTIC ASSISTED KIDNEY TRANSPLANTATION - A PROSPECTIVE STUDY: FIRST FACTS AND FIGURES

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Since the beginning of robot-assisted kidney Transplantation (RAKTX) by Dr. Mani Menon this method began to spread. First in the US and in recent years also in Europe. To date, approximately 60 live donations to transplant centers in Barcelona Spain, Toulouse France and the University of Homburg (Germany) and the University of Halle (Germany) are carried out by robotic assisted technique successfully.

We will report from the results of the first 11 robotic assisted kidney transplantations at the University of Halle Germany.

Standardly the Kidney donation was performed laparoscopically hand assisted. The decision which kidney was used for the donation was established by the function and vessel abnormalities.

The robotic-assisted transplantation was routinely performed on the right side for Primary transplantations, or even on the left side for second transplantations. We collected data from the donor, the recipient, immunological risks, operation time, blood lose, complications, the kidney function after Transplantation, pain, rejections and inflammation markers.

Our results show that there are no higher risks of rejections or intraoperative complications for the RAKTX. The operation time is about 35% longer as the open surgery, but there is less blood loos and less pain syndromes afterwards. The ischemic time is about 25% longer for the robotic Transplantation. The inflammatory markers are less than for open surgery and even the hospitality is shorter. After RAKTX 80% of the recipients shows a polyuria.

After the first RAKTX in 2016 our Center performed till now 11 RAKTX. We can confirm that this method is save for Centers with experience in robotic and transplant surgery. There is no higher risk for rejections or complications as for the open surgery. But because of the minimal inversivity, there are less inflammatory markers. These fact caused less pain for the recipient, a shorter stay in Hospital and, that's the main thing, less risk of rejection.

OS231 RIGHT KIDNEYS IN LIVING DONOR KIDNEY TRANSPLANTATION: IS THE RISK OF TECHNICAL GRAFT LOSS REAL?

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Background: The left kidney (LK) is preferred by transplant surgeons, because its vein is always long and thick walled, and makes suturing easier. The right kidney vein (RKV) however, is generally shorter and thinner walled, and well known for technical difficulty during venous anastomosis, and can result in graft loss. We examined our living donor (LD) and recipient transplant data and compared the incidence of technical graft loss and early graft function in RKs and LKs.
Methods: All recipients who received an LD kidney between January 2015 and December 2016 are included. The donor and recipient data was retrospectively analyzed. Technical graft loss was defined as graft thrombosis within 7 days after transplant.
Results: From January 2015 to December 2016, kidney transplants were carried out in 49 adult recipients. Right and LK donor and recipient demographics and graft function are given in Table 1 and 2.

No graft was lost for technical reasons in either group. Twenty one kidneys out of 49 were RKs (43%), which had significantly lesser uptake on diethylenetriaminepentaacetic acid (DTPA) than LKs (44.28 ± 2.39 vs 51.28 ± 2.01%, $p < 0.0001$), but with no statistical difference in serum creatinine (SC), 7 days after transplant (97.85 ± 19.08 vs 110.75 ± 45.07 μmol/L) and last follow-up (90.04 ± 14.19 vs 94.10 ± 26.43 μmol/L). The donor warm ischemia (DWI) for RKs and LKs was 3.90 ± 2.42 vs 3.18 ± 1.49 and recipient warm ischemia (RWI) was 50.85 ± 17.14 vs 45.96 ± 10.41 min respectively. RKs with multiple arteries (4 out of 7) had longer RWI compared to LKs with multiple arteries (69.0 ± 5.131 vs 64.0 ± 0.707 min).

Conclusion: Based on our data, we have shown that RKs are not a risk factor for graft thrombosis in LD transplantation, and that implantation of RKs is as safe as LKs, and with similar outcomes. Although RKs have the potential for disaster, detailed pre-operative assessment of RKV CT imaging, experience of the surgeon and meticulous technique are vital for success in such cases.

OS232 RENAL GRAFT IMPLANTATION ON VASCULAR PROTHESIS: A LARGE MULTICENTER STUDY

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Chu De Nantes, France

Introduction & Objectives:

Kidney transplantation with renal artery implanted on a vascular prosthesis is no comment, hard and risky. The objective of this study was to evaluate the overall survival and the specific survival of the transplant in this context.

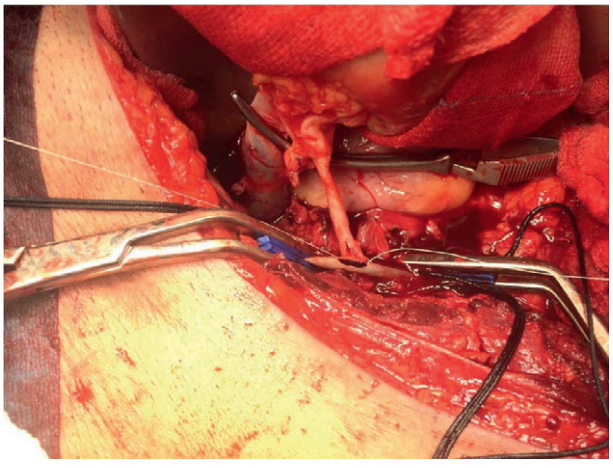
Material & Methods: Patients included in this study were drawn from the multicentric cohort from 10 transplantation centers. This was a retrospective study. The different complications were reported and a prognostic score was created.

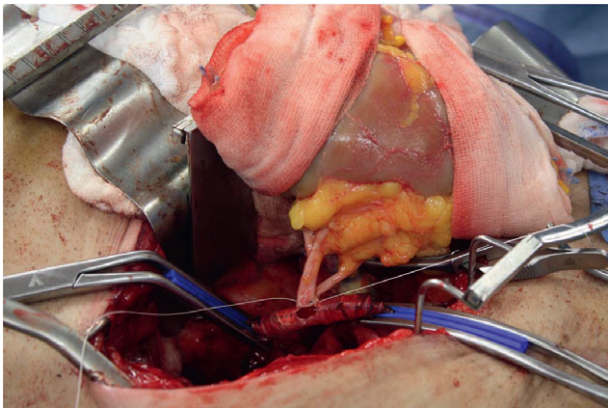
Group 1 consisted of patients with kidney transplantation using artery anastomosis on a vascular prosthesis (figure 1). Group 2 consisted of patient with the same vascular profile than group 1 but with artery anastomosis performed on a native artery. And group 3 consisted of patients without any history of arteriopathy.

Results: Thirty-four patients were included in group 1, 108 patients were included in group 2 and 1713 patients were included in group 3. Transplant's overall survival in group 1 was lower than group 2 and group 3 ($p = 0.1107$). Transplant's median survival was 9 years in group 1 and respectively 7.7 years and 12 years in group 2 and 3.

In group 1, graft dysfunction was mostly caused by a nephrologic dysfunction and come back in hemodialysis (80%) or mortalis. In group 1, the transplant function stops were mainly linked a nephrologist degradation and a return to dialysis (80%) and following a recipient of deaths directly attributable to renal transplantation (10%). In group 2, it was found excess mortality ($p = 0.0016$), more serious complications ($p > 0.0001$) and vascular complications ($p < 0.0001$) in comparison to groups 1 and 3.

Conclusions: Kidney transplantation with arterial anastomosis of vascular prosthesis, in selected patients, would give the same results if not higher than those observed in patients with vascular same profile (group 2) but whose arterial anastomosis is remote of the prosthesis.





Translational Kidney Infection

OS233 CMV-SPECIFIC CD4 + CD137 + IFNγ+ T CELLS IN CMV-SERONEGATIVE INDIVIDUALS PROTECT FROM CMV VIREMIA FOLLOWING TRANSPLANTATION WITH A CMV-SEROPOSITIVE KIDNEY

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Background: A primary infection with cytomegalovirus (CMV) is one of the major threats after transplantation of a CMV-seropositive (CMV^+) donor organ into a CMV-seronegative (CMV^-) individual. Risk assessment for CMV-infection involves measurement of anti-CMV IgG. However, CMV-specific T-cell immunity may exist without measurable anti-CMV IgG. The aim of this study is to assess CMV-specific T-cell immunity in a cohort of CMV^- individuals and the clinical relevance with respect to CMV-infection following transplantation.

Methods: In a cohort of 28 CMV^- and 14 CMV^+ individuals, CMV-specific cytokine-producing and proliferating T cells were assessed prior to transplantation using the CD137 multi-parameter assay and CFSE-dilution, respectively. CMV-specific humoral immunity was evaluated using the B-cell ELISPOT assay.

Results: In 46% of CMV^- individuals, CMV-specific $CD137^+IFN\gamma^+CD4^+$ T cells were detected above background (median values amounted to 0.01% vs. 0.58% in CMV^+ individuals). CMV-specific proliferating $CD4^+$ T cells were detected above background in 58% of the CMV^- individuals (median values amounted to 0.26% vs. 6.34% in CMV^+ individuals). CMV-specific IgG-producing antibody secreting cells (ASC) were barely detected in CMV^- individuals (1 vs. $45/10^5$ in CMV^+ individuals). However, a positive association was observed for CMV-specific $CD137^+IFN\gamma^+CD4^+$ T cells and CMV-specific IgG ASC ($Rs = 0.52$, $p < 0.05$). In 46% of CMV^- individuals a CMV-viremia developed following transplantation. CMV-specific $CD137^+IFN\gamma^+CD4^+$ T cells were associated with protection from a CMV-viremia following transplantation, i.e. positive responses were detected in 10/15 non-viremic vs. 3/13 viremic recipients of a kidney transplant from a CMV^+ donor ($p = 0.03$).

Conclusion: A solitary CMV-specific T-cell response without detectable anti-CMV antibodies is frequent and clinically relevant as it yields significant protection to infection following transplantation with a kidney from a CMV^+donor.

OS234 PRE-TRANSPLANT CMV-SPECIFIC T-CELL IMMUNITY IS AN ADDITIONAL INDEPENDENT VARIABLE PREDICTING CMV INFECTION AFTER KIDNEY TRANSPLANTATION

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Baseline CMV infection risk stratification is based on donor/recipient (D/R) IgG-serostatus and clinical variables such as use of T-cell depletion therapy and AR. However, CMV-specific T-cell immunity (CTI) controls viral replication and its assessment may add useful information guiding decision-making regarding preventive strategies.

Methods: 317 consecutive kidney transplants (KT) were analyzed to evaluate main baseline clinical and immune factors associated to CMV infection and disease. Also, we added pre-transplant CTI against two dominant CMV antigens (IE-1, pp656) using the IFN-γ ELISPOT assay.

Results: 63/317(19.9%) patients displayed infection and 33/317(10.4%) were diagnosed of CMV disease. 109/317(34.4%) received rATG induction, 105/317 (33.1%) received prophylaxis, 37/317(11.7%) were D+/R-, 207/317(65.3%) were D+/R+, 73/317(23.0%) were D-. Out of all clinical and demographic variables, D/R serostatus, rATG, DGF and AR discriminated CMV infection (OR 4.324 $p < 0.001$ OR 2.373, $p = 0.003$, OR 1.896 $p = 0.027$ and OR 1.982 $p = 0.055$). D/R serostatus and rATG correlated with CMV disease (OR 4.962 $p < 0.001$ and OR 3.898 $p < 0.001$). Negative CTI to IE-1 and pp65 discriminated at-risk patients of CMV infection (OR 2.496 $p = 0.002$ and OR 2.192 $p = 0.006$) and disease (OR 5.484 $p = <0.001$ and OR 5.789 $p < 0.001$). Interestingly, a double negative CTI for both antigens significantly correlated with CMV infection (OR 2.511, $p = 0.001$) and disease (OR 6.569, $p < 0.001$).

In the multivariate analysis, prophylaxis therapy (OR 0.074 $p < 0.001$), D+/R- serostatus (OR 17.196 $p < 0.001$), AR (OR 2.445 $p = 0.028$), rATG (OR 11.012 $p < 0.001$) and double negative CTI (OR 2.099 $p = 0.032$) were independent predictors of infection. Prophylaxis (OR 0.214 $p = 0.005$), D+/R- serostatus (OR 7.127 $p < 0.001$), rATG (OR 10.431 $p < 0.001$) and double negative CTI (OR 5.698 $p < 0.001$), independently predicted disease.

Conclusions: Pre-transplant CTI should be added as an additional tool to predict the immune-risk of CMV infection after KT.

OS235 PROSPECTIVE RANDOMIZED TRIAL FOR PREDICTING CMV INFECTION ACCORDING TO BASELINE CMV-SPECIFIC T-CELL IMMUNITY IN KIDNEY TRANSPLANT PATIENTS

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Despite the use of either anti-viral prophylaxis (PF) or pre-emptive (PE) therapy given based on donor/recipient IgG-serostatus, CMV reactivation persists after kidney transplantation (KT), negatively impacting on allograft outcome. CMV-sp T-cell immunity (CTI) controls viral replication and its absence has been associated to higher infection risk, regardless recipient IgG-serostatus.

Methods: Multicentre prospective randomized trial, evaluating CTI against main CMV antigens (IE1, pp65) using the IFN-γ ELISPOT assay (T-spot.CMV) in 160 CMV-IgG seropositive KT stratified into two groups according to their baseline IE-1-sp CTI and randomized to receive 3-mo PF or PE therapy and followed for 12-mo. All patients received basiliximab®, tacrolimus, MMF and prednisone but a subset (20%) received rATG induction. We report the results of an interim analysis of 90% of patients achieving at least 6-mo of follow-up.

Results: ITT analysis showed that incidence of CMV infection in negative CTI patients was 4/16(25%) in PE and 10/15(66.6%) in PF patients ($p = 0.02$) and 2/47(4.2%) in PE and 23/48(47.9%) in PF within positive ones ($p < 0.001$). CTI did not discriminate rATG-treated patients at risk of infection. Among patients on basiliximab®, negative CTI recipients receiving PE or PF therapy did not show higher risk of infection than positive CTI patients. However, when patients experiencing acute rejection and receiving rescue therapy were excluded of the analysis, negative CTI on PE therapy displayed significantly higher risk of infection (HR 4.86 95%CI 1.006–22.172 $p = 0.041$) than positive CTI. Sensitivity, specificity, PPV and NPV of CTI predicting CMV infection was 33.3%, 89.3%, 70%, 67.6%, respectively.

Conclusions: Preliminary data strongly suggest that baseline IE-1-sp CTI using the T-spot.CMV identifies seropositive patients at high risk of CMV infection and thus, should be highly recommended as an additional baseline immune-risk stratification tool in patients awaiting for KT.

OS236 THE EFFECT OF LOW-DOSE VS. STANDARD-DOSE VALGANCICLOVIR FOR PREVENTION OF CYTOMEGALOVIRUS DISEASE IN KIDNEY TRANSPLANT RECIPIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Valganciclovir is importantly used to prevent post-transplant CMV infection among kidney transplantation patients. However, the dose of such drug being used still remains controversial since the continuous use of such drug decrease kidney functions and induces leukopenia in some of the cases. Accordingly, the purpose is to measure the appropriate dose of the drug required for preventing CMV.

Methods: A systematic review and meta-analysis using a fixed-effects model was performed We searched the Cochrane Central Register, OVID MEDLINE, EMBASE, and Pubmed until March 15, 2017. We review the reference lists of relevant reviews, registered trials, and relevant conference proceedings. Definition of low dose valganciclovir group is 450 mg and standard dose one is 900 mg.

Results: Four trials were included, consisting of a total of 725 patients In the pooled analysis. As a result of analyzing the two groups, the CMV incidence showed tendency to decrease in the low dose group. However, no statistical significant was indicated ($p = 0.109$). Upon completion of the research, the GFR value, graft loss, tacrolimus level, fungal and candida infection indicated no difference between the two groups. However, the biopsy proven rejection decreased by 0.397 times in the low dose group in comparison to the standard group ($p = 0.002$) and the leukopenia event decreased by 0.416 times in the low dose group in comparison to the standard group ($p = 0.001$) as well.

Conclusions: The dose of valganciclovir used to prevent the post-transplant CMV infection was adjusted to 450 mg. As a result, such dose was effective in preventing CMV viremia and the side effects such as leukopenia caused by the drug also decreased. In the future, the dose of valganciclovir being used should be adjusted to 450 mg in order to prevent the CMV infection as well as to enhance the economic effects.

OS237 COST BENEFIT OF CYTOMEGALOVIRUS DISEASE PREVENTION IN KIDNEY TRANSPLANT RECIPIENTS USING LOW DOSE VALGANCICLOVIR

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[1]Otc, Kuwait; [2]Halim, Kuwait; [3]Alotaibi, Kuwait

Prophylaxis for cytomegalovirus infection is highly recommended for kidney transplant recipients. Using valganciclovir in low dose is still under investigation. Our aim was to assess the cost effectiveness of 450 mg valganciclovir (VGC) prophylaxis compared with 900 mg for kidney transplants.

Materials and methods: In a prospective trial, 201 kidney transplants were randomized to receive 450 mg VGC prophylaxis (group1, $n = 100$) or 900 mg daily (group2, $n = 101$) for the first 6 months post-transplant. Patients were studied for incidence of CMV disease, leucopenia attacks, rejection episodes and graft outcome and associated costs in one year duration. Direct costs associated with acquisition of immunosuppressive medications, diagnosing rejection, and hospitalizations were included.

Results: Demographic features of the studied groups were comparable. More patients have received tacrolimus in group 1, while in group 2 more patients were maintained on cyclosporine (p0.001). We found that the cost of CVM prophylaxis in patients of group 1 was significantly lower (by 50% at 6 months, $p < 0.001$) with lower leucopenia attacks (p 0.04) and lower doses of granulocyte colony stimulating factor (by 30% at 6 months, p 0.03) compared to group 2. Higher doses of mycophenolate mofetil (p 0.04) among group 1 patients were protective therefore they experienced less rejection episodes (p0.01).In group2; there were more cytomegalovirus infections requiring full treatment (p0.052) and more BK virus nephropathy (p0.03). Graft and patient outcomes were satisfactory in both groups. Mean estimated glomerular filtration rates were above 60 ml/min at baseline, at 6 months and at 12 months post-transplant for both groups.

Conclusion: Low dose valganciclovir for cytomegalovirus prophylaxis after renal transplant is safer, effective without breakthrough infection and less costly than using usual dose.

OS238 IMMUNOLOGICAL SIGNS OF CYTOMEGALOVIRUS REINFECTION AFTER KIDNEY TRANSPLANTATION

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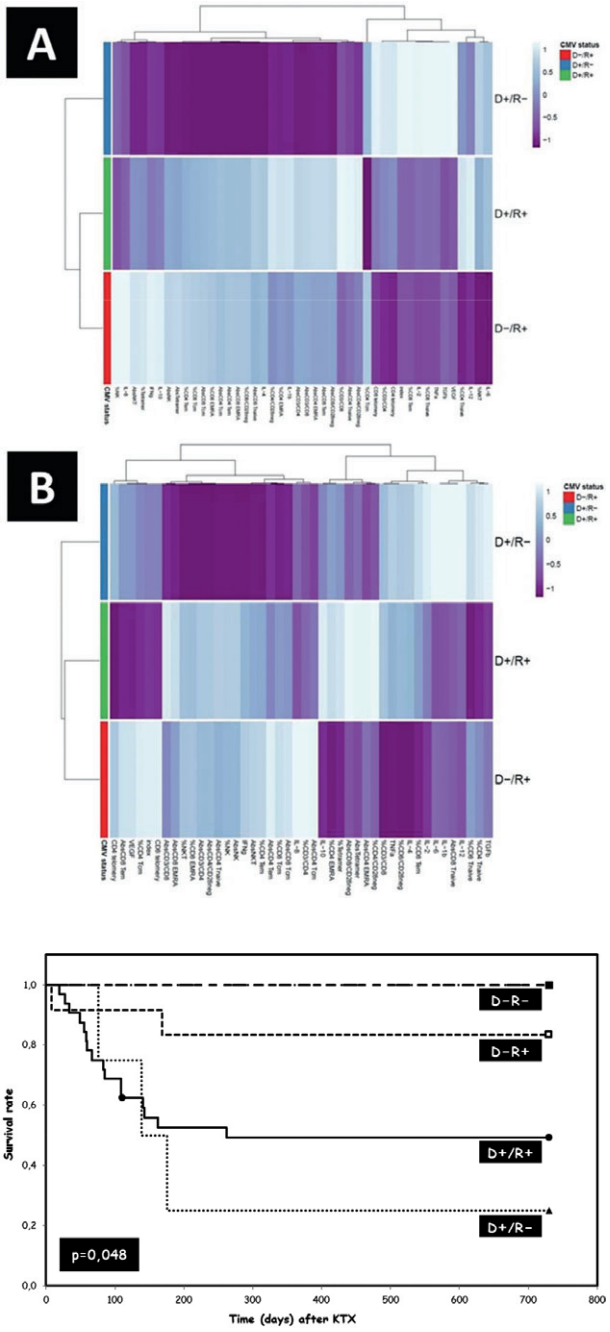
Background:

Human cytomegalovirus (CMV) infection remains major complication after kidney transplantation. Regrettably, the virus may not be only transferred from infected donor to the uninfected recipient, beginning primary infection, but also to CMV already infected causing reinfection. Unfortunately, little is known how cytomegalovirus transmitted from an infected donor to an infected recipient modulates the recipient's already suppressed immunity, and what the clinical consequences are.

Methods/Materials: To investigate these issues, 52 middle-aged kidney recipients were followed quarterly up to two years after transplantation.



Immune parameters associated with CMV infection like T, B, and natural killer lymphocytes, naïve and memory T subsets, CD28 expression, relative telomere length, cytomegalovirus-specific lymphocytes, and serum cytokines were measured at each time point. Patients were also monitored for signs of impaired immunity, including cytomegalovirus viremia and other common infections.

Results: We found that cytomegalovirus reinfection from an infected donor negatively impacts the immunity of an infected recipient, in comparison to recipients who received kidneys from uninfected donors. Two years after transplantation the entire landscape of measured parameters is different when compared between CMV-positive recipients who received an organ from infected or uninfected donor (Figure 1). Also, the frequency of CMV viremia was higher in CMV reinfection individuals when compared to CMV-positive recipients that received a kidney from CMV negative donor (Figure 2). Nevertheless, susceptibility to other than CMV infection was comparable across infected recipients regardless of donor status.

Conclusion: Cytomegalovirus strongly impacts the immune system in kidney transplant recipients and promotes immune exhaustion. Thus, recipients with prior exposure to cytomegalovirus are at high risk of re-infection.

OS239

INCIDENCE OF CYTOMEGALOVIRUS DISEASE IN KIDNEY TRANSPLANT RECIPIENTS RECEIVING EVEROLIMUS AND REDUCED TACROLIMUS DOSES

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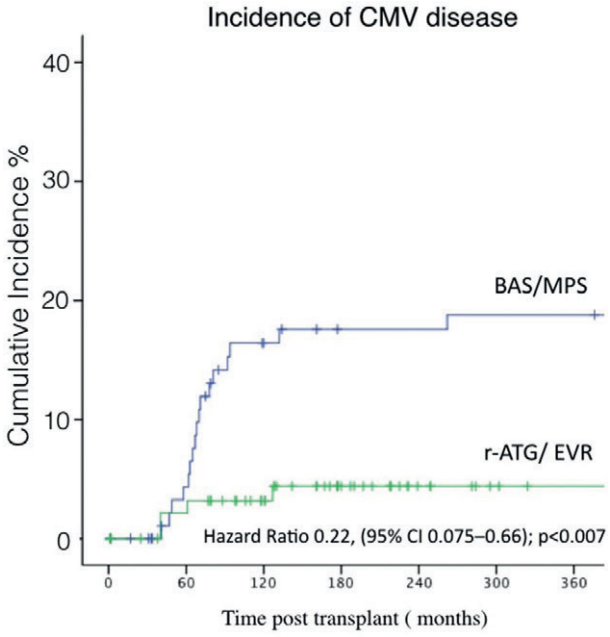
Background: Cytomegalovirus (CMV) infection remains a major complication of solid organ transplantation. It is responsible for increased morbidity, mortality, and reduced allograft survival. Clinical data suggest that mTOR inhibitors may have an anti-CMV effect.

Methods/Materials: We retrospectively analyzed all low immunological risk patients from Jan 2013 to December 2016 in a single transplant center. They received a single 2.25 mg/kg dose of antithymocyte globulin, tacrolimus, everolimus, and prednisone (r-ATG/ EVR, $n = 100$) or basiliximab, tacrolimus, mycophenolate, and prednisone (BAS/MPS, $n = 100$). None of them received pharmacological CMV prophylaxis.

Results: Patients on r-ATG/ EVR showed a 78% proportional reduction (4% vs. 17%, HR 0.22, 95% CI 0.075–0.66; $p < 0.007$) in the incidence of CMV disease compared to BAS/MPS. There were no differences in the incidence of biopsy-proven acute rejection (5.0% vs. 5.0%, p 0.956)

Conclusion: In de novo kidney transplant recipients receiving no pharmacological CMV prophylaxis, reduced-dose tacrolimus and everolimus had a lower incidence of CMV disease compared to standard tacrolimus dose and mycophenolate.



OS240

HIGHER DEGREE OF CMV REACTIVATION IN CMV R+/ IGRA- THAN R+/IGRA+ RENAL TRANSPLANT RECIPIENTS

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Background: Cytomegalovirus(CMV) infections after kidney transplantation (KTx) contribute to adverse clinical outcomes. Guidelines recommend different length of prophylaxis or pre-emptive antiviral treatment based on CMV serotype risk groups. Recently also assays for CMV-specific T-cell response have been launched, but these are not well studied with regards to treatment allocation.

Material and Method: From August 2016 to March 2017 a cohort of 56, at Tx, CMV seropositive KTx patients were investigated for CMV specific CD8 + T-cell response by the CMV IGRA test(QuantiFERON) before and 8 weeks after Tx. All patients were subjected to a pre-emptive anti-CMV approach and plasma CMV DNA quantitation by RT-PCR (LLOD = 36 and LLOQ = 200 IU/mL) was performed at least once a week. Patients with CMV PCR >600 IU/mL received valganciclovir.
Results: Pre Tx 6/56(10.7%) seropositive patients had a negative CMV IGRA result. Eight weeks after Tx, 2 of the 6 IGRA negative patients had converted and showed a positive CMV IGRA response. All patients with a negative result at 8 weeks were also negative pre Tx. The 50 CMV IGRA positive patients had a mean IFNγ level of 10.1 $\pm$ 7.1 IU/mL (range 0.2 to 24.2 IU/mL) at Tx. Eight weeks post Tx the mean IFNγ level 12.2 $\pm$ 6.0 IU/mL (range 0.8 to 22.7 IU/mL) was not significantly changed from pre Tx ($p = 0.26$).

Among the 6 CMV IGRA negative patients, 5(83.3%) showed CMV reactivation during the first 8 weeks after Tx and 3(50.0%) presented with a CMV DNA > 600 IU/mL and started valganciclovir. Out of the 50 CMV IGRA positive patients 4 had suboptimal CMV surveillance and 25/46(54.3%) showed CMV reactivation with 6(13.0%) patients presenting CMV DNA >600 IU/mL.
Conclusion: In this study a higher share of treatment dependent CMV reactivation was shown in patients that were CMV seropositive/IGRA negative at time of KTx compared to CMV seropositive/IGRA positive. The clinical utility of CMV IGRA test for treatment allocation in this population needs further studies.

Translational Intestine Other

OS241 SUCCESSFUL TRANSPLANTATION OF A HUMAN TISSUE ENGINEERED BOWEL (HTEB) IN AN ATHYMIC RAT MODEL

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Background: Intestinal failure is a devastating clinical condition. The objective of this study was to transplant human-based engineered neo-intestines into athymic rats to assess their viability and the regeneration of the essential components for digestion and absorption.
Methods/Materials: TEB was developed by wrapping bioengineered innervated human intestinal circular smooth muscle sheets around tubular scaffolds. TEBs were implanted in the omentum of athymic rats. After 6–8 weeks, TEBs were transplanted to the native small intestine of the same rats. At the time of sacrifice, TEBs were analyzed histologically and functionally.
Results: TEB biopsies before anastomosis revealed maintenance of cell morphology and function as demonstrated by histology and physiology testing. At time of harvest, TEB was pink in color and healthy with food digest observed inside the lumen. Potassium chloride caused a rapid and robust contraction of the smooth muscle which was inhibited in the presence of calcium channel blocker. This indicated the maintenance of the voltage-dependent calcium channels in the smooth muscle of TEB following anastomosis. Neural function was confirmed using electrical field stimulation (EFS). EFS caused relaxation of the smooth muscle of TEB. This relaxation was partially inhibited in the presence of nitric oxide synthase inhibitor, indicating functional nitrergic neural population. Histological analysis: H&E demonstrated maintenance of smooth muscle circular alignment around the lumen of TEB. Re-epithelialization of TEB was also observed with well-defined crypts and villi structures. Alcian blue stain demonstrated the presence of mucin, confirming the presence of Goblet cells.
Conclusion: The results shown in this study demonstrated the successful transplantation of a fully functional engineered intestinal tissue in rats. Rats gained weight over the study period and TEB acquired epithelial components with villi structures.

Clinical Intestine Immunology

OS242 DONOR-SPECIFIC HLA ANTIBODIES AFTER COMBINED INTESTINAL AND VASCULARISED COMPOSITE ALLOTRANSPLANTATION

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Oxford Transplant Centre, United Kingdom

Background: Combining a vascularised composite allograft (VCA) with intestinal transplantation can be used to achieve primary abdominal closure. As the inclusion of a VCA raises the possibility of an enhanced alloimmune response, we investigated the incidence and clinical effect of de novo donor specific HLA antibodies (dnDSAs) in a cohort of patients receiving an intestinal transplant with or without a VCA.
Methods: The retrospective clinical study includes 34 recipients of deceased donor intestinal and VCA transplants performed between 2008 and 2016. Pre-transplant HLA antibody status and crossmatch data were available for all patients.
Results: Thirty-four intestinal transplants were included. One patient underwent a second small bowel and abdominal wall transplant. All organs were retrieved from DBD donors. There were 10 modified multivisceral transplants (10/34, 29.4%) and 24 isolated small bowel transplants (24/34, 70.6%). An abdominal wall was used in 20 cases (20/34, 58.8%). All patients received alemtuzumab induction and tacrolimus maintenance immunosuppression. There were no episodes of intestinal rejection without VCA rejection. Post-transplant monitoring of the HLA sensitisation status was available for 31/34 patients. In 9/31 (29%) patients the sensitisation status did not change, in 8/31 (26%) sensitisation increased without occurrence of dnDSA but 14/31 (45%) patients developed dnDSAs. In the VCA group, fewer patients developed dnDSAs; 33.3% VCA vs. 61.5% non-VCA. A multivariate analysis revealed that the existence of dnDSAs ($p = 0.043$) and specifically the combination of HLA class I and II dnDSAs ($p = 0.005$) significantly influenced graft survival.
Conclusion: In this study, 45% intestinal transplant patients developed dnDSA following transplant, but there is no evidence that the addition of a VCA increases the incidence of dnDSA formation compared to transplantation of the intestine alone.

Basic Intestine Ischemia-reperfusion and preservation

OS243 TRANILAST PRE-TREATMENT ATTENUATES INTESTINAL ISCHEMIA REPERFUSION INJURY

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Background: Intestinal ischemia reperfusion injury (IIRI) is unavoidable during intestinal transplantation and leads to poor outcomes. Tranilast (TL) is a HO-1 inducing drug used for the treatment of rheumatoid arthritis, Crohn's disease and severe atopic dermatitis. Given its anti-inflammatory and anti-oxidant properties, we hypothesized that TL may reduce IIRI injury in a rat model.
Methods/Materials: In a validated rat model of IIRI (isolated clamping of the superior mesenteric artery), 3 groups were tested: 1/Sham (laparotomy only); 2/ 60' Ischemia + 60' reperfusion + TL; 3/60' Ischemia + 60' reperfusion + Vehicle. At the end of this period, the animals were sacrificed by exsanguination under anesthesia. To test effect on survival, 10 further animals per group underwent the same procedure and survival after 7 days was recorded. TL (.65 mg/g) was administered by oral gavage 24, 12 and 3 hours before IIRI. The measured endpoints were: histology (Park/Chiu score), plasma biomarkers for enterocyte damage (L-lactate, I-FABP), intestinal permeability (Using chamber), tissue pro- and anti-inflammatory cytokines (RT-PCR), endotoxin translocation (Limulus Amebocyte Lysate Pyrogent kit), HO-1 protein (Western blot) and 7-day survival.
Results: IIRI led to severe damage of the intestinal wall, both structurally and functionally. These alterations were linked with increased endotoxin plasma levels and up regulation of pro-inflammatory cytokine in tissue. TL pre-treatment attenuated these parameters and improved 7-day survival (see Table) and up-regulated HO-1 expression.
Conclusion: Tranilast pre-treatment improves intestinal permeability, reduce inflammation, lowers endotoxin translocation and improves survival probably *via* HO-1 upregulation.

Endpoints *Median (range)*	Sham	Vehicle + IIRI	TL + IIRI	ANOVA
Park-Chiu (0-8)	0,0 (0,0-0,3)	4,9 (2,5-6,7) ††††	2,0 (0,0-3,0)**	<0,0001
Villus length (μm)	263 (215-289)	85 (67-136) ††††	210 (146-320) ***	<0,0001
TEER (Ω* cm²)	49 (36-69)	11 (8-23) ††††	32 (26-39)****	<0,0001
L-lactate (mmol/L)	1,5 (1,0-1,9)	3,9 (2,5-5,1) †††	2,0 (1,0-2,8)**	0.0001
I-FABP (WB band density)	0,1 (0,01-0,02)	0,7 (0,3-1,4) †	0,1 (0,01-0,7)	0.0136
Endotoxin (U/ml)	0,04 (0,02-0,09)	0,2 (0,2-0,4) †††	0,12 (0,007-0,20)**	0.0002
IL-1β (-ΔΔCt)	0,15 (-1,6-1,5)	1,8 (1,3-2,9) ††	1,0 (-0,3-1,3) **	0.0015
IL-6 (-ΔΔCt)	0,3 (-3,2-2,4)	4,2 (3,6-5,4) †††	2,0 (0,7-2,7) ***	0.0003
TNF-α (-ΔΔCt)	0,03 (-1,5-1,4)	0,7 (-0,3-1,2)	-0,18 (-1,69-0,98)	NS
IL-10 (-ΔΔCt)	-1.0 (-1.7--0.09)	1.5 (0.3-2.8)	2.4 (1.4-3.8)	NS
IL-13 (-ΔΔCt)	0.03 (-1.7-2.7)	1.6 (0.7-3.5)	3.4 (2.6-8.0)*	0.0017
IFN-γ (-ΔΔCt)	-5,4 (-7.1--3.8)	-0.8 (-1.5-0.8) ††††	-2.4 (-5.6--2.2)*	<0.0001
HO-1 (WB band density)	0,2 (0,1-0,3)	0,3 (0,2-0,6)	0,7 (0,6-1,7) **	0.0008
7-day survival (%)	100%	10%	50%	0.0075 (Mantel-Cox)

Legend: *TEER*: Transepithelial electrical resistance, WB: Western Blot, *NS*: Not significant, *= significance TL vs Vehicle, † = significance Sham vs Vehicle

NS	P > 0.05
*/†	P ≤ 0.05
**/††	P ≤ 0.01
***/†††	P ≤ 0.001
****/††††	P ≤ 0.0001

Clinical Intestine Other

OS244

INTESTINAL TRANSPLANTATION FOR ADULTS IS LESS EXPENSIVE COMPARED TO LONG-TERM HOME PARENTERAL NUTRITION

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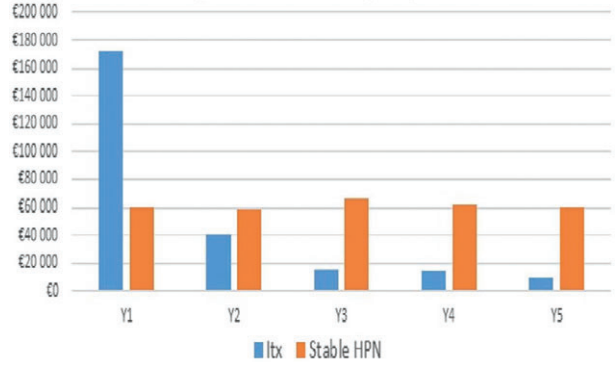
University Hospitals Leuven, Belgium

Background: The primary treatment of intestinal failure is home parenteral nutrition (HPN) while intestinal transplantation (ITx) is reserved for when severe complications occur. In renal failure, transplantation has been promoted over dialysis because transplantation reduces the costs. The aim was to compare the costs of uncomplicated, adult HPN patients to a cohort of ITx patients at our institution.
Methods: First, we collected the data from our cohort of stable, long-term (>2 years) HPN patients (min. 5 year follow-up). The first two years after start of HPN were excluded to identify the stable cost of HPN. Second, we collected the costs of our cohort of ITx patients, transplanted between 1/1/2000 and 31/12/2015. Next, we compared the costs between stable HPN patients and ITx in this 5 years-period.
Results: There were 21 HPN patients in this cohort. Median duration of HPN was 8.6 years. HPN was administered 4.1 days (σ = 1.6) per week at 5767 total kcal (2385–10890). Indications were short bowel syndrome (SBS) (57%), intestinal dysmotility (24%), mechanical obstructions (14%) and mucosal disease (5%). There were 12 ITx patients. The main underlying disorders were SBS (67%) and diffuse portomesenteric thrombosis (20%). The 5-year patient survival was 83.3%. For HPN patients, the total annual costs remained stable at a median of € 59 524 (€ 58 731 - € 65 807). HPN costs (basic costs and treatment of complications) accounted for 76% of these costs. After ITx, the first year costs were € 172 133 (122 483 - 351 407) which then drops to € 8 832 (3 270 - 38 723) in year 5 (Figure 1).

Figure 1: Total cost per year



Conclusions: ITx has a high initial cost compared to stable, adult HPN patients. From year 2 onwards, the cost of ITx is less compared to long-term HPN. By year 4, the additional costs incurred in year 1 of ITx are recovered making the procedure cost effective.

OS245

INTESTINAL TRANSPLANTATION IS COST EFFECTIVE IN THE TREATMENT OF COMPLICATED INTESTINAL FAILURE

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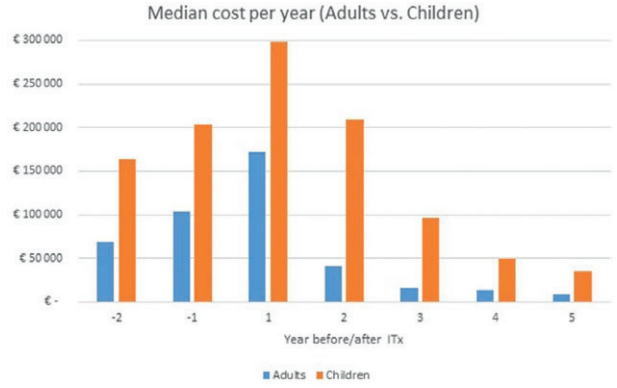
University Hospitals Leuven, Belgium

Background: When life-threatening complications occur due to home parenteral nutrition (HPN), intestinal transplantation (ITx) is indicated. ITx is the most expensive organ transplant but the cost effectiveness is unknown. Our aim is to compare the costs of complicated HPN before ITx to the costs after ITx at our institution.
Methods: A retrospective analysis was performed of our cohort of ITx patients, transplanted between 1/1/2000 and 31/12/2015. For those patients followed at our center pre-ITx, the costs before ITx, including the HPN care were included up to 2 years before surgery. All costs for pre-transplant screening were excluded from the pre-transplant data.
Results: 16 patients were included in this study (see Table). For 8 patients, financial data were available pre-transplant. The underlying disorders for the adults were short bowel syndrome (SBS) (67%), diffuse portomesenteric thrombosis (25%) and chronic intestinal pseudo-obstruction (8%). 2 children had SBS and 2 had congenital mucosal disease. Indications for ITx are included in the Table. The 5-year patient survival was 86.7%. The total median costs in year -2 (day 720 – 366 pre-ITx) was € 90 891 (60 682–342 299) and year – 1 (day 365- 1 pre-ITx) was € 134 006 (83 854 - € 275 712). After ITx, the costs of the first year were € 185 662 (122 483 - 571 301). In year 2, there was a 76% reduction in overall costs to € 44 893 (3 905-293 985) due to a reduction of hospitalizations (year 1: 145 days, year 2: 37). In adult patients, the costs drop much faster while remaining quite high until year 3 in children (Figure).
Conclusion: Intestinal transplantation, while being an expensive procedure, was cost effective in adults by the second year. In children, ITx was cost effective from the third year onward, because of more complicated treatment of underlying congenital disease.

Patient	Gender (M/F)	Gender (M/F)	Pediatric or Adult	Underlying intestinal condition	Indication ITx	Graft type
1	F	56	Adult	Ischemia	LF + RS	cLi-ITx
2	F	57	Adult	Ischemia	LF + RS	cLi-ITx
3	M	2.8	Pediatric	Volvulus	LF + RS	cLi-ITx
4	F	26	Adult	CIPO	RS + Liver fibrosis	ITx
5	F	41	Adult	Volvulus + EH	LVA	ITx + KTx
6	M	43	Adult	ST (APS)	RB	MVTx
7	F	40	Adult	Ischemia	RS	ITx
8	F	9	Pediatric	Volvulus + Colitis	LF + RS	cLi-ITx + KTx
9	F	36	Adult	Volvulus	LF + RS	cLi-ITx
10	F	57	Adult	CD + KF	KF	ITX + KTX
11	M	29	Adult	CD	LF + RS	ITX
12	M	23	Adult	Splanchnic Thrombosis (NET)	RB	MVTx
13	M	3.8	Pediatric	Microvillus inclusion disease	LF + RS + LVA	cLi-ITx
14	M	47	Adult	Splanchnic Thrombosis (Cirrhosis)	LF + RS	MVTx
15	M	55	Adult	Ischemia	Ultra-short bowel -> pre-emptive	ITx + KTx
16	M	17	Pediatric	MMHS	Therapy resistant pancreatitis + obstructions	ITx + PTx

Legend: ***APS***= anti phospholipid syndrome, ***CD***: Cohn's Disease, ***CIPO***= Chronic intestinal pseudo-obstruction, ***cLi-ITx***= combined Liver-Intestinal Transplant, ***EH***= Enteric hyperoxaluria, ***KF***= Kidney Failure, ***LF***= Liver Failure, ***LVA***= Loss of vascular access, **MMHS** = Megacystis-microcolon-hypoperistalsis syndrome ***ITx***: Isolated Intestinal Transplantation, ***KTx***: kidney transplantation, ***MVTx***: multivisceral transplantation, ***NET***= Neuro-endocrine tumor, ***PTx***= Pancreas transplantation, **RB**=Recurrent bleeding, ***RS***= Recurrent Sepsis, ***ST***= Splanchnic thrombosis



Clinical Intestine Immunosuppressive agents

OS246

BELATACEPT AND BASILIXIMAB MAINTENANCE IN INTESTINAL TRANSPLANTATION

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Introduction: Belatacept (CTLA4Ig) and Basiliximab (IL-2 receptor antagonist) are emerging maintenance treatments in solid organ transplantation due to the lack of nephrotoxic effects. The impact on the development of de novo donor specific antibodies (DSA) as well as clinical safety in challenging immunological settings has yet to be explored.

Methods: Kidney function and immunological events were analysed in our cohort of intestinal transplant recipients (n = 34). We identified the patients demonstrating a significant decline in their pre-transplant glomerular filtration rate (eGFR) after intestinal transplantation (ITx). Rejection episodes and development of dnDSA were monitored closely.
Results: From October 2008 to December 2016, 34 patients underwent ITx. All our intestinal transplant recipients received lymphocyte-depleting induction therapy using Alemtuzumab followed by Tacrolimus monotherapy for maintenance immunosuppression. Six patients (17.6%) demonstrated a mean eGFR decline of 45mls/min (range 25–70mls/min). Decline was noted at a median of 45 days (range 7–720 days) post transplantation. All 6 patients were switched to Belatacept and median time to switch was 208 days (range 23–1195 days). Two of these patients were switched to Basiliximab due to intolerance to Belatacept. Five patients (83.3%) demonstrated an immediate improvement in eGFR. Four of them patients returned to pre-transplant eGFRs within 4 weeks.
Post-transplant monitoring of HLA sensitisation status was available for 31/34 patients; overall 14/31 (45%) patients developed dnDSAs. There were 3 bowel rejection episodes in the Belatacept/Basiliximab group, two (66%) of them were followed by the development of dnDSA.
Discussion: Belatacept or Basiliximab based immunosuppressive regimen can be beneficial in intestinal transplantation. Majority of patients demonstrated an improvement of their eGFR. The application of Belatacept or Basiliximab as a "rescue" medication has to be discussed critically.

Clinical Intestine Metabolic complications

OS247 LONG-TERM OUTCOME OF RENAL FUNCTION AFTER ADULT INTESTINAL TRANSPLANT AT SMALL VOLUME SINGLE CENTER: INCLUDING TWO-CASES OF RENAL TRANSPLANT

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Purpose: Renal dysfunction is a well-known higher occurrence complication after intestinal transplantation (ITx) when compared with heart, lung, or liver transplantation. Here we provide a clinical analysis of renal function after adult ITx.
Methods: We retrospectively analyzed 8 adult intestinal transplant patients with at least 6 months survival from 2004 to 2016. Glomerular filtration rate (GFR) measurements were performed at baseline, 3 months, 6 months post-transplantation and yearly thereafter. Median follow-up duration was 53.5 months (8 – 153 months).
Results: All were isolated ITx, performed using 3 living-donor ITx and 5 deceased–donor ITX. Actual graft and patient survival was 75% and 87.5%, respectively. Mean baseline GFR was 97 (74–128) mL/min/1.73 m^2. GFR 1 year post-transplant had decreased over 50% of the baseline (43.5 mL/min/1.73 m^2). Renal dysfunction was observed in 4 patients. Two patient developed acute renal failure due to acute rejection and sepsis. One of these patients fully recovered her renal function, the second patient was died. Another two patients developed chronic renal failure and required hemodialysis (HD) within 6 year, 3 year, respectively. The first Living donor ITx patient lost her renal function progressively over 6 year post-ITx. She received a renal graft from the same living donor as her intestine after 3 year of HD. The other patient (deceased donor ITx) received kidney transplantation from his son after 1 year of HD.
Conclusion: In our center, 50% of the adult ITX patients developed renal dysfunction and half of the patients developed chronic renal failure requiring kidney transplantation. The median measured GFR decreased over 50% at 1–year post-transplantation. To obtain an accurate assessment of renal function, frequent direct measurements of GFR should be performed to facilitate early diagnosis of renal impairment and subsequent strategies that improve renal function after ITx.

Clinical Intestine Allocation

OS248 MULTIVISCERAL TRANSPLANTATION: THE FIRST CZECH EXPERIENCE WITH 6 CASES

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Introduction: The small bowel (SBT) and/or multivisceral transplantation (MVT) is the treatment option for selected patients with short bowel syndrome as well as other diseases. The SBT is associated with high rate of rejection and infectious complications and also few possible technical difficulties, mainly related to recipients previous surgeries. Although the SBT/MVT will serve only few patients per year, such patients may not have other treatment options.
Methods: There were six full MVT performed since Dec 2014. The indication was diffuse portomesenteric thrombosis in 3 cases, desmoid in 2 and short bowel syndrome in 1 case. All 6 received multivisceral graft including: Stomach, pancreas, liver and small bowel, two patients together with spleen. Immuno-suppressive regime based on alemtuzumab induction followed with tacrolimus and steroids was used.
Results: There were no major surgical complications observed in all cases, the first case had one episode of mild bowel rejection, treated successfully with steroids, discharged 34 days after surgery, doing well now 27 months after MVT. The second patient developed steroid resistant small bowel rejection 17 days after the MVT, died 68 days after the MVT from pneumonia and sepsis. Third patient developed pylorostenosis, which was treated endoscopically. Fourth patient had no complications, fifth bled to death on table, sixth died from resistant infection and sepsis two months after MVT.
Conclusion: The MVT can serve only few patients comparing to other organ transplants. The program started in Czech Republic in December 2014 with sequence of two MVT cases. The first MVT was successful, the overall mortality in our small series comes as high as 50%. The indications should be taken with special caution, especially in cases with short bowel syndrome, such patients may have relatively good life on parenteral nutrition. Risks from MVT should be carefully balanced with potential benefits.

Clinical Liver Cancer

OS249 INTENTION-TO-TREAT SURVIVAL BENEFIT SELECTS PATIENTS WITH HEPATOCELLULAR CANCER WAITING FOR LIVER TRANSPLANTATION

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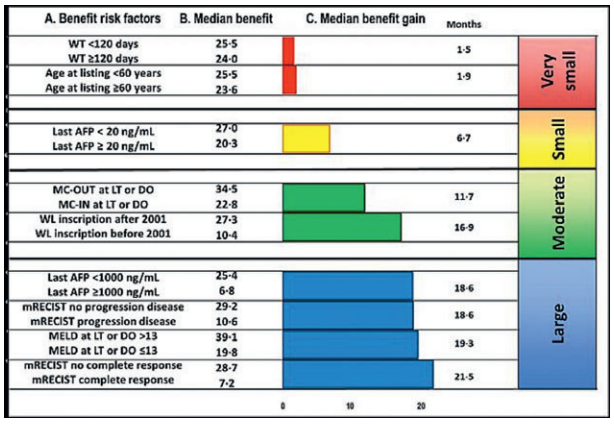
The debate about the best approach to select patients with hepatocellular cancer (HCC) waiting for liver transplantation (LT) is still ongoing. This study aims to identify the best variables allowing to discriminate "high-" and "low-benefit" patients. To do so, the innovative concept of intention-to-treat (ITT) survival benefit of LT has been created. Data of 2103 adult HCC patients consecutively enlisted during the period 1984-2015 were analyzed. Three rigorous statistical steps were used in order to create the ITT survival benefit of LT: the development of an ITT LT and a non-LT survival model, and the individual prediction of the ITT survival benefit of LT defined as the difference between the median ITT survival with (based on the first model) and without LT (based on the second model) calculated for each enrolled patient. Four variables (MELD, alpha-fetoprotein, Milan-Criteria status and radiological response) displayed a high effect in terms of delta-benefit. According to these risk factors, four benefit groups were identified. Patients with three-four factors ("no-benefit group", $n = 405/2103$; 19·2%) had no benefit of LT compared to alternative treatments. Inversely, patients without any risk factor ("large-benefit group", $n = 108$; 5·1%) yielded the highest benefit from LT reaching 60 months. Conclusion

The here presented innovative ITT transplant survival benefit allows to better select HCC patients waiting for LT. The obtained stratification may lead to an improved and more equal way for organ allocation. Patients with no benefit should be de-listed, whilst patients with large benefit ratio should be prioritized for LT.



OS250 TREATMENT OF POST-LIVER TRANSPLANT ACUTE REJECTION AND HEPATOCELLULAR CANCER RECURRENCE: AN UNTOLD STORY

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Several studies investigating the role of immunosuppression (IS) and hepatocellular cancer (HCC) recurrence after liver transplantation (LT) have been recently published. On the opposite, no studies exist on the correlation between post-LT acute rejection (AR) and the risk of HCC recurrence. The aim of the present study was then to investigate an homogeneous population of HCC patients in relation to this specific topic. A total of 781 HCC patients transplanted during the period February 1985–June 2016 in three European LT centres (namely, Brussels, Innsbruck and Mainz) were enrolled for the study: patients with early or late (<6 or >60 months) recurrence, follow-up <24 months and lack of information were excluded. A total of 581 patients were then analyzed for a Propensity-Score-Matching (PSM). Possible confounders for the PSM were: LT period, waiting-time, gender, age, HCV-status, radiological-response, alpha-fetoprotein, pathological major lesion >5 cm and number of lesions >3, pathological Milan Criteria(MC)-OUT-status, multifocality, poor-grading, macro- and micro-vascular invasion, pre-LT locoregional treatment(s).One hundred sixteen patients with AR treated with steroid boluses were compared with 115 patients without AR ($n = 70$) or with an untreated AR ($n = 45$). The groups were homogeneous regarding to the PSM covariates. In all the recurred cases, HCC recurrence followed the AR episode. HCC recurrences were markedly increased in the treated group (19 vs. 1; $p < 0.0001$). Five-year recurrence rate was 17.0 vs. 0.9% ($p < 0.0001$). At Cox-regression analysis, risk factors for HCC recurrence were HCV-status (HR = 6.3; $p = 0.001$), radiological progression (HR = 5.5; $p = 0.004$), log10-alpha-fetoprotein (HR = 2.8; $p < 0.0001$), pathological MC-OUT-status (HR = 5.1; $p = 0.005$), and AR treatment (HR = 18.9; $p = 0.005$). Locoregional treatments were protective (HR = 0.2; $p = 0.009$). When the entire population of 581 cases was investigated, AR treatment maintained its statistical relevance

OS251 LIVING DONOR APOLT-ALPPS FOR IRRESECTABLE COLORECTAL LIVER METASTASES: THE LIVING DONOR RAPID PROCEDURE

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Background: Recently, the Norwegian SECA trial suggested deceased donor liver transplantation (DDLT) as promising palliative therapy for patients with irresectable CRLM (i-CRLM)with 5 year OS > 60% notwithstanding early tumor recurrence. The Oslo group reported on one patient with i-CRLM, who underwent Resection And Partial Liver segment 2-3 transplantation from deceased donor with Delayed total hepatectomy ("RAPID" procedure).

Aim: To report the first case worldwide of Living Donor RAPID procedure (LD-RAPID).

Methods: A 49-year-old woman with i-CRLM and no extra-hepatic disease underwent first a left hepatectomy followed by implantation of her son's left lateral segments 2-3 according to the APOLT technique plus transection of the right portal vein (ALPPS concept). At POD 10, completion of right hepatectomy was performed.

Results: Donor's postoperative course and the long term FUP (POM 14) were uneventful.

The recipient had no complications after Stage 1. After stage 2 she developed a slight "small for size syndrome" and a late bile leak from biliary anastomosis which spontaneously resolved.

At POM 5 extra hepatic tumor recurrence was observed (positive liquid biopsy, bone and small bilateral lung metastases < 5 mm).Systemic chemotherapy and local radiation therapy were started. At POM 14 she is asymptomatic, in excellent general condition, with stable disease and negative liquid biopsy.

Conclusion: Living Donor APOLT-ALPPS procedure (i.e. LD-RAPID) is feasible and safe for both donor and recipient and may represent a paradigm shift in the management of i-CRLM.

OS252 LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA IN NON-ALCOHOLIC STEATOHEPATITIS (NASH) COMPARED TO NON-NASH PATIENTS

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Background: Non-Alcoholic Steatohepatitis (NASH) related Hepatocellular Carcinoma (HCC) is the fastest growing indication for liver transplantation (LT) for HCC in North America. Information regarding LT in this specific population is scarce. We aimed to examine differences in characteristics and outcomes of patients who had LT for NASH-HCC (NASH) vs. HCC from other liver diseases (non-NASH).

Methods: Patients with HCC who received a LT over a 10-year period were analyzed using a two-centre retrospective study design. Subgroup analysis stratified patients according to explant pathology (within and beyond Milan).

Results : Between 2004-2014, 929 patients were transplanted for HCC. 60/929 (6.5%) had HCC with NASH as the underlying disease and 869/929 (93.5%) had other etiologies. The proportion of LT for NASH-HCC significantly increased over time (2004–2009 4% vs. 2010–2014 9.2%, $p = 0.001$). There were no significant differences between groups for pre-transplant or explant tumor characteristics. In each group, 31% of the tumors were beyond Milan criteria. The actuarial 1-, 3- and 5-year overall survival was 98%, 96% and 80% in NASH vs. 95%, 84% and 78% in non-NASH ($p = 0.1$). Tumor recurrence was 13.3% in NASH vs. 14% in non-NASH ($p = 0.9$). No differences in tumor recurrence were observed in patients within and beyond Milan in the NASH group. However, the recurrence rate in the non-NASH group was 8.8% in those within Milan and 29.2% in beyond Milan, $p < 0.001$. Multivariate Cox Regression demonstrated NASH status to be a protective factor for recurrence among patients with tumors beyond Milan, HR 0.207 (0.05–0.86), $p = 0.029$.

Conclusion: This is the largest cohort to date examining LT in patients with NASH related HCC over long term follow up. Overall outcomes are similar between NASH and non-NASH etiologies. The hypothesis that advanced HCC associated with NASH may have a more favorable prognosis after LT than LT for HCC associated with other conditions deserves further study.

OS253 A RANDOMIZED, MULTICENTER, OPEN-LABEL PHASE 3 TRIAL OF SIROLIMUS IN LIVER TRANSPLANTATION WITH HEPATOCELLULAR CARCINOMA: MULTIVARIATE ANALYSIS OF FACTORS INFLUENCING OVERALL SURVIVAL

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Background: Patients receiving liver transplantation (LT) for hepatocellular carcinoma (HCC) are at a high risk of tumor recurrence as the main cause of death. In the SiLVER-trial the effect of Sirolimus on HCC recurrence after LT was investigated and found to increase disease-free survival and survival in the first few years, but the effect was insignificant past 5 years. Multivariate analysis of data.

Patients and methods: Data of 508 patients included in the intention to treat analysis from the randomized, multicenter SiLVER-trial were analysed in a univariate bivariate and multivariate Cox proportional hazards regression model of OS after LT with HCC as a time-dependent covariate.

Results: 110 items were included in the univariate and bivariate analysis. Various factors (concomitant disease, tumor-specific, donor-derived and procedure specific) had significant influence on OS. In the bivariate model, the absence of Sirolimus led to a significantly increased risk for death (HR 12.46; 95%-CI: 7.96–19.50, $p < 0.0001$). In the multivariate analysis this effect vanishes, whereas the Sirolimus-containing treatment group reveals a 30%-decreased death-risk (HR:0.70; 95%-CI: 0.49–0.99; $p = 0.046$). Sirolimus-treatment regardless of the treatment group significantly improved OS in patients (HR 0.70; 95%-CI: 0.49–0.99, $p = 0.048$). Other strong predictors for OS were age, AFP<10 ng/ml prior to LT, cardiovascular disease and renal impairment.

Conclusion: The presence of Sirolimus in LT for HCC significantly decreases the overall-risk for survival. Although Sirolimus did not significantly improve recurrence free survival in LT after HCC, this multivariate analysis of the data from the randomized, SiLVER international clinical trial strongly indicates Sirolimus use prolongs survival after LT for HCC.

*for the SiLVER-study group.

OS254 COMBINING 18F-FDG PET WITH SEROLOGIC MARKERS OF BIOLOGIC TUMOR AGGRESSIVENESS IDENTIFIES SUITABLE LIVER TRANSPLANT PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

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Introduction: 18F-FDG-uptake on positron emission tomography (PET) was shown to identify suitable liver transplant patients with hepatocellular carcinoma (HCC) beyond the Milan criteria. The aim of this study was to analyze the prognostic importance of 18F-FDG PET when being combined with other pre-LT available serologic markers of biologic tumor activity without implementing macromorphologic tumor features.
Methods: 119 liver transplant patients with HCC were included. Pretransplant 18F-FDG PET distinguished between PET+ (increased FDG-uptake compared to normal liver tissue) and PET– (no increased FDG-uptake) tumors. The impact of PET data along with macromorphologic (tumor size and number, Milan criteria) and biologic (TACE, alpha-fetoprotein [AFP], C-reactive protein [CRP]) tumor features on HCC relapse risk was analyzed.
Results: Five-year overall recurrence-free survival rates in patients with PET– ($n = 75$) and PET+ ($n = 44$) tumors were 93.3% and 42.6% ($p < 0.001$). PET-positivity (HR = 8.4; $p = 0.001$), AFP-level >400 ng/dl (HR = 5.9; $p = 0.011$), CRP level >1 mg/dl (HR=4.9; $p = 0.01$) and Milan Out status (HR = 3.6; $p = 0.028$) were identified as independent predictors of post-LT HCC relapse. The following risk groups were defined: low-risk (18F-FDG-non-avid); intermediate risk (18F-FDG-avid + AFP ≤400 ng/dl + CRP ≤1 mg/dl); high-risk (18F-FDG-avid + AFP >400 ng/dl or CRP >1 mg/dl). Recurrence-free survival rates at 5-years post-LT were 93.3%, 83.9% and 25.8% in the low-, intermediate- and high-risk subsets ($p < 0.001$). There was no outcome difference between low- and intermediate-risk liver recipients ($p = 0.223$). Thereby, the number of suitable transplant candidates increased from originally 69 Milan In patients to 88 patients with either low- or intermediate-risk HCC (+28%).
Conclusion: We were able to demonstrate that a purely tumor biology based risk stratification accurately predicts outcome. The pool of eligible liver transplant patients with advanced HCC stages may, thus, be safely expanded.

OS255 SAFETY OF INTRAOPERATIVE BLOOD SALVAGE DURING LIVER TRANSPLANTATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA; SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The use of intraoperative blood salvage (IBS) during liver transplantation (LT) is highly effective to reduce the need for allogeneic blood transfusion. However, the risk-benefits of IBS during LT for hepatocellular carcinoma (HCC) are not clearly defined. IBS possibly increases the risk of cancer recurrence and mortality by the potential danger of re-infusion and systemic dissemination of cancer cells. This systematic review provides an overview of the current understanding by conducting a meta-analysis of the literature, including an unpublished sample.
Methods/Materials: Relevant articles up to March 2016 were searched with EMBASE, MEDLINE (OvidSP), Web-of-science, Scopus, Cochrane, PubMed Publisher, Cinahl Ebsco and Google Scholar. In addition, we analyzed unpublished individual-level data from a sample of 202 HCC patients undergoing LT with or without IBS in a single center with median follow-up of 32 months (Birmingham 2017). Quality assessment of included studies was done by validated checklist by Downs and Black. Meta-analysis was performed for recurrence-free survival and overall survival. Hazard ratios and associated statistics were estimated from published time-to-event-analyses according to Tierney et al. (2007). Generic inverse variance method with a random-effects model was used for meta-analysis (RevMan5).
Results: Six retrospective studies representing 1128 HCC patients undergoing LT, including an unpublished series, met inclusion criteria. Use of IBS during LT carried no increased risk of HCC recurrence (HR 0.79, 95% CI 0.57 –1.11, p = 0.81)(Fig. 1). Overall survival was not affected by use of IBS (HR 1.37, 95% CI 0.93–2.04, p = 0.12). We found little evidence for between-study heterogeneity.
Conclusion: Currently available evidence suggests that use of IBS during LT in patients with HCC is safe and there was no difference in recurrence-free or overall survival between patients who received IBS compared to those who did not.

OS256 PREDICTORS OF OUTCOMES AFTER WAITING LIST DROP-OUT DUE TO HCC PROGRESSION: A SINGLE CENTRE RETROSPECTIVE STUDY

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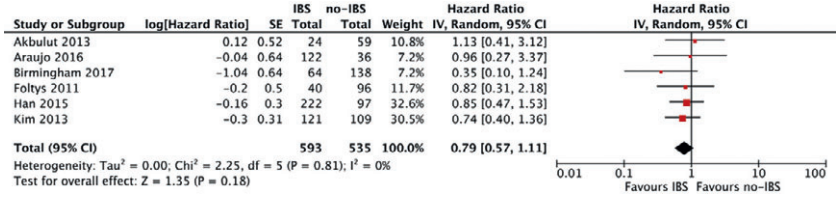
Background: There is scarce information on the outcomes of patients with HCC after drop-out due to tumor progression. For that reason most studies consider drop-out as a fatal event. The aim of this study was to characterize this population, and examine how tumor factors and treatment after delisting affect overall survival after delisting.
Methods: Patients with HCC who were delisted from the liver transplant waitlist due to tumor progression, between January 2000 and December 2016 were analyzed using a retrospective cohort study design. Descriptive statistics, in addition to survival analysis and Cox regression were used to determine predictors for overall survival.
Results: 105 patients were delisted due to tumor progression. Of the patients, 85.6% were male. The median age was 58 years. The maximum median number of tumors was 2 (1–4) and the maximum median tumor size was 4 cm (2.6–5.4 cm). After delisting, 35.2% of patients received treatment in the form of TACE, RFA, sorafenib, radiation, or other therapies. The overall median survival for all patients was 3.3 months (1.4–11.0). 43/105 (41%) patients were alive 6 months after delisting. The 3, 6, and 12 month actuarial survival for patients who received any treatment after delisting was 86%, 65%, and 42% vs. 35%, 26%, and 12% for patients who did not ($p \leq 0.001$). Multivariate Cox regression demonstrated that significant predictors of survival after delisting included female sex (HR 0.49 [0.26–0.91] p = 0.025), maximum tumour size (HR 1.11 [1.0–1.24] p = 0.048) and treatment after delisting with sorafenib (HR 0.50 [0.29–0.84] p = 0.01).
Conclusions: Patients with HCC awaiting liver transplant who are delisted due to tumor progression may in fact experience a survival benefit from therapy after delisting. This study is one of the first to demonstrate this relationship, and emphasizes the role of active disease management to prolong survival despite a palliative prognosis. Further study is warranted in this area.



Translational Artificial Organ Other

OS257 GENERATION AND TRANSPLANTATION OF BIOENGINEERED BILIARY TISSUE FOR REPAIR AND REPLACEMENT OF THE EXTRAHEPATIC BILIARY TREE

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Background: Treatment of common bile duct (CBD) disorders such as biliary atresia is limited to liver transplantation or hepaticojejunostomy due to the lack of suitable tissue for surgical reconstruction. Here, we explore the potential of bioengineering biliary tissue for transplantation and biliary reconstruction in vivo.
Methods: Primary human cholangiocytes were mechanically isolated from deceased organ donors with ethical approval and informed consent ($n = 8$) and propagated and characterized as Extrahepatic Cholangiocyte Organoids (ECOs) using our established methodology. Bioengineered tissue was generated by seeding ECOs on Polyglycolic Acid (PGA) or collagen scaffolds. Biliary reconstruction was achieved in immunodeficient NSG mice by partially replacing the gallbladder wall with a patch of ECO populated scaffold (ECO-patch; $n = 8$), or replacing a length of the native CBD with ECO populated collagen tubes (ECO-tubes; $n = 11$). Fibroblast-populated ($n = 9$) or acellular scaffolds ($n = 2$) were used as negative controls. Biliary tree patency was confirmed using magnetic resonance cholangiopancreatography (MRCP).
Results: ECOs closely resemble primary cholangiocytes in their transcriptomic profile (r: 0.92) and functional properties (ALP, GGT). ECO-populated scaffolds form biliary tissue-like structures, maintain their functionality (ALP, GGT) and marker expression (CK7, CK19). All ECO-transplanted animals exhibited graft integration in the biliary tree with a patent lumen, biliary marker (CK7, CK19) expression, ALP activity and prolonged survival vs. controls (ECO-patch, $p = 0.0027$; ECO-tubes, $p = 0.0082$; log-rank test). All fibroblast reconstructions failed, due to lumen occlusion by fibrotic tissue.
Conclusion: We demonstrate that ECO-populated scaffolds can successfully reconstruct the biliary tree in vivo. To our knowledge, this is the first application of regenerative medicine in cholangiopathies and first organ reconstruction using human primary cells expanded in vitro.

Clinical Composite Tissue Donation and donor types

OS258 VASCULARIZED COMPOSITE ALLOGRAFT (VCA) DONATION AND TRANSPLANTATION: A SURVEY OF PUBLIC ATTITUDES IN THE UNITED STATES

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Background: Vascularized composite allograft (VCA) transplantation has emerged as a groundbreaking surgical intervention to return identity and function following traumatic injury, congenital deformity, or disfigurement. While public attitudes toward traditional organ/tissue donation are favorable, little is known about attitudes toward VCA donation and transplantation.
Method: An online survey was conducted of 1,485 U.S. residents to assess VCA donation attitudes and the impact of information about VCA transplantation on willingness to donate VCA organs. We also assessed their opinions about authorization of VCA donation, media exposure to VCA transplantation, and health care system distrust.
Results: Most respondents were willing to donate hands/forearms (67.4%) and legs (66.8%), and almost half (48.0%) were willing to donate the face. Three-quarters (74.4%) of women were willing to donate the uterus; 54.4% of men were willing to donate the penis. Multivariable logistic regression showed that VCA donation willingness was more likely among whites and Hispanics ($p < 0.001$), registered organ/tissue donors ($p < 0.001$), and those with less healthcare system distrust ($p < 0.001$) and media exposure to VCA transplantation ($p = 0.003$). Providing brief information about VCA transplantation led to a net increase in the number (percentage) of respondents who were willing to donate each VCA body part. 23% of currently registered donors would be less likely to register as a donor in the future if VCA organs were included in the standard organ donation registration process. Body mutilation, identity loss, and the reaction of others to seeing familiar body parts on a stranger were common reasons among those unwilling to be a VCA donor.
Conclusion: Attitudes toward VCA donation are favorable overall and learning about VCA transplantation is likely to increase willingness to be a VCA donor. These findings may help guide the development and implementation of VCA public education campaigns.

Clinical Composite Tissue Other

OS259 THE INTERNATIONAL REGISTRY ON HAND AND COMPOSITE TISSUE ALLOTRANSPLANTATION (IRHCTT)

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Background: The primary purpose of the IRHCTT is to collect information on voluntary basis. At present it includes upper extremity (UET) and face allotransplantations (FT).
Methods: 26 unilateral and 34 bilateral UET, for a total of 60 patients have been reported. In the majority of cases the level of amputation was distal, but there were also 9 arm transplantations.

Twenty-nine cases of partial or total FT have been reported. In the majority of cases the deficit included cheek, nose, chin, lips and perioral area.

In both types of transplantation the immunosuppressive therapy included tacrolimus, mycophenolate mofetil, sirolimus and steroids; polyclonal or monoclonal antibodies were used for induction.
Results: Patient survival in UET was 96.7%: 1 patient died after simultaneous face and bilateral hand transplantation and another one after bilateral arm transplantation; while in FT it was 86.2% (four patients died including a case of simultaneous face and bilateral hand transplantation). Graft survival in UET was 83.3%: in 5 cases it occurred in the first period after transplantation (poor vascularization or infectious complications) and in other 5 during the follow-up (chronic rejection/graft vasculopathy). Graft survival in FT was 93.1% (one face graft was removed for unknown cause and another one for chronic rejection).

In UET 72.4% of the recipients experienced at least one episode of acute rejection within the first post-transplant year and 60% in FT. Six cases of chronic rejection in UET and two in FT have been reported. Complications included, as in solid organ transplantation, opportunistic infections, metabolic complications and malignancies.

UET recipients developed protective sensibility, 90% of them tactile sensibility and 82.3% developed a partial discriminative sensibility. They were able to perform most daily activities. FT recipients improved their aesthetic aspect and could perform some activities which were impossible before the transplantation.

Translational Composite Tissue Other

OS260 DIFFERENCES IN THE ENGRAFTMENT AND SURVIVAL OF TOLERANCE INDUCING HUMAN HEMATOPOIETIC CHIMERIC CELLS FOLLOWING INTRAVENOUS AND INTRAOSSEOUS CELL DELIVERY

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Background: Vascularized composite allotransplantation (VCA) represents a promising method of reconstruction for patients with severe face and limb injuries. As alternative to current cellular therapies supporting VCA we propose application of ex vivo created human hematopoietic chimeric cells (HHCCs). The aim of this study was to assess in vivo the difference in engraftment and survival of CD34-derived HHCCs after intravenous or intraosseous cells' delivery in a nude rat model.
Methods: Thirty-eight *ex vivo* fusions were performed to create HHCCs. Briefly, CD34 + cells from two bone marrow (BM) donors were stained separately with PKH26 and PKH67 dyes and fused with polyethylene glycol. Double PKH26 and PKH67 stained HHCCs ($1–2 \times 106$) cells were sorted and injected intravenously or intraosseously to the nude rat recipients and their presence in peripheral blood (PB), BM, and lymphoid organs was detected by anti-human HLA-ABC staining and evaluated by confocal microscopy and flow cytometry.
Results: *In vivo* studies confirmed that HHCCs were present in PB of the nude rat recipients up to 6 weeks after cells intraosseous and intravenous injection. Additionally, HHCCs migrated from the injected to the contralateral femur bone and to the lymphoid organs (lymph nodes, spleen) and liver. At 6 weeks after injection the number of HHCCs in the nude rat peripheral blood and bone marrow compartment was higher after intraosseous cell delivery (0.58% and 6.58%, respectively) compared to intravenous cell delivery (0.11% and 1.8%, respectively).
Conclusions: *In vivo* studies confirmed engraftment, migratory properties and long-term survival of HHCCs. Improved engraftment into the bone marrow compartment was observed after intraosseous HHCC delivery. Application of HHCCs as a supportive therapy via intraosseous injection represents a novel approach for tolerance induction in solid organ and VCA transplantation.

Basic Composite Tissue Immunosuppressive agents

OS261 THE INTRAGRAFT VASCULARIZED BONE MARROW COMPONENT AND RECIPIENT T REGULATORY CELLS FACILITATE TOLERANCE INDUCTION AFTER POST TRANSPLANT HIGH DOSE CYCLOPHOSPHAMIDE TREATMENT IN VCA

Georg Furtmüller[1], Byoungchol Oh[1], Madeline Fryer[2], Sudipto Ganguly[1], Veronika Malek[1], Xianyu Zhou[1], Giorgio Raimondi[1], Jeffrey Dodd-O[1], Damon Cooney[1], Cory Brayton[1], W. P. Andrew Lee[1], Leo Luznik[1], Gerald Brandacher[1]

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Background: VCA is viable treatment option for devastating tissue defects. However, the life-long need of immunosuppressive medications curtails its wider use. Unique VCA-features such as an intragraft vascularized bone marrow compartment may favor tolerance induction.
Methods: Skin, SOT (heart), and VCA (orthotopic hind limb) were performed across a full MHC mismatch barrier in wild type and thymectomized animals. Recipient animals were treated with a non-myeloablative dose of TBI and a T-cell depleting antibody 24 hours prior to transplantation. In selected groups, donor BM and splenocytes (DBM) were injected at the time of transplantation. CyP was administered on POD 3 (PTCy). Chimerism, Vβ analysis, MLR's and 2° transplants were performed. Donor- and host-derived Treg depletion pre and post transplantation was performed.
Results: Controls (n = 5/group) rejected skin, SOT and VCAs acutely with a mean survival of 14 ± 1, 9 ± 2, and 8 ± 1, days respectively. The combination of PTCy and DBM prolonged VCA and non-VCA survival indefinitely in 7/8 skin, 7/8 heart, however, in VCA DBM was not required to achieve 100% long term (150 days) allograft survival N=(20/20). PTCy-treated thymectomized recipients (N = 6, >110 days) did not reject the VCA, compared to untreated controls (N = 3, MST 8d). Mixed chimerism was shown in skin/heart transplantation plus DBM (6.8% ± 3.1%), in VCA recipients ± DBM at 22.51% ± 5.96% and 30.17% ± 8.72%, and at 24.96 ± 4.12 in thymectomized recipients. Vβ-TCR staining showed decreased expression of donor-specific TCRs in wild type animals and MLRs showed donor-specific unresponsiveness with robust 3rd party reactivity in long-term survivors. In-vivo, tolerant animals challenged with 2° skin transplants accepted donor matched Balb/c skin (250 days) while 3rd party FVB/N skin was acutely rejected (15 ± 2 days). In VCA, donor/recipient-derived Treg depletion did not abrogate graft tolerance. Chimerism and graft loss ensued after recipient Treg compared to controls. Tregs were comparable in the two groups. Toxicity analyses are ongoing.
Conclusions: Repeated injections of hydrogel loaded with Tacrolimus promote indefinite graft survival in a rat hind limb transplantation model with an up to 3 times lower total dose of Tacrolimus. They furnished higher levels of mixed hematopoietic chimerism in comparison with controls. Pending toxicity data will show whether the hydrogel is superior to conventional immunosuppression in terms of side effects. The results suggest that a hydrogel-based drug delivery system may be a feasible approach for immunosuppression in VCA.

Translational Composite Tissue Other

OS262 ACHIEVING INDEFINITE VASCULARIZED ALLOGRAFT SURVIVAL USING REPEATED INTRA-GRAFT INJECTIONS OF AN INFLAMMATION-RESPONSIVE HYDROGEL FOR TACROLIMUS DELIVERY

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Background: The life-long need for immunosuppression is a major drawback to a broader application of vascular composite allotransplantation (VCA). The opportunity to treat the exposed VCA grafts locally could reduce the side effects related to systemic immunosuppression. Here we demonstrate that periodic injections of a hydrogel loaded with Tacrolimus subcutaneously into the graft induce indefinite VCA survival. Further, we compare the hydrogel therapy to conventional systemic immunosuppression in terms of toxicity and tolerance markers.
Methods/Materials: Brown Norway-to-Lewis hind-limb transplantations were performed. Rats were randomly divided in two groups (n = 6 per group): Controls (systemic treatment with Tacrolimus, 1 mg/kg daily) and experimental group (Intra-graft injection of 1 mL hydrogel loaded with 7 mg Tacrolimus, repeated every 70 days). Graft survival was monitored for 280 days or until grade III rejection. Tacrolimus (LC-MS/MS), toxicity markers, hematopoietic chimerism and Tregs (Flow Cytometry) in blood and skin biopsies were examined.
Results: All grafts survived until the endpoint of 280 days post transplantation, except for one from the experimental group, who underwent rejection and was sacrificed after 149 days. Mixed hematopoietic chimerism was detectable but declining until the endpoint, with experimental animals having higher levels

OS263 MUSCLE FUNCTION RESTORATION FOLLOWING TRANSPLANTATION OF CHIMERIC CELLS OF MYOBLAST AND MESENCHYMAL STEM CELL ORIGIN

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Background: Allogeneic stem cell therapies aim to restore muscle tissue after traumatic loss or muscular dystrophies. Limited engraftment due to allogeneic rejection is the major challenge. Muscle Derived Chimeric Cells (MDCC), created via ex vivo fusion of myoblast (MB) and mesenchymal stem cells (MSC), represent a promising therapeutic option. The aim of this study was to characterize human MDCC in vitro and to assess MDCC efficacy in restoration of muscle function in Duchenne Muscular Dystrophy (DMD) mdx/scid mice model.
Methods: MDCCs phenotype, genotype, proliferation, dystrophin expression (DE) and myogenic differentiation were tested. Lymphocyte proliferation assay was performed to evaluate MDCC allogenicity. To test efficacy of MDCCs in vivo, mdx/scid mice received intramuscular injections to gastrocnemius muscle (GM): Group 1 – vehicle (60mcl PBS), Group 2 – 0.25x106 of MSC and 0.25x106 MB, Group 3 - 0.5x106 of MB/MSC MDCC. Therapeutic effect was monitored by muscle function tests. DE was evaluated at day 7 and 90 after MDCC delivery.
Results: MDCCs phenotype, genotype, proliferation, dystrophin expression (DE) and myogenic differentiation were confirmed. Proliferation of responder lymphocytes after stimulation with MDCC was 5.49% (SI = 3.15), compared to positive controls of 55% (SI = 31) after stimulation with 3rd party lymphocyte and 10% (SI = 5.8) after stimulation with MB parent cells. MDCC survival and engraftment to GM was confirmed by DE of 16.18% at day 7 and 16.5% at 90 days and DE was co-localized with HLA-ABC expression. MDCC recipients showed increase in muscle force (p = 0.04) and improved fatigue tolerance compared to vehicle group.
Conclusion: This study confirmed efficacy of MDCC therapy in restoration of muscle function, which correlated with DE in the GM of mdx/scid mice. MDCC therapy represents a novel approach for restoration of muscle function in muscular dystrophy, traumatic loss and for regeneration of muscle components of VCA.

Basic Composite Tissue Other

OS264 INDUCED PLURIPOTENT STEM CELL (IPS) DERIVED SCHWANN CELLS TO ENHANCE FUNCTIONAL RECOVERY FOLLOWING NERVE INJURY AND LIMB ALLOTRANSPLANTATION

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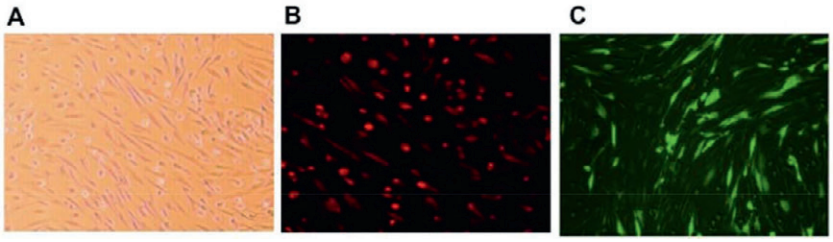
Background: Stem cell based therapies with the potential to enhance the pace of nerve regeneration have provided new aspects for functional recovery after reconstructive transplantation. In this study, a novel cell-based approach utilizing human induced Pluripotent Stem Cell-derived Schwann Cells (iPSC-SCs) supported by the effect of various nerve growth factors was investigated to improve functional recovery in a rodent chronic denervation limb transplant model.
Materials and Methods: Experiments were first conducted in a chronic tibial denervation and later implemented into a hind limb transplant rat model. Human iPSC-SCs were generated through dual SMAD inhibition and isolated by FACS. For Schwann cell differentiation, CD49d+ cells were isolated. Growth factor delivery systems were constructed using fibrin gel containing growth factor GDNF with or without chondroitinase.
Results: Figure 1 shows successful derivation of Schwann Cells Precursors (SCPs); cells assume a typical SCs long fusiform bipolar morphology (1A), stain positive to S100 (1B), and were also transfected with a green fluorescent protein (GFP) adenovector (1C). In growth factor delivery group, five weeks after repair, histomorphometry demonstrated a significant increase in the number of regenerating myelinated axons in the GDNF+chondroitinase group



as compared to GDNF, chondroitinase, and negative control groups. In cellular therapy group, animals treated with iPSC delivery demonstrated significantly greater axonal diameters and myelin thickness compared to control group. EMG functional testing did not show any significant difference, neither at 5 nor at 12 weeks, although there was a positive trend in the IPS group observed at 12 weeks.
Conclusion: SCs precursors can be isolated from human iPS cells. Growth factor delivery vehicles and chondroitinase result in higher axonal counts. Human iPS cells result in greater axon diameter. Further studies are needed to demonstrate functional benefits

OS265 SHORT AND LONG TERM GRAFT SURVIVAL AFTER KIDNEY TRANSPLANTATION IN EUROPE

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Background: Improvement of kidney survival after transplantation has mainly been studied in the American population. There, it was found that improvement mostly occurred on the short term after transplantation. Since the European transplantation reality and survival times considerably differ from the American situation, we investigated changes in survival over the past three decades in Europe, accounting for the important changes in donor and recipient characteristics over time.
Methods: We performed a European cohort study based on the Collaborative Transplant Study database. Analyses were restricted to first, single kidney transplantations with adults and deceased donors between January 1st 1986 and December 31st 2015. In total, 140 979 transplantations were included. The primary outcome was the cause-specific (death-censored) hazard rate of kidney failure after transplantation. In the Cox model, we included a flexible time-dependent effect for the continuous covariate 'transplant year' in order to quantify improvement on both the short and long term. All estimates were adjusted for the changing demographics.
Results: There was significant, linear improvement ($p < 0.001$) in graft survival from 1986 to 2015. Also, improvement was more pronounced on the short term than on the long term after transplantation ($p < 0.001$). These changes were conditionally independent of the changing donor and recipient age (both increased significantly with $p < 0.001$).
Conclusion: In Europe, similar to what was noted earlier in the US, improvement of kidney graft survival over the past decades occurred primarily on the short term after transplantation, and to a lesser extent on the long term. We also concur with the results found in the United States that improvement in graft survival after kidney transplantation is not influenced by the increased risk profiles of donors and recipients.

OS267 FACTORS ASSOCIATED WITH USAGE OF A WEB-BASED PATIENT PORTAL AMONG KIDNEY AND LIVER TRANSPLANT RECIPIENTS

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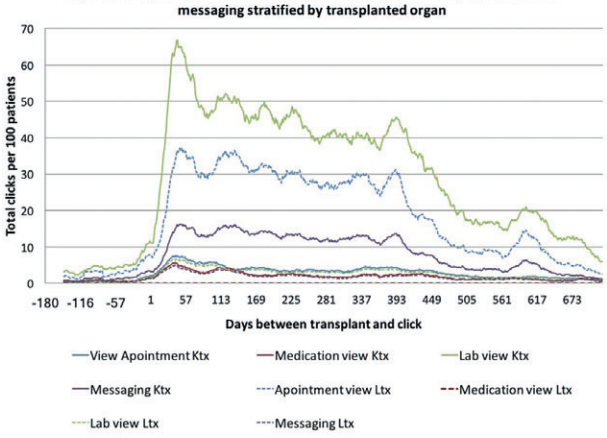
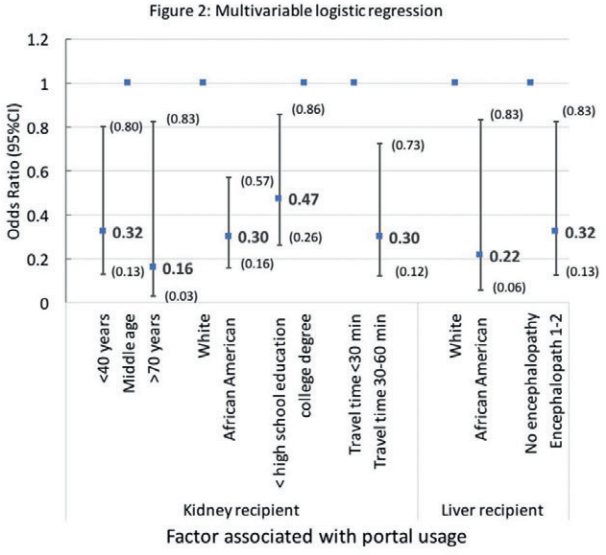
Background: Little is known about the characteristics of kidney transplant (KTx) and liver transplant (LTx) recipients who use web-based patient portals to manage medications, view labs, view appointments, and message clinical providers.
Methods: We examined all KTx and LTx recipients at a large U.S. transplant center from March 2014-March 2016, linked with Cerner data on web-based portal access (web-based clicks). Portal action timestamps (e.g. clicks, messages, etc.) per patient in the year post-transplant was assessed for each portal function, including view of medication list, lab results, and messaging to clinical providers. Multivariable logistic regression was used to determine predictors of portal usage functions.
Results: Among 376 transplant recipients, 254 (68%) received a KTx and 122 (32%) received a LTx. Among KTx recipients, mean portal usage varied across function, where KTx recipients viewed labs, viewed medications, and messaged clinical providers an average of 166, 10, and 47 times per year, respectively. On average, LTx recipients viewed labs 89 times/year, viewed medications 9 times/year, and messaged clinical providers 9 times/year. Portal usage was higher among KTx recipients, and for both KTx and LTx recipients, use of portal functions was highest early post-transplant, and decreased thereafter (Figure 1).

In multivariable logistic models, characteristics associated with lower portal usage among KTx recipients included age <40 and >70 years (vs. middle age groups), African American (vs. white race),<="" p="">
Conclusion: Targeted education about specific functions within the portal to some patients, including young and old patients, African Americans, and those with lower education levels, may increase portal acceptance and use.

Figure 1: Frequency of clicks to view appointment, medication, lab results and messaging stratified by transplanted organ





Clinical Kidney Other

OS268

COAGULATION PROFILE IN PATIENTS WITH CHRONIC KIDNEY DISEASE BEFORE AND AFTER KIDNEY TRANSPLANTATION

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Background: Patients with chronic kidney disease (CKD Pt) experienced thrombotic and hemorrhagic complications; but, the underlying causes remain unclear. Furthermore, the effect of kidney transplant (KT) on the coagulation abnormalities of CKD Pt remains controversial. This study aimed to establish the profile of hemostatic problems in CKD Pt and to demonstrate the role of KT in correcting theses abnormalities
Methods: In this retrospective study, 557 KT recipients (KTR) who did not receive peri-operative plasmapheresis or exhibit graft failure within 1 month after KT were included. Pt blood were collected before surgery, on post-operative days (POD) 7, 14, and 28 for the analysis of hemostatic parameters: platelet function assay, protein S (PS), protein C (PC), anti-thrombin III (AT III), homocysteine, lupus anticoagulant, anticardiolipin antibody, clotting factor VIII, and clotting factor IX. We also investigated differences in coagulation profiles in accordance with the dialysis modality.
Results: Before KT, KTRs demonstrated increased levels of homocysteine and D-dimer compared with reference value. Pt receiving hemodialysis (HD) demonstrated elevated D-dimer ($p = 0.0273$) and decreased PS ($p = 0.0186$), PC ($p < 0.0001$), and AT III ($p < 0.0001$) activity levels compared to patients receiving peritoneal dialysis (PD). Pt with PD had higher levels of homocysteine ($p < 0.0001$) and fibrinogen ($p < 0.0001$) than those undergoing HD. In total, 80.9% of Pt exhibited ≥ 1 thrombophilic factor at pre-transplantation, and the proportion of these Pt decreased to 47% at POD 28 ($p < 0.0001$). The renal function of Pt with no thrombophilic factors was better than that of Pt with ≥ 1 thrombophilic factor at all post-operative assessments ($p < 0.01$ at POD 7, 14, and 28)
Conclusion: CKD Pt can exhibit hypercoagulability, which might be caused by reduced renal function *per se*. Both HD and PD seemed to aggravate the pro-thrombotic tendency of CKD Pt. Most thrombophilic risk factors in CKD Pt were corrected after KT

OS269

GRAFT OUTCOME AFTER TREATMENT OF HCV POSITIVE KIDNEY TRANSPLANT RECIPIENT WITH RITONAVIR-BASED DIRECT ANTI-VIRAL AGENT (CASE SERIES)

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Objectives: The pharmacokinetics of antiviral agents in kidney transplant recipients are influenced by two factors: graft function and drug–drug interactions.
Patients and methods: Two kidney transplant recipient with modest graft function and one kidney transplant recipient with excellent graft function who are maintained on immunosuppressive drugs (steroid, tacrolimus and mycophenolate mofetil) and afflicted by HCV started to receive Ombitasvir/paritaprevir/ritonavir medication for HCV eradication within the period extending from 2/2016 to 1/2017.

Tacrolimus doses were decreased to 0.5 mg /week with close follow up for tacrolimus trough level every other day till obtaining satisfactory tacrolimus level then weekly. Graft function was assessed with each visit. Liver function tests was withdrawn just before starting the medication, monthly after starting the medication, 1 month, 3 month and 6 month after stop the medication.HCV PCR was withdrawn before starting the medication, 1 month after starting the medication, 1, 3 and 6 months after stop medication.
Results: Three kidney transplant recipients received Ritonavir-based direct anti-viral agents and reached 3-month and 6-month sustained viral response without affection of the graft outcome. High Fk level was found on starting DAA with rise of serum creatinine. Strict follow up and regular modification of tacrolimus doses is important to avoid tacrolimus trough level overshooting and the subsequent rise of serum creatinine (3 case reports).
Conclusion: Eradication of HCV in kidney transplant recipient who are maintained on tacrolimus-based immunosuppressive protocol could be achieved successfully using Ritonavir-based direct antiviral agents without affection of graft function but needs strict modification and follow up of tacrolimus trough level.

OS270

A PROSPECTIVE TRIAL USING A HAEMOSTATIC POWDER - HAEMOCER - TO REDUCE THE INCIDENCE OF LYMPHOCELES AFTER KIDNEY TRANSPLANTATION

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Background: Lymphoceles can occur after kidney transplantation with a reported frequency of 20%. Aim of this prospective, non-randomized trial was to assess whether the standardized application of the haemostat HaemoCer (BioCer Entwicklungs-GmbH CE1275) has an effect on lymphocele rate.
Methods: At Vienna University Hospital, the center specific lymphocele rate was assessed over a period of one year (April 2011- April 2012). In 183 consecutive kidney transplanted patients lymphocele rate was 18.03%. In order to detect a reduction of lymphocele rate from 20% down to 10% with a 1-group $\chi 2$ test with a two-sided significance level of 5% and a power of 80%, at least 108 patients were to be included. For a defined period of time HaemoCer was used prospectively intraoperative in all patients with kidney transplantation as standard haemostat (ethics committee of the Medical University of Vienna; EK 1125/2013).
Results: In this period 155 patients were transplanted and included in the prospective evaluation. Two patients did not receive HaemoCer. Of 153 patients receiving HaemoCer, 5 lost their organs within 10 days and one patient succumbed to cardiac complications on day 4. These patients were excluded. Of the remaining 147 patients, 15 developed lymphoceles (10.2%, 95% CI: 6.2 - 16.2%). Compared to the published and the center lymphocele rate of 20% and 18.03% after kidney transplantation, this represents a significant reduction ($p = 0.003$ and 0.013 respectively).
Conclusion: Lymphoceles after kidney transplantation seemed to be significantly reduced when HaemoCer™ was prospectively applied as standard intraoperative haemostat. The magnitude of the effect warrants randomized evaluation.

OS271 BREAKTHROUGH IN THE MANAGEMENT OF ATYPICAL HEMOLYTIC UREMIC SYNDROME AFTER KIDNEY TRANSPLANTATION: A NATIONWIDE STUDY

Julien Zuber[1], Nassim Kamar[2], Marie Frimat[3], Moglie Le Quintrec[4], Philippe Gatault[5], Noemie Jourde-Chiche[6], Raphael Gaisne[7], Lionel Couzi[8], Antoine Thierry[9], Dominique Bertrand[10], Johnny Sayegh[11], Charlotte Colosio[12], Jean-Philippe Rerolle[13], Rebecca Sberro-Soussan[1], Mayvonne Hourmant[7], Claire Pouteil-Noble[14], Eric Rondeau[15], Christophe Legendre[1], Veronique Fremeaux-Bacchi[16]

[1]Necker Hospital, France; [2]Rangueil Hospital Toulouse, France; [3]Chru Lille, France; [4]Chu Montpellier, France; [5]Chu Tours, France; [6]Chu Marseille, France; [7]Chu Nantes, France; [8]Chu Bordeaux, France; [9]Chu Poitiers, France; [10]Chu Rouen, France; [11]Chu Angers, France; [12]Chu Reims, France; [13]Chu Limoges, France; [14]Chu Lyon, France; [15]Chu Tenon, France; [16]Chu Hegp, France

Background: Targeted blockade at C5 with eculizumab has revolutionized the management of atypical hemolytic uremic syndrome (aHUS). However, renal function improvement upon eculizumab treatment is less striking for transplanted kidneys than native kidneys. Moreover, the different strategies, relying on either prophylactic or curative use of eculizumab, have never been properly evaluated in a large cohort.
Methods: Through a nationwide, multicenter and retrospective study, we aimed to compare plasma therapy and eculizumab in preventing and treating aHUS recurrence after adult kidney transplantation. All the enrolled adult patients had been thoroughly investigated for complement abnormalities at a central laboratory.
Results: A total of 95 patients with aHUS, the majority of which were female (n = 63), underwent 132 kidney transplantations. Extensive genetic workup identified single variants in *CFH* (n = 36), *CFI* (n = 6), *MCP* (n = 3), *C3* (n = 11), *CFB* (n = 1), combination of complement variants (n = 4) and anti-CFH (n = 7) antibodies. To prevent aHUS recurrence, either plasmapheresis alone or eculizumab therapy was used in 21 and 35 cases, respectively. The rate of aHUS recurrence was a way lower in the eculizumab group than those in the groups without prophylaxis or with prophylactic plasmapheresis (Figure 1). A single case of late aHUS recurrence was observed in the eculizumab group, occurring 21 months after eculizumab discontinuation and leading to graft loss 4 months later. Overt clinical recurrence occurred in 61 cases, 35 and 17 of which were treated with plasmapheresis alone and eculizumab, respectively. One-year death-censored graft survival was significantly lower in the recipients who experienced a recurrence. However, eculizumab significantly improved graft survival when compared to plasmapheresis and supportive therapy (Figure 2).
Conclusion: Eculizumab greatly outperformed plasmapheresis in preventing and treating aHUS recurrence after kidney transplantation.

Figure 1

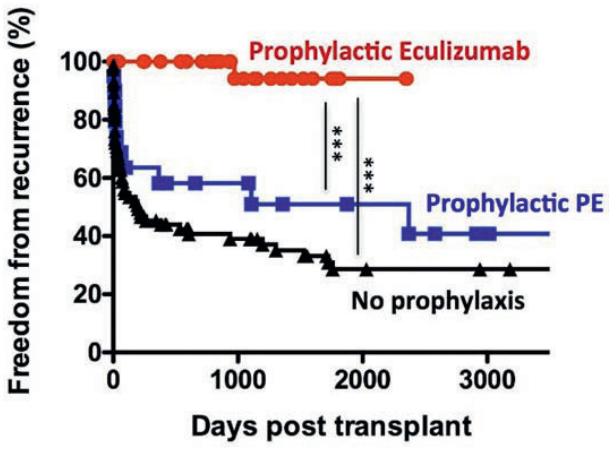
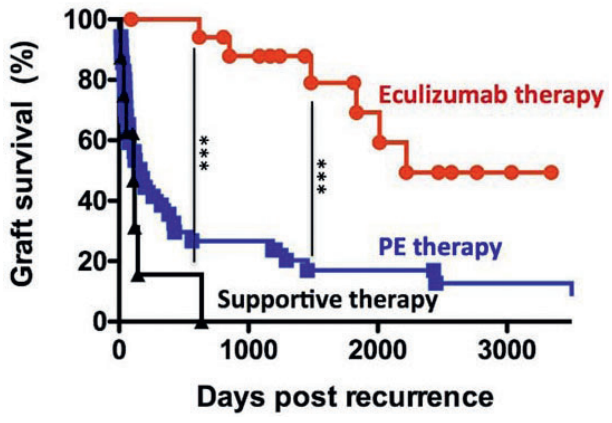


Figure 2



OS272 A CALL FOR ACTION: PREVALENCE OF FRAILTY AND MILD COGNITIVE IMPAIRMENT IN ADULT KIDNEY TRANSPLANT CANDIDATES AT THE TIME OF TRANSPLANTATION IN SWITZERLAND

Manuel Wehrle[1], Oliver Mauthner[2], Jeremy Walston[3], Sandra Engberg[4], Isabelle Binet[5], Michael Dickenmann[6], Dela Golshayan[7], Karine Hadaya[8], Uyen Huynh-Do[9], Stefano Calciolari[10], Sabina De Geest[11]

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Background: Frailty represents a state of vulnerability and a decline in functioning across multiple physiological body systems. There is growing evidence that frailty and mild cognitive impairment (MCI) are valuable criteria to predict poor outcomes in adult kidney transplant (KT) candidates. There is, however, limited information about the prevalence of both conditions in KT patients. We assessed the prevalence of frailty and MCI in adults at the time of kidney transplantation.
Methods: This is the baseline assessment of a prospective cohort study nested in the Swiss Transplant Cohort Study (STCS). A convenience sample of 74 adult deceased- and living donor KT candidates (mean age 51.6 $\pm$ 13.7 years, 36.5% female) of 5 Swiss transplant centers were included. Frailty and MCI were measured using the Fried Frailty Instrument (frail, pre-frail, robustness) and the Montreal Cognitive Assessment Test, respectively. Descriptive and inferential analysis was performed.
Results: The prevalence of frailty, pre-frailty, and robustness was 10.8%, 45.9% and 40.5%, respectively (Figure 1). 45.9% of participants had MCI and of those 24.2% had MCI and were frail or pre-frail. There was no significant association between frailty and MCI at time of transplantation. Prevalence of frailty was not significantly associated with age, gender, education, depression status or comorbidities.
Conclusion: The prevalence of frailty/pre-frailty and MCI in renal transplant candidates in Switzerland is high, yet more patients are pre-frail compared to international findings (see Figure 1). Given that pre-frailty can be targeted with interventions, incorporating frailty screening would allow healthcare professionals to systematically identify individuals at risk and initiate pre-habilitation before transplantation.

OS273 KIDNEY TRANSPLANTATION IN HIV+ PATIENTS IS ASSOCIATED WITH A HIGH RATE OF SERIOUS INFECTIOUS DISEASE

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Background: Kidney transplantation (KT) in HIV+ recipients has nowadays become a common clinical practice among several centres, but long-term outcomes are still lacking. This study assesses the results obtained in HIV+ patients transplanted in our centre over the last 10 years.
Methods: From July 2007 to November 2016, 29 deceased donor KTs were performed on 28 HIV+ recipients with viral-immunological response to antiretroviral therapy (ART). Immunosuppressive therapy consisted of Tacrolimus/Cyclosporine, Mycophenolate Mofetil and early steroid withdrawal (at day 5 after KT).Basiliximab and/or Antithymocyte Globulins were used as Induction Therapy.
Results: Recipients mean age was 48 $\pm$ 10, male gender 76% and Caucasian race 48%. In 72% of cases the graft came from Expanded Criteria donors. The average number of HLA mismatches was high (3.9 $\pm$ 1.2). ART included a protease inhibitor (PI) in 72%. Twenty-seven out of 29 pts met the viral-immunological criteria of eligibility (CD4-T count > 200 mmc/mL and HIV-RNA undetectable). In 2 cases CD4-T count wasn't persistently > 200 mmc/mL. Fifteen major infective events - sepsis (3), viral pneumonia (2), CMV disease (2), aspergillosis (1), mucormycosis (1), West-Nile encephalitis (1), other (5) - occurred in 11 patients (38%). HIV reactivation occurred in 4 cases. Biopsy proven acute rejection (AR) occurred in 15 patients (51.7%) (cellular = 6, mixed = 4, humoral = 5) at median time of 2 months after KT. Tac trough levels at the time of AR were lower than target. Patient and graft survival at 1 year were 100%, but decreased to 80% and 77% respectively at 5 years. Four deaths occurred, three due to infections. Four grafts were lost due to chronic rejection, in 3 cases associated with immunosuppressive minimization because of cancer or infection.
Conclusion: The KT in HIV+ recipient is feasible, but serious infective events must be kept in mind as the main risk for patient survival.

OS274 LONG-TERM OUTCOMES OF STRATIFIED DESENSITIZATION THERAPY BASED ON IMMUNOLOGICAL RISK IN LIVING DONOR KIDNEY TRANSPLANTATION

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Background: Desensitization therapy has enabled highly sensitized kidney transplant recipients to receive kidney transplantation (KT) which had not been possible in the past. We previously reported the impact of desensitization with rituximab (RTX), plasmapheresis (PP) and IV immunoglobulin (IVIG) in KTRs based on crossmatch testing, panel reactive antibody and donor-specific anti-HLA antibody. In this study, we investigated the long-term outcomes of desensitization in highly sensitized KT since Jan, 2010.
Methods: A total of 434 patients were treated with desensitized protocol. The patients were divided into 3 groups depending on desensitized methods: RTX/PP/IVIG (RPI group; n = 44), RTX monotherapy (RTX group; n = 62), and the control group (CON group; n = 326). Allograft biopsy was conducted in 298 subjects. We compared the development of acute rejection, rejection free survival, allograft function, allograft and patient survival and infectious complications over 7 years.
Results: Overall allograft survival rate for 7 years was 94.9% (CON group, 96%; RIT group, 96.8%; RPI group, 84.8%). The incidence of biopsy-proven acute rejection (BPAR) in the RPI group was higher than in the CON and RTX groups ($p < 0.01$ for both). Rejection free survival and allograft survival was inferior in the RPI group compared to the other groups ($p < 0.001$ for both). The RPI group suffered to a higher incidence of infection than the CON and RTX groups ($p < 0.01$ and $p < 0.05$, respectively). In the Cox-regression analysis, BPAR was an independent risk factor for allograft survival ($p < 0.01$), and patient survival was affected by age, presence of bacterial infection and history of BPAR ($p < 0.05$ for both).
Conclusion: In the long-term follow-up, allograft and patient survival of the RPI group was inferior to the other groups. Although desensitization provides an opportunity of KT in a high risk immunologic setting, both strict monitoring and sufficient prophylaxis are needed to improve outcomes.

OS275 ABO INCOMPATIBLE KIDNEY TRANSPLANTATION: LOW RISK OF INFECTIONS AND EXCELLENT PATIENT SURVIVAL

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Background: ABO incompatible (ABOi) kidney transplantation (KT) may be associated with high risk of rejection/graft loss along with life threatening infections and increased mortality. We aimed to determine the outcomes and rates of infectious complications of patients who underwent ABOi KT in our center.
Methods: Patients who underwent ABOi KT between 2007 and 2015 were included. We used a stable desensitization protocol throughout this period, which included Rituximab 2 weeks prior to KT and therapeutic plasma exchange (TPE) 2-4 sessions prior to KT and on-demand after KT. Each session of TPE was followed by intravenous immunoglobulin (IvIg) 100 mg/kg. Further IvIg was given 2 weeks after KT to complete a total dose of 2 g/kg. All patients received piperacillin/tazobactam intravenously during the period of TPE. Patients were induced with thymoglobulin and received prednisone, mycophenolate mofetil and tacrolimus as primary immunosuppressive agents. Patients were given valganciclovir for 3 months and Sulfamethoxazole / trimethoprim for 6 months.
Results: A total of 71 patients received ABOi KTx; mean age of the recipient and the donor was 39 and 29 y respectively. The majority was from blood group A donor to blood group O recipient (41%) and blood group B donor to blood group O recipient (30%). Acute cellular rejection (excluding borderline) was observed in 9% and antibody mediated rejection (AMR) in 7%. Graft survival in the first year was 94%, two grafts were lost due to AMR, one due to primary non-function and one due to renal vein thrombosis. Urine infections developed in 30%, BK nephropathy in 1%, none developed CMV disease or pneumocystis pneumonia. Only 4% were admitted in the first year due to sepsis. None of the patient died in the first year.
Conclusion: ABOi KT with our protocol offers excellent patient survival rates and low risk of serious infections. We speculate that prophylactic use of antimicrobials and high dose IvIg contributed to the excellent outcomes.

OS276 PROVISION OF HIGHLY SPECIALIZED AFTERCARE BY THE TRANSPLANT CENTER STRONGLY IMPROVES PATIENT AND ALLOGRAFT SURVIVAL IN LONG-TERM FOLLOW-UP AFTER KIDNEY TRANSPLANTATION

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Despite rapid medical advancements in the field of transplantation, mean kidney allograft survival remained at a standstill. If and to what extent a highly specialized aftercare of kidney transplant recipients (KTRs) impacts patient and allograft outcomes, however, remains unknown.

We hypothesized that highly specialized aftercare by transplant centers compared to local nephrologists ultimately improves patient and allograft survival. We analyzed 1328 KTRs between 1998 and 2015. KTRs treated regularly in our transplant center were compared with those followed by local nephrologists.

In total 824 KTRs (62.0%) were followed in our transplant center and 504 KTRs (38.0%) were followed by local nephrologists. Multivariate analysis identified 4 independent factors, associated with strong adherence to the transplant center provided aftercare: shorter distance to the transplant center ($p < 0.001$), living donation ($p < 0.001$), early registration to the waiting list ($p = 0.009$), and shorter initial hospital stay ($p = 0.004$). No differences were observed for age, sex, and time on dialysis ($p > 0.05$). KTRs followed in our transplant center showed significantly better patient survival (72.7% vs. 50.4% after 15 years; $p = 0.001$) and death-censored allograft survival (85.0% vs. 64.4% after 15 years; $p < 0.001$). These differences were equally observed in deceased and living donor KTRs of a first allograft. Retransplant KTRs followed in our transplant center showed superior death-censored allograft survival ($p = 0.035$), but no differences for patient survival.

Our data strongly indicate that aftercare by the transplant center is highly associated with superior patient and allograft survival. The observed wide differences may be attributed to highly specialized immunological and infectious screening protocols, careful and critical guidance of immunosuppression, and more comprehensive medical care. Despite long distances must be encouraged to make use of transplant center provided aftercare.

Translational Others Immunology

OS278 MODULATORY EFFECTS OF CYTOMEGALOVIRUS (CMV) SPECIFIC HYPERIMMUNOGLOBULIN (CMVIG) ON CMV PROTEIN-MEDIATED ACTIVATION OF DIFFERENT EFFECTOR CELL POPULATIONS OF CELL-MEDIATED IMMUNITY

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Background: Cytomegalovirus-specific hyperimmunoglobulin (CMVIG) as part of CMV prophylaxis after solid-organ transplantation can reduce the risk for CMV disease and overall mortality. These effects have been attributed to its neutralizing activity and to yet poorly-understood modulatory effects on cellular immunity. Herein, we investigated the influence of CMVIG (Cytotect® CP Biotest) on CMV protein-mediated activation of different effector cells of the innate and adaptive immune system.
Methods/Materials: CMV antigen-specific antibodies within this CMVIG preparation were detected by ELISA. Modulatory effect of CMVIG on NK cells and APC as well as the efficacy of CMV pp65 and IE-1 protein and of lysate of CMV-infected fibroblasts (CMV lysate) to reactivate T cells for cytokine production was assessed by ELISpot and by flow cytometry applying intracellular cytokine staining (ICS) in freshly isolated PBMCs of healthy donors.
Results: CMVIG comprised substantial concentrations of IgG antibodies with activity against pp65, IE-1 (1:25,000 dilution) and CMV lysate (1:400,000 dilution). In PBMCs, CMVIG induced a strong IFN-g and measurable TNF secretion from NK cells, which was dampened in the presence of CMV proteins. Incubation of PBMCs of CMV-seropositive donors with varying concentrations of CMVIG-opsonized pp65 or CMV lysate resulted in significantly increased numbers of IFN-γ-secreting cells. ICS analysis of stimulated PBMC identified elevated numbers of IFN-γ and TNF-producing CTL as well as IL-10-producing Th cells.
Conclusion: The observed capacity of CMVIG to activate NK cells and to promote the reactivation of CMV antigen-specific CTL may contribute to an improved control of CMV replication and related clinical complications.

Basic Composite Tissue Immunology

OS279 PREVENTING OF REJECTION OF VASCULARIZED COMPOSITE ALLOGRAFTS BY TARGETING T CELL METABOLISM

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Background: Upon antigen recognition and co-stimulation, T lymphocytes upregulate the metabolic machinery necessary to proliferate and sustain effector function. This metabolic reprogramming in T cells regulates T cell activation and differentiation. Therefore, we investigated to prevent graft rejection in vascularized composite allotransplantation (VCA) via inhibition of glycolysis and glutamine metabolism.
Methods: Fully MHC-mismatched orthotopic hind limb transplants were performed from Balb/C to C57BL/6 mice. Recipients in the experimental groups were given various combinations of CTLA4 Ig (0.5 mg) on day 0, 2, 4 and 6 post-transplant and triple metabolic inhibitors (2-DG, metformin and DON). Allograft survival was followed and flow cytometric analysis was performed to evaluate mixed chimerism and Foxp3 expressing Treg cells.
Results: Continuous triple metabolic inhibitor therapy induced long term survival more than 100 days[GB1] . 30 days treatment of triple therapy induced 39.5 days MST and combination with CTLA4 Ig and triple therapy induced 44 days MST indicating continuous metabolic inhibitors are necessary for long-term allograft survival. Mixed chimerism was detected in recipients receiving triple therapy with 0.3% in T cells, 0.15% in B cells and 0.8% in CD11b cells. Combination with CTLA4 Ig and 30 days of triple therapy induced increased mixed chimerism with 0.9%, 1.17%, and 6.96% respectively. However, increased CD4 + CD25 + Foxp3- T cells were found in both groups while CD4 + CD25 + Foxp3 + T cells were maintained representing ongoing antigen recognition by T cells.
Conclusion: These data support the notion that the inhibition of glycolysis and glutamine metabolic pathways represents a potent means to prevent acute rejection

Translational Kidney Immunology

OS280 PRETRANSPLANT SERUM BAFF LEVELS ARE ASSOCIATED WITH PRETRANSPLANT HLA - IMMUNIZATION AND RENAL ALLOGRAFT SURVIVAL

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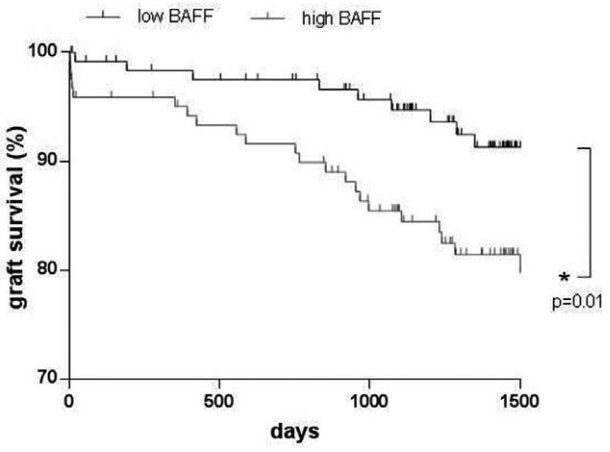
Background: The essential function of B cell–activating factor (BAFF) is regulating the survival and differentiation of B cells. In renal transplantation, B cells are involved in generating donor-specific antibodies (DSAs) and contribute to the development of acute antibody-mediated rejection (AMR).
Methods: The objective of our retrospective single-center study was to determine, by ELISA analysis of pretransplant serum BAFF levels in 249 patients undergoing renal transplantation for end-stage renal disease, the association between preformed human leukocyte antigen (HLA) antibodies, the occurrence of AMR, and 4-year survival of renal allografts.
Results: Pretransplant serum BAFF levels were significantly higher in HLA-antibody-positive patients (3262 $\pm$ 2796 pg/ml) than in HLA-antibody-negative patients (2252 $\pm$ 1425 pg/ml; $p < 0.0001$). Compared with patients with low pretransplant BAFF levels, patients with high pretransplant BAFF levels ($\geq$2137 pg/ml) experienced significantly lower 4-year allograft survival rates (80% vs. 91%; $p = 0.01$; Fig. 1) Coexistence of high pretransplant BAFF levels and post-transplant AMR was associated with the worst allograft survival rates. Univariate analysis of relative risk for allograft loss showed that high serum BAFF levels and the presence of HLA or DSA antibodies before transplant (relative risk, 2.3; 95%CI, 1.2–4.7) and the development of AMR after transplant were relevant. In a multivariate model only occurence of AMR after transplant was an independent risk factor for allograft failure.
Conclusion: Elevated pretransplant serum BAFF levels negatively affect renal allograft survival and should be considered a risk factor for allosensitization and subsequent renal allograft loss. BAFF neutralization before transplant may offer a therapeutic approach to improving graft survival in high-risk patients with elevated BAFF levels.

Fig.1



Basic Kidney Immunology

OS281 BKV CLEARANCE TIME CORRELATES WITH THE EXHAUSTION STATE AND T-CELL RECEPTOR REPERTOIRE SHAPE OF BKV-SPECIFIC T-CELLS IN RENAL TRANSPLANT PATIENTS WITH SEVERE BKV INFECTION

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Reactivation of the BK polyomavirus is known to lead to severe complications in kidney transplant patients. The current treatment strategy relies on decreasing the immunosuppression to allow the immune system to clear the virus. Recently we demonstrated a clear association between the resolution of BKV reactivation and reconstitution of BKV-specific CD4 + T-cells. However, the factors determining the duration of the clearance of the viral infection remain unknown.

Here we apply a combination of in-depth multiparametric flow cytometry and CDR3 beta chain receptor repertoire analysis of BKV specific T-cells to a cohort of 5 kidney transplant patients with BKV reactivation. This allowed us to track the TCR repertoires at single clone levels during the clinical course of BKV infection.

The number of BKV-specific T-cells in peripheral blood did not affect the duration of BKV infection. In contrast, the diversity of the T-cell receptor repertoire as well as exhaustion status of BKV-specific T-cells correlated with the duration of viral clearance. This duration was further found to be independent of hyperexpanded, immunodominant BKV-specific T-cell clones and of the overall magnitude of cellular immunity. Rather, the diversity of BKV-specific TCR repertoire in peripheral blood: high diversity of the repertoire and lack of PD1 and TIM-3 exhaustion markers on BKV-specific T-cells is associated with short remission time.

Our data demonstrate that the quality (exhaustion status and shape of the repertoire) rather than quantity of BKV-specific T-cells determines the remission time after BKV reactivation.

OS282 PREVENTION OF DONOR SPECIFIC ANTIBODY PRODUCTION AFTER SKIN ALLOGRAFTING BY MOBILIZATION OF ENDOGENOUS STEM CELLS USING A COMBINATION OF AMD3100 AND LOW-DOSE FK506 IN RATS

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Background: We have developed a stem cell mobilizing strategy that enables long-term liver and kidney allograft survival without sustained immunosuppression in small and large animals using a safe combination of two FDA approved drugs AMD3100 and low-dose FK506 (AF). Furthermore no increase in serum DSA levels was detected in animals displaying long-term survival even after donor skin grafts were rejected. Therefore the purpose of this study is to determine if AF combination treatment prevents de novo DSA production in a rat model of skin allograft rejection.
Methods: Split thickness skin allografts from Dark Agouti rats were transplanted into adult Lewis recipients. Recipient animals were divided into AF treatment group (AMD3100 1 mg/kg and FK506 0.1 mg/kg, s.c., every other day for 14 days) and control group (same volume of saline, s.c.). Serum levels of DSA including both IgG and IgM were measured by flow cytometry at 14 days, 1 and 2 months after skin transplantation. The sensitization to donor antigens in Lewis rats at 2 months after skin allografting was further confirmed by transplanting donor DA kidneys.
Results: Skin allografts were rejected in 8–10 days after transplantation in both groups. Serum levels of DSA-IgG increased 6 to 10 folds in control animals ($n = 10$), but only 2 to 3 folds in animals treated with AF combination ($n = 11$) at 1 month and remained at similar levels at 2 months after skin transplantation. All control animals ($n = 5$) died within 7 days after kidney transplantation. DSA deposition and AMR in kidney allografts were confirmed by histological studies. In contrast, about 64% (7/11) of animals with AF treatment after skin allografting survived over 3 weeks without antibody mediated rejection and no increase in serum levels of DSA at 14 days after kidney transplantation.
Conclusion: Mobilizing endogenous stem cells with AF combination treatment does not prolong skin allograft survival but prevents de novo DSA production after allograft rejection.

Basic Kidney Immunology

OS284 CMV AND ALLOPEPTIDE CROSS-REACTIVE T CELL CLONES IN ACUTE REJECTION OF KIDNEY ALLOGRAFTS

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Background: Both CMV- and allo-specific effector memory T cells have been implicated in transplant pathologies and predictive role of those cells for acute rejection has been discussed.
Methods: Peripheral CMV - and allo-specific T cells were assessed in 30 living donor kidney transplant (LDKT) recipients by ELISPOT method prior to and 6M after kidney transplantation. Recipients' PBMC were stimulated with CMV specific antigens (IE-1, pp65) and with allo-antigens (inactivated donors' cells) and seeded into the 96-well IFN-λ ELISPOT (AID, Germany) plate. The numbers of spots were measured and counted semi-automatically with ELISPOT reader (AID, Germany). The presence of heterologous immunity was tested in additional 7 LDKT recipients, PBMC were stimulated with CMV specific antigens (IE-1, pp65, CMV lysate) and with inactivated donors' cells in MLC reaction for 6 days. Proliferated CD8 + CellTracedim CMV-specific T cells were labeled with pentamers and sorted by FACS sorter. T cell receptor repertoires of sorted cells were sequenced by using NGS Ion Torrent™ technology.
Results: Pretransplant CMV-IE-1 specific IFN-γ ELISPOT provided stronger acute rejection predictive power than allo-specific IFN-γ ELISPOT (IE-1: 75% sensitivity and 72.7% specificity vs. allo: 50% sensitivity and 64.6% specificity). Cross-reactive CMV specific T cell clones were found in 6 out of 7 patients prior to transplantation. In 3 out of 6 graft biopsies the identical cross-reactive T cells clones to peripheral ones identified prior to transplantation were found (Tab.1).
Conclusions: Peripheral and intrarenal CMV/ALLO -peptides cross-reactive T cell clones explain better rejection predictive power of CMV specific memory effector T cells over allospecific ones. Critical role of heterologous immunity in kidney allograft rejection is suggested.

Table 1 The number of TCR clones found in kidney biopsies.

TCR reactive both to:	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6
CMV and donor antigens	1	1	3	0	0	0
Donor antigens	3	1	6	0	1	2
CMV IE-1	1	0	0	8	1	0
CMV pp65	1	7	5	11	1	0
CMV lysate	2	11	2	12	3	0

OS285 STRATEGY FOR ANALYSIS OF DONOR-SPECIFIC ANTIBODY REPERTOIRE: PAIRED IMMUNOGLOBULIN HEAVY AND LIGHT CHAIN ANALYSIS OF INDIVIDUAL MEMORY B CELLS

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Antibody-mediated rejection (ABMR) is the most challenging immunological barrier to overcome in human transplantation and one of the most prevalent causes of kidney allograft loss. Detection of circulating donor-specific antibodies (DSA) against donor HLA identifies sensitized patients at high risk of ABMR. In order to fully characterize the donor-specific antibody repertoire, identify its targets and investigate the associated pathogenic mechanisms it is necessary to determine the full-length paired immunoglobulin heavy and light chains (IgH, IgL) expressed by individual donor-specific B cells from sensitized kidney transplant patients. Unfortunately, this methodology has so far only been successfully applied to plasmablast populations, since antigen-specific memory B cells are present at very low frequencies in the blood and contain small amounts of Immunoglobulin mRNA. Here, we establish a methodology using combined polyclonal activation of circulating memory B cells with single cell IgH-IgL paired sequencing analysis, as an approach for evaluating antigen-specific memory B cells in sensitized transplant patients. PBMC from healthy donors were stimulated for 0 h, 6 h, 24 h, 48 h with TLR7 and TLR8 agonist plus IL-2 to differentiate memory B cells (CD19 + CD27 +) to plasmablasts (CD19 + CD20int/lowCD27 + CD38bright) as determined by flow cytometry. We found plasmablasts increased in proportion over time, from 1.12%±0.37 (0 h) to 1.78%±1.42 (6 h), 6.05%±2.02 (24 h) and 20.1%±3.39 (48 h). CD19 + CD20int/lowCD27 + CD38bright plasmablasts were single cell sorted, bar coded, and underwent next generation sequencing to obtain paired IgH and IgL sequences. Forty-eight hour stimulation of memory B cells led to a 6-fold increase of detectable paired IgH-IgL, relative to resting memory B cells, and reached a level comparable to freshly isolated blood plasmablasts. We observed significantly higher levels of CD38 ($p < 0{,}0001$) on those cells that yielded productive paired IgH-IgL sequences than in cells where sequences were not obtainable.

OS286 GLYCOLYTIC AND GLUTAMINOLYTIC METABOLISM SUPPORTS IL-15 INDUCED INFLAMMATORY RESPONSE OF TEMRA CD8 FROM KIDNEY TRANSPLANT RECIPIENTS

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Rational: The accumulation of TEMRA CD8 in kidney transplant recipients (Tx) is associated with a higher risk of graft loss. Nevertheless, factors leading to their accumulation and activation remain ill-defined and alternative therapeutics are needed to control their inflammatory response. Thus, we hypothesized that the effector functions of TEMRA are triggered by proinflammatory cytokine IL-15 and that drugs interfering with specific metabolic processes would constitute an alternative to control their pathogenicity.

Method: TEMRA, NAÏVE and EM CD8 were purified from Tx with stable graft function at 1 year ($n = 56$) and from healthy volunteers (HV). Survival, proliferation and activation were monitored upon stimulation with IL-15 + /- aCD3. Inflammation of HUVEC induced by soluble factors secreted by IL-15 stimulated TEMRA was monitored. Contribution of glycolysis, glutaminolysis and oxidative phosphorylation to TEMRA response was tested using specific inhibitors.

Results: We show that IL-15 combined with TCR stimulation induces the rapid activation of TEMRA CD8 from Tx (upregulation of CD25 and CD69) and fosters the endothelium activation (upregulation of CX3CL1 by HUVEC) in an IFN-g and TNF-a dependent manner. IL-15 induces anti-apoptotic signals and promotes vigorous proliferation dependent on PI3K/Akt, p38MAPK and ERK pathways. Resting TEMRA cells are metabolically more active than naive and EM (high ATP reservoir and a high expression of genes involved in glycolysis, glutaminolysis and PP pathway). Upon stimulation, TEMRA adapt their metabolism by sustaining an increased mitochondrial respiration and glycolysis. Finally the inhibition of glycolysis and to a lesser extent of glutaminolysis is effective at preventing the endothelium inflammation induced by Tx TEMRA CD8.

Conclusion: We have demonstrate that IL-15 is a potent activator of TEMRA CD8 in Tx and that selective glycolytic and glutaminolytic inhibition blunts the TEMRA induced inflammation of the endothelium.

OS287 QUANTITATION OF ALLOANTIBODY-HLA BINDING KINETICS USING A NOVEL BIOSENSOR ASSAY TO IMPROVE IMMUNOLOGICAL RISK ASSESSMENT IN TRANSPLANTATION

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Introduction: There is uncertainty regarding the clinical significance of HLA-specific alloantibodies detected by solid-phase assays. Alloantibodies cross-react with several HLA limiting our ability to assess immunological risk before transplantation and to perform efficient immune monitoring, facilitating early intervention, after transplantation. We hypothesised that the strength of alloantibody binding to HLA relates to their pathogenic potential and developed a biosensor assay to assess alloantibody-HLA binding kinetics in real time.

Methods: The reactivity patterns of human HLA-specific monoclonal antibodies (mAb) were characterised using Luminex single antigen beads (SAB) and also by complement-dependent cytotoxicity (CDC; large panels of cells typed at 2-field resolution) and flow cytometry (using single HLA expressing cell lines) assays. Bio-layer interferometry kinetic assays (Octet Red 96) were developed to assess specific mAb-HLA interactions (based on 1:1 interaction model).

Results: SAB analysis showed mAb reactivity to a range of HLA class I molecules (Table 1 shows two representative mAb). Despite high MFI level mAb-HLA interactions detected by SAB, only a subset of these showed complement engagement and cell lysis and these interactions were of higher affinity compared to CDC negative interactions. There was correlation between the mAb-HLA binding affinity and the output from the functional assays, whereas interactions detected only by SAB had the lowest (or un-recordable) affinity constants (results of C1q-SAB assays will be presented at the meeting).

Table 1

Monoclonal Antibody	HLA	SAB MFI	CDC with molecularly typed cells (median score)	CDC interpretation	Flow Cytometry: median FI with SALs (median FI negative control)	K_D (M)
WIM8E5	**A*11:01**	17497	8	Strong positive	229 (8)[1]	3.21E-08
	A*25:01	19816	7	Strong positive	NT	7.67E-08
	A*68:01	18131	8	Strong positive	NT	1.92E-07
	A*31:01	18299	6	Positive	45 (10)[2]	2.56E-07
	A*01:01	17951	6.5	Positive	81 (10)[1]	3.32E-07
	A*02:01	17382	3	Weak positive	115 (9)[1]	4.96E-07
	A*24:02	17410	2.5	Negative	21 (9)[2]	1.08E-06
	A*23:01	17880	2	Negative	NT	2.06E-06
Monoclonal Antibody	**HLA**		**CDC with molecularly typed cells (median % cell kill)**	**CDC interpretation**	**Flow Cytometry: median FI with SALs (median FI negative control)**	**K_D (M)**
WK1D12	**B*27:05**	14926	60%	Strong positive	133 (11)[2]	4.59E-08
	B*40:01	16206	60%	Strong positive	NT	5.38E-08
	B*07:02	15976	42%	Positive	407 (11)[1]	7.22E-08
	B*13:02	15756	12%	Negative (positive with B13 homozygous cells	41 (11)[2]	1.01E-07
	B*48:01	13486	25%	Negative	NT	1.51E-07
	A*66:02	5524	20%	Negative	NT	2.96E-05

CDC: Complement Dependent Cytotoxicity; FI: Fluorescence Intensity; SALs: Single HLA expressing cell lines; NT: not tested. All biolayer interferometry interactions were performed using five 2-fold dilutions of analyte (the average K_D is shown). [1] SALs created using transduction (higher HLA expression compared to trasfection); [2] SALs created using transfection. Flow cytometric positive cut-off: median FI ≥ 3 x FI of negative control. Sensitising HLA indicated in **bold**. CDC was interpreted based on all reactive cells and the results from controls.

Antibody interactions to the corresponding sensitising HLAs were of the highest affinity, indicating the presence of immunological memory.
Discussion: Assessment of alloantibody-HLA binding kinetics provides important information that might improve immunological risk assessment in clinical transplantation. Further research is required to investigate the clinical utility of this approach.

Translational Kidney Immunology

OS288 IMPACT OF T-CELL DEPLETION ON CMV-SPECIFIC MEMORY T AND B-CELL HOMEOSTATIC PROLIFERATION AFTER KIDNEY TRANSPLANTATION

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CMV infection is the most common opportunistic infection after kidney transplantation (KT), with a negative impact on kidney allograft outcome. Transplant recipients are at higher risk of CMV infection because of immunosuppression, particularly when using T-cell depleting agents such as rabbit anti-thymocyte globulin (rATG). CMV-specific T cell responses are crucial for controlling viral replication. Whether CMV-specific memory T and B cells repopulate after rATG treatment and how they influence on CMV infection has not been well documented yet.
Methods: We evaluated CMV-specific memory T and B cell responses using the IFN-Y and IgG ELISPOT assays in 70 consecutive kidney transplant patients receiving either rATG ($n = 42$) or anti-IL2R monoclonal antibodies (basiliximab®) ($n = 28$) followed by tacrolimus, MMF and steroids. We monitored the kinetics of T and B-cell responses against two dominant CMV antigens (IE-1, pp65) at baseline, two weeks and at one, three and six months KT and evaluated their impact on CMV infection.
Results: rATG-treated patients showed a generalized abrogation of CMV-sp T-cell frequencies over the first 6 months as compared to basiliximab-treated patients that also showed reduced CMV-sp T-cell frequencies over time. RATG-treated patients showed lower CMV-sp T-cell frequencies at 2 weeks ($p < 0.05$) but fully recovered by months 3 and 6 for pp65 and IE-1, respectively as compared to baseline (P = NS). No impact on CMV-sp T-cell responses was observed regarding the type of preventive strategy used. Notably, patients not recovering sufficient CMV-sp T-cell frequencies more likely developed infection after KT. CMV-sp memory B-cell frequencies were not influenced by the use of T-cell depletion nor basiliximab®.
Conclusions: rATG induction significantly impacts on early CMV-sp memory T-cell responses after transplantation, although a rapid CMV-sp T-cell homeostatic proliferation might be observed in some patients thus, driving protection against CMV infection.

Translational Liver Allocation

OS289 A NOVEL LEARNING ALGORITHM TO PREDICT INDIVIDUAL SURVIVAL AFTER LIVER TRANSPLANTATION FOR PRIMARY SCLEROSING CHOLANGITIS

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Background & Aims: Deciding who should receive a liver transplant (LT) depends on 1) medical urgency and 2) transplant utility. While there are tools that work effectively for the first task, there are none for the second, which requires estimating the likelihood of long-term survival after LT. Most survival scores are validated through discriminative tests (c-statistics), which by definition compare predicted outcomes between patients. Assessing post-transplant survival utility is not discriminate; instead it should be "calibrated" to be effective. There are currently no such calibrated models. We developed and validated a novel calibrated model to predict individual survival after LT for Primary Sclerosing Cholangitis (PSC).
Methods: We applied a software tool, PSSP, to learn a model for predicting individual survival distributions for novel patients. We included adult patients in the Scientific Registry of Transplant Recipients ($n = 2769$) who received a LT for PSC between 2002 and 2013. We developed a novel evaluation measure, D-calibration, to validate this model. Calibrations of the model generated by PSSP were also compared to a model obtained by traditional Cox regression.
Results: The learned PSSP model showed an excellent D-calibration ($p = 1{\cdot}0$), and passed the single-time calibration test (Hosmer-Lemeshow p-value of over 0·05) at 0·25, 1, 5 and 10 years. In contrast, the model based on Cox regression showed worse calibration on long-term survival and failed at 10 years (Hosmer-Lemeshow p value = 0.027). The calculator and visualizer are available at: http://pssp.srv.ualberta.ca/calculator/liver_transplant_2002.
Conclusion: We present a new tool that will help transplant candidate selection committees decide objectively whether a specific PSC patient is eligible for a LT, by estimating the utility of that LT, based on that individual's survival distribution.

Clinical Liver Allocation

OS290 IMPACT OF "RESCUE ALLOCATED" LIVERS ON OUTCOMES AFTER LIVER TRANSPLANTATION: A PROPENSITY SCORE MATCHING ANALYSIS

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Background: Liver graft offers that are declined by at least 5 transplant centers are considered for "rescue allocation" (RA), leaving a free choice for the recipient. The aim of this study was to compare the postoperative outcomes of patients who received a donor liver through a RA procedure or according to MELD score priority (standard allocation, SA).
Methods: From January 2011 to April 2015, a consecutive series of first and elective liver transplantation (LTs) were analyzed before and after propensity score matching (PSM) on recipient characteristics.
Results: Overall, 249 LTs were retrospectively analyzed: 64 (25.8%) with RA liver grafts and 185 (74.2%) through a SA procedure. RA livers came from older donors (68.1 vs. 58.2 years; $p < 0.001$), had a higher Euro-Transplant Donor Risk Index (2.2 vs. 1.6; $p < 0.001$), and a longer cold ischemia time (9.1 vs. 7.0 hours; $p < 0.001$). Compared to SA group, recipients of RA livers had a lower MELD score (10.5 vs. 21.7; $p < 0.001$), were more frequently at home (89.1 vs. 49.2%; $p < 0.001$), and most of them had a hepatocellular carcinoma (82.8 vs. 13.5%; $p < 0.001$). RA recipients were less frequently transfused (78.1 vs. 91.4%; $p < 0.01$), had shorter operative time (470 vs. 431 minutes; $p = 0.01$) and hospital stay (36.5 vs. 48.2 days; $p = 0.02$). ICU stay was similar between groups. Delayed graft function (32.8 vs. 29.7%; $p = 0.64$), primary non-function (1.6 vs. 3.2%; $p = 0.87$), retransplantation (7.8 vs. 8.6%; $p = 0.99$), severe complication (grade 3-4) according to Dindo-Clavien's classification (36 vs. 44.8%; $p = 0.12$) and 3-months mortality rates (12.5 and 9.1%; $p = 0.44$) were similar between RA and SA groups. Graft and patient survival at 1 and 3 years were similar between the two groups. All these results were maintained after PSM.
Conclusion: Rescue-allocated livers – i.e. refused by at least 5 centers - can be safely transplanted without increased morbidity or mortality compared to standard allocated livers, thereby enlarging the donor pool.

Clinical Liver Donation and donor types

OS291 LIVING DONOR (LD) LIVER TRANSPLANTATION (LT) PROVIDES BETTER OUTCOME THAN DECEASED DONOR (DD) IN CHILDREN LESS THAN TWO YEARS WITH BILIARY ATRESIA (BA): RESULTS IN 342 PEDIATRIC RECIPIENTS

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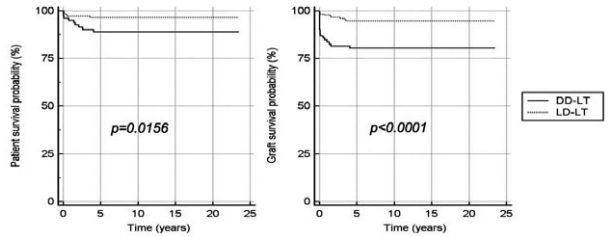
Background: BA is the main indication for LT in pediatric age. Donor-selection strategy is still matter of debate.
Methods: LT performed at our Institution between 1993 (beginning of our LD-program) and 2015 were retrospectively analyzed. Patient and graft survivals were studied in BA patients according to age at LT and donor-type (LD vs DD). Among 609 children, recipients of 649 grafts, the indications for LT were as follows: BA (56.1%), cholestatic diseases (19.4%), liver malignancies (7.5%), fulminant hepatitis (4.3%) and others (12.7%). For BA recipients, 150 DD and 216 LD grafts were used.
Results: *Considering overall series*: median age was significantly lower for BA (median: 1.0y; range: 0.3–15.7) comparing to other indications (3.9y; 0.1–22.4) ($p < 0.0001$). Overall 5y patient and graft survivals were 86.9% and



Overall patient and graft survival in BA recipients transplanted before 2 years of age (264 patients)

82.2%% for non-BA respectively, vs. 95.1%% and 88.8% for BA patients ($p = 0.0001$ and $p = 0.0033$). *Considering BA patients:* median age was significantly lower for LD-LT (0.9y; 0.4–10.8) comparing to DD-LT (1.4y; 0.3–15.7) ($p < 0.0001$). Overall re-transplantation rate was 9.3%. 5y patient survival was non-significantly higher for patients transplanted at >2y-old (97.4%) comparing to those transplanted <2y-old (94.1%) ($p = 0.9127$); conversely, 5y graft survival was significantly better when LT was realized <2y-old (90.0% vs 84.1%) ($p = 0.0316$). In the subgroup of children <2y-old, 5y patient and graft survivals were significantly better after LD-LT (96.6% and 90.6% respectively), than after DD-LT (88.9% and 81.5%) ($p = 0.0156$ and $p < 0.0001$).
Conclusions: 1) BA constituted the main indication for LT in children; 2) The use of LD-LT allowed to transplant children at younger age, when compared with DD-LT; 3) In the subgroup of BA children <2y-old, LD-LT provides significantly better outcome.

Clinical Liver Allocation

OS292 EXTENDED DONOR CRITERIA IN LIVER TRANSPLANT – CALL FOR CAUTION

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Background: The study was designed to identify major extended donor criteria (EDC) predictive of graft failure after liver transplant (LT) in the MELD-score era.
Methods: We have analyzed 465 consecutive LTs in a single-center setting and examined the EDC: donor age >65 years, BMI >30, malignancy, drug abuse history, mechanical ventilation >7 days, aminotransferases >3x normal, serum bilirubin >3 mg/dL, serum-Na+ >165 mmol/L, positive hepatitis serology, macrosteatosis >40%, and cold ischemia time (CIT) >14 h. Primary- and delayed non-function (PNF and DNF), short- (90-day), mid- (1-year) and long-term (5-year) graft survival were of primary interest.
Results: Grafts from donors without EDC were transplanted in 112 cases, whereas 353 patients received marginal organs with at least one EDC. Graft and patient survival did not differ between these groups. The multivariate analysis identified macrosteatosis (HR 10.5 95%CI 3.6–30.3, $p < 0.001$), donor age (HR 2.0 95%CI 1.1–3.4, $p = 0.034$), and CIT (HR 2.0 95%CI 1.1–3.8, $p = 0.025$) as major EDC predictive of graft failure. Concomitant presence of a maximum of two major EDC was observed and it increased the PNF-, short-, mid-, and long-term graft failure rates in comparison to cases without major EDC (2.4 vs. 11.4%, 3.3 vs. 17.1%, 7.5 vs. 25.7%, and 7.5 vs. 28.6% respectively; all $p < 0.05$). Lower 5-year graft survival in the cases of major EDC was observed after controlling for labMELD-score with a cut-off value of 20 (log-rank $p = 0.001$). Regarding death due to liver failure, 5-year patient survival was 93.2%±1.8% in the non-major-, and 85.1%±2.5% in the major EDC-group ($p = 0.014$).
Conclusion: Older donor, fatty liver and long CIT decrease long-term patient-, and short- and long-term graft survival, and place the graft at risk for long-term failure irrespective of recipients' labMELD-score. These three major criteria outweigh the rest of the EDC and should be used with caution.

Clinical Liver Donation and donor types

OS293 SHIPPING OF SPLIT-LIVERS RESULTS IN A HIGHER RETRANSPLANTATION RATE BUT DOES NOT AFFECT OVERALL PATIENT'S SURVIVAL: AN ANALYSIS FROM THE EUROTRANSPLANT LIVER FOLLOW-UP REGISTRY

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Introduction: Split liver transplantation (SLT) has been perceived as an important strategy to increase the supply of liver grafts by creating 2 transplants from 1 allograft. Eurotransplant (ET) Liver Allocation System (ELAS) envisages that the (Extended) right lobes (E)RLs after splitting (usually in the pediatric center) are almost exclusively shipped to a second center within the Eurotransplant area. Whether the specificity in the ELAS policy impacts on graft and patient survival in comparison to whole liver transplantation (WLT) remains unclear.
Methods: Data on all LT performed between 2007 and 2013 were retrieved from the ET Liver follow-up Registry ($n = 5351$). Data on $n = 5013$ (269 (E) RLL, 4744 whole liver) Ltx could be included.
Results: Cold ischemia (CIT) times were significantly prolonged for SLT ($p < 0.001$). Patient survival was not different between (E)RLL and WLT. In the univariate analysis SLT had a significantly higher risk for retransplantation ($p = 0.021$). For WLT the risk for death gradually and significantly increased with labMELD scores of >20. For (E)RL-Tx this effect was seen already with labMELD scores of >14.
Conclusions: Within ET, SLT results in a higher retransplantation rate but similar survival compared to WLT. Our results suggest that SLT outcome could be further improved by an allocation algorithm allowing for short CIT and an optimized SLT/recipient match.

OS294 MILD HEPATIC STEATOSIS IN DONORS IS NOT A RISK FACTOR FOR POST-TRANSPLANT COMPLICATIONS IN ADULT LIVING DONOR LIVER TRANSPLANTATION

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Background: In living donor liver transplantation (LDLT), potential donors with steatosis raise concerns regarding an increased donor risk as well as poor recipient outcomes. The aim of this study is to evaluate the effects of mild macrovesicular steatosis (15–30%) on the outcome of both donors and their recipients following LDLT.
Method/Materials: Among 468 donors who underwent right hepatectomy between January 2010 and December 2015, 109 (23.2%) selectively underwent liver biopsy within a median of 9 (IQR, 6–22) days before the operation. Donors were categorized into 2 groups: D1 (macrovesicular steatosis <15%, $n = 95$) and D2 (macrovesicular steatosis 15–30%, $n = 14$). Donor groups were compared in terms of serum AST, ALT, INR, and bilirubin levels on postoperative day (POD) 1 to 7 and postoperative complication rate. Their respective recipient groups (R1 and R2) were compared in terms of early allograft dysfunction (EAD) and 90-day mortality rate.
Results: In donors, there was no significant difference in terms of age (33.2 ± 8.3 in D1 vs. 36.6 ± 6.7 in D2, $p = 0.1$) and body mass index (BMI) (26.9 ± 4.0 in D1 vs. 27.4 ± 3.0 in D2, $p = 0.6$). In D2, bilirubin levels were significantly higher on POD 6 and 7 (POD6; 1.8 ± 1.7 in D1 vs. 3.2 ± 4.1 in D2, $p = 0.03$), which returned to within the normal range by POD 15 in both groups. There was no significant difference in terms of postoperative complication rate (29.5% in D1 vs. 35.7% in D2, $p = 0.7$).

In recipients, Group R1 and Group R2 had similar MELD scores and POD7 INR and bilirubin levels. Despite a slightly increased EAD rate in R2 (21.1% in R1 vs. 28.6% in R2, $p = 0.8$), none of the recipients receiving a mildly steatotic graft had 90-day mortality (8.4% in R1 vs. 0% in R2).
Conclusion: The present study shows that in adult LDLT, utilization of living liver donors with mild hepatic steatosis (<30%) is safe for both donors and their respective recipients.

OS295 AGAINST THE CLOCK! GRAFT IMPLANTATION TIME MATTERS IN MARGINAL GRAFTS PREDICTING INFERIOR OUTCOMES

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Background: Marginal livers are increasingly utilized in the era of organ shortage. Our objective was to determine whether prolonged warm ischemic time during liver transplantation (LT) affects outcome of marginal organs.
Methods/Materials: 714 consecutive cadaveric primary LT between 2009 and 2014 at our institution were stratified according to low risk (DRI<1.8) [LR] and high risk (DRI>1.8) [HR] grafts as well as liver implantation time (IT) <45 and >45 minutes. Allograft and remote organ outcome was retrospectively analyzed.
Results: LR livers were significantly more often allocated to sicker patients (UKELD 56 vs 55, p = 0.004; MELD 17 vs 15, p < 0.0001) while HCC patients were likely to receive HR grafts (22% vs 16%, p = 0.0681). Both LR and HR grafts had comparable cold ischemic time, donor hepatectomy time and steatosis. Short- and long-term allograft and kidney function as well as overall non-malignant survival (patient 3y 91% vs 87%, graft 3y 87% vs 81%; p = 0.1382 and p = 0.1236) were similar for recipients of LR and HR grafts. IT>45 min subgroups had prolongation of each and every step in implantation (IVC anastomosis, PV anastomosis, arterialization time). Short-term but not long-term allograft and renal functions were significantly worse in recipients with long anastomotic (>45 min) time irrespective of organ risk stratification. Best overall patient (3y 90%) and graft (3y 86%) survival was achieved for fastest implantation of LR grafts (LR + IT<45 min). LR + IT>45 min and HR + IT<45 min achieved comparable survival outcome though inferior to the former. Most importantly, the worst transplant outcome occurred in prolonged implantation of high risk organs (HR + IT>45 min, patient 3y 73% and graft 3y 67%) (p = 0.0026 and 0.0073). This significance remained true when de novo/recurrent malignancy was excluded as cause of death.
Conclusion: Implantation time is critical for outcomes after LT and should be considered in graft-recipient matching as well as surgeons training.

OS296 RESULTS FROM DONATION AFTER CIRCULATORY DEATH LIVER TRANSPLANT IN RECIPIENTS OLDER THAN 60 YEARS

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Hospital Universitario 12 De Octubre, Spain

Background: Due to organ scarcity, donation after circulatory death (DCD) has become an acceptable alternative to donation after brain death (DBD). The decreased recovery capability associated with aging might compromise the ability of older patients to tolerate an aggression such as a liver transplant (LT), especially when combined with the deleterious effects of a suboptimal graft (DCD).
Methods/Materials: 713 LT have been performed between January 2006 and December 2015. 73 (10,2%) were from DCD (Maastricht II). We compare results in patients younger and older than 60 years (<60 vs. >60) after DCD LT.
Results: Average MELD scores were 15.3 + 4.6 (<60) and 13.7 + 4.9 (>60) (p = 0,16). Hepatocellular carcinoma was more frequent in the >60 group (63.9% vs.; 37.8%; p = 0.26). There were no significant differences found in ischemic times, pump flow rates or HCV infection rate (56.8% <60; 58.3% >60; NS). Patient survival for younger patients following DCD LT at 1, 3 and 5 years (91.9%; 85.7% and 85.7%) was significantly higher than that of the >60 group (72.2%; 57.9%; 54.9%; p = 0.004). Graft survival rates at 1, 3 and 5 years were 89.5%; 84.5% and 81.2% (<60) vs. 75%; 65.2% and 58.6% for the >60 group (p = 0.00). The most frequent cause of death among >60 was HCV recurrence (21.4%), while the <60 group showed a similar incidence of HCV recurrence, intraabdominal infection, primary non-function (PNF) and cerebrovascular accident (25%). There were no differences in graft PNF rates. 21% of patients in the <60 group underwent retransplantation, a significantly higher number than those in the >60 group (5.6%; p = 0.04). Ischemic cholangiopathy showed a similar incidence in both groups (33.3%).
Conclusion: Although liver transplantation for older patients has been shown to have acceptable if somewhat poorer results; when studying DCD LT both patient and graft survival decrease significantly in recipients over 60 years. These results might discourage the use of DCD grafts in this particular group.

OS297 LIVER TRANSPLANT OUTCOMES FROM DECLINED LIVER ALLOGRAFTS: IS IT WORTH THE RISK?

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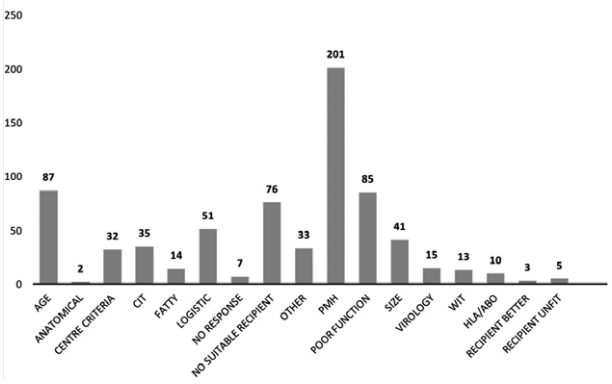
Background: Marginal liver grafts supplement the organ pool but there lacks a clear definition on marginality. In an era where nearly 200grafts/year are non-utilised upon offering, we aimed to analyse whether previous refusal by other transplant centres had any impact on transplant outcomes.
Methods: Organ offer of all adult liver transplants (LT) performed in December 2010–2015 were analysed. Data on previous refusal was captured from NHSBT EOS database. The reasons for refusal by other centres were categorised in to 03 groups; *quality*, *logistics* and *other reasons not specified*. Transplant outcomes were then analysed.
Results: Total of 206/909 (22.6%) LT were performed from grafts refused by at least one other centre. Majority [141(68.4%)] were DBD grafts. Donor liver dysfunction existed in 79 (38%) meanwhile 80(39%) donors had out-of-hospital cardiac arrest. Reasons for refusal are illustrated in Fig 1. The average refusal rate was 3.5/organ (4.2 vs. 3.2; DCD vs. DBD respectively). 44% (DBD) and 65% (DCD) grafts were refused by >4 transplant centres (p = 0.006). When refused by >1 centre, there was no agreement on reason for refusal in 65% of cases. By category, reasons for refusal were *organ quality (n = 120; 58%), logistics (n = 67; 33%)* and *other reasons (n = 19; 9%)*. Main indication for transplantation was ALD (n = 55 patients; 26.7%), Median UKELD was 53 (32–68). 90-day mortality due to graft failure was 8/206 (3.8%); 6 were from quality refusal group, but none were DCD's. There was no difference in the 3 refusal groups in terms of post-operative complications (p = 0.6), rejection (p = 0.9) and in graft survival (p = 0.9).



Conclusion: The mortality rate due to graft failure is within acceptable rates, and these data highlight diverse opinions on graft assessment and acceptability amongst transplant surgeons. Most of the centres refused grafts claiming quality issues, this was proven to be correct only in minority of cases.

OS298 SURGICAL FACTORS AND NOT DONOR TYPE PER SE ARE RISK FACTORS FOR ACUTE KIDNEY INJURY AFTER LIVER TRANSPLANTATION

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Background: Because Liver Transplantation (LT) using DCD has been shown to be risk factor for Acute Kidney Injury (AKI), we reviewed results at our center.
Patients and Methods: AKI was defined as decrease >50% eGFR (CKD-EPI) within 48 h postreperfusion (RIFLE). 106 first LT-only [63 DBD (59%) & 43 DCD (41%)] without pre-existing renal dysfunction (eGFR>60 ml/min/1,73 m2, no renal replacement therapy) were performed from 2012 to 2016. Incidence/risk factors for AKI were assessed. Data: mean (IQR).
Results: Incidence of AKI was 33% (35/106). AKI-patients were more hospitalized before LT [9/16 (56%) vs 26/89 (29%), p < 0.01], with higher labMELD [16 (10–23) vs 12 (8–16), p = 0.01]. Donor type [11/43 DCD (25%) vs 24/63 DBD (39%), p = 0.16], donor hepatectomy time [38 min (26–50) vs 35 (25–42), p = 0.37], cold ischemic time [6 h (4.1–7.6) vs 5.1 (3.4–6.4), p = 0.21], time for anastomosis [44 min (35–49) vs 42 (38–48), p = 0.53], postreperfusion

syndrome [19/46 (42%) vs 27/46 (58%), p = 0.07] were similar between AKI & non-AKI groups. AKI was more frequent if lungs were procured first in the donor [23/48 (48%) vs 11/56 (19%), p < 0.01]. Recipient surgery was longer in the AKI group [5.2 h (3.9–6.3) vs 4.3 (3.4–4.8), p < 0.01]. AKI was more frequent if platelets were transfused during LT [19/42 (56%) vs 15/59 (44%), p = 0.03]. Blood volume administrated from the cellsaver was larger in the AKI-patients [834 ml (300–750) vs 408 (0–550), p = 0.03]. AKI-patients have a higher peak AST [1235 U/L (310–1858) vs 812 (429–978), p = 0.04]. Haemoglobin [8.8 g/dl (7.4–9.9) vs 10 (8.5–11.7)] & platelets [69x103 (50 × 103–87 × 103) vs 89 × 103 (50 × 103–118 × 103)] at day 1 postreperfusion were significantly lower if AKI occurred. After multivariable analysis, thoracic procurement before liver [OR 5.75 (1.76–18.77), p = 0.004] & recipient surgery duration [OR 1.64 (1.15–2.32), p = 0.006] were only risk factors for AKI.
Conclusion: Rapid donor/recipient surgery and not donor type are key factors to prevent AKI-post-LT.

OS299 THE USE OF OCTOGENARIAN LIVER GRAFTS: THE LESSONS LEARNED AFTER MORE THAN 200 TRANSPLANTS

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Background: Elderly grafts may provide favorable long-term results after liver transplantation (LT). However, they are associated with an increased risk for ischemic-type biliary lesions (ITBL) and hepatitis C virus (HCV) recurrence after LT compared to standard donor grafts.
Materials/methods: This was a retrospective, case-control analysis on use of elderly liver grafts (≥80 years) for LT at a single institution. From 01/2001 thru 09/2016, 1753 LT were performed at our Institution. After removing UNOS 1A, ABO-incompatible LT and donors and/or recipients <18 years(*n* = 125), 217 LT with deceased donors ≥80 years vs. 299 LT with donors 18–49 years were selected. A Propensity Score Match (caliper 0,2) was done for the risk of post-LT death using as covariates: model for end-stage liver disease (MELD), HCC, HCV, cold (CIT) and warm ischemia time (WIT). Finally, a total of 217 recipients of grafts≥80 years (Group A) were compared with 182 recipients of standard donor grafts (18–49 years, Group B). The primary end-point was graft and patient survival rate. The secondary end-point was assessment of ITBL and HCV-related graft loss.
Results: Graft survival was 86.7%, 80.3%, and 72.9% at 1, 3 and 5 years in Group A vs. 95.2%, 88.1%, and 85.8% in Group B (p = 0.002, log rank). In Group A vs. Group B, HCV-related graft loss was 11/217 (5.1%) vs. 5/182 (2.7%) (p = 0.3); incidence of ITBL was 25/217 (11.5%) vs. 3/182 (1.6%) (p < 0.0001), and incidence of ITBL-related graft loss was 6/217 (2.8%) vs. 0 (0%) (p = 0.03).

Conclusions: Although associated with a 5-year graft survival rate of 73%, liver donor grafts≥80 years have a 2-fold increased odds for HCV-related graft failure and a 3-fold increased odds for ITBL, respectively. Novel antiviral treatments and continued management of ITBL will likely contribute to further improvements of these results, reducing the gap between elderly and standard donor grafts.

Clinical Liver Allocation

OS300 THE UK-DCD-RISK-SCORE - A NEW PROPOSAL TO DEFINE FUTILITY IN DCD LIVER TRANSPLANTATION

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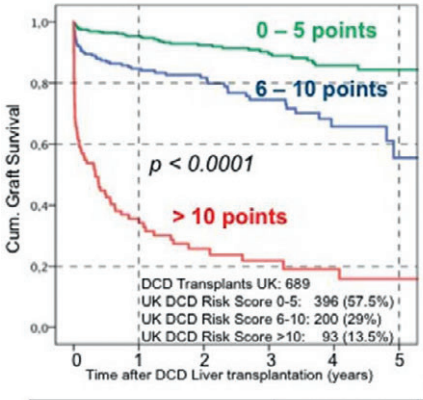
Background: Primary-non-function (PNF) and ischemic cholangiopathy (IC) are the most feared complications leading to graft loss in DCD liver transplantation. With this analysis we aimed to design a new score on risk assessment in liver transplantation donated after circulatory death (DCD) based on donor, graft and recipient parameters.
Methods: Using the United Kingdom (UK) national DCD database, a risk analysis was performed in adult recipients of DCD liver grafts in UK between 2000 and 2015 (*n* = 1153). A new risk score was calculated (UK-DCD-Risk-Score) on the basis of regression analysis, and validated using the UNOS (United Network for Organ Sharing) database (*n* = 1617) and our own DCD liver transplant database (*n* = 315). Finally, the new score was compared with two other available prediction systems, the DCD risk scores from UCLA and Kings-College-Hospital, London.
Results: Seven strongest predictors of DCD graft survival were identified: functional donor warm ischemia, cold ischemia, recipient MELD, recipient age, donor age, previous OLT, and donor body-mass-index (BMI). A combination of these risk factors (UK-DCD-Risk-Model) stratified best recipients in terms of graft survival in the entire UK-DCD-database (Figure 1) as well as in the UNOS and in our own DCD population. Importantly, the UK-DCD-Risk-score significantly predicted graft loss due to primary-non-function or ischemic cholangiopathy. The new prediction model was superior to other available systems, as demonstrated by a C statistic of 0,79 compared to 0,71 and 0,65, respectively.
Conclusions: The UK-DCD-Risk-Score is a reliable tool to detect high risk and futile combinations of donor and recipient factors in DCD liver transplantation. It is simple to use and offers a great potential to better decide which DCD graft should be rejected or may benefit from functional assessment and further optimization by machine perfusion.

Figure 1: The UK-DCD-Risk-Score



Parameter	Parameter cut-off	Score - Points
Donor age (years)	≤ 60	0
	> 60	2
Donor BMI (kg/m²)	≤ 25	0
	> 25	3
Functional Donor warm ischemia (min)	≤ 20	0
	> 20 to ≤ 30	3
	> 30	6
Cold ischemia (hrs)	≤ 6	0
	> 6	2
Recipient age (years)	≤ 60	0
	> 60	3
Recipient lab MELD (points)	≤ 25	0
	> 25	2
Retransplantation	no	0
	yes	9
Total Score points		0 - 27

Outcome parameter	Low Risk (0-5 points)	High Risk (6-10 points)	Futile (>10 points)	*p* value (high Risk vs. Futile)
Cause of graft failure:				
- Primary-non-function (n/%)	2 (0.5%)	2 (1%)	25 (26.9%)	*0.0001*
- Hepatic artery thrombosis (n/%)	1 (0.3%)	4 (2%)	9 (9.7%)	*0.005*
- Intrahepatic Cholangiopathy (n/%)	5 (1.3%)	6 (3%)	15 (16.2%)	*0.0001*
Graft Survival (5 years)	> 80%	60%	< 20%	*< 0.0001*
	No routine graft treatment needed	Graft optimization suggested	Not without graft optimization	

Clinical Liver Biomarkers and molecular changes

OS301 RESULTS OF LITMUS (NCT 02541916): THE LIVER IMMUNE TOLERANCE BIOMARKER UTILIZATION STUDY

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Background: We have reported a novel biomarker gene set for the identification of tolerance in murine models of rapamycin-induced cardiac tolerance and spontaneous hepatic tolerance. GeXP multiplex RT-PCR was used to amplify 22 prominent immunoregulatory genes, in cardiac and liver grafts, that correlated with the pathological and biochemical parameters of transplanted organs. Subsequently, an eight gene expression panel, consisting of the increased expression of 6 immunoregulatory genes and the decreased expression of 2 pro-inflammatory genes, was found to have specificity and sensitivity.
Methods: In this Phase 2A single center study, we examined whether an eight-target and 5 housekeeping gene expression panel (panel) in the peripheral blood mononuclear cells (PBMC) identified operationally tolerant liver transplant recipients. We first measured the panel in PBMC from 54 adult liver transplant recipients who were a minimum of 3 months post transplant and who had no evidence of rejection. Patients with the tolerant gene profile were weaned off immunosuppression (IS) to confirm that the gene profile identified tolerance.
Results: Of the 54 patients studied, 16 had the tolerance gene profile in their PBMC. Age, gender, indication for transplant, and CNI choice did not correlate with having the tolerant profile (Table). 12 patients agreed to enter the withdrawal phase of the study. Prior to withdrawal, a liver biopsy was performed and 2 patients were excluded as their biopsies showed recurrent autoimmune disease and rejection Of the 10 remaining patients 6 have now been weaned off of IS; 3 are undergoing withdrawal and 1 developed acute cellular rejection which was easily reversed.
Conclusion: These data suggest that the immune tolerance profile identified in preclinical models expressed both by PBMC and the liver may have specificity and sensitivity to identify operationally tolerant recipients allowing for withdrawal of IS.

	Tolerant Profile Positive (n = 16)	Tolerant Profile Negative (n = 38)	p Value
Age (years)	55 ± 18.4	51.4 ± 11.3	0.124
Gender			
Male	9	25	0.507
Female	7	13	
Diagnosis			
Alagille Syndrome	1		
Alcoholic Cirrhosis	1	11	
Autoimmune Hepatitis	1	1	
Biliary Atresia	1		
Budd-Chiari	1		
Cirrhosis, unknown		1	
Fulminant Hepatic Failure		1	
Hepatitis, unknown	1		
Hepatitis B	1	8	
Hepatitis C	5	9	
Malignancy	1		
Maple Syrup Urine Disease		1	
NASH	2	2	
Primary Biliary Cirrhosis	1	2	
Sickle Cell		1	
Wilson's Disease		1	
Time from Transplant (mos)	101.1 ± 83.4	92.6 ± 61.5	0.68
Transplant Type			
Living Donor	4	5	0.286
Deceased Donor	12	33	
CNI			
CsA	4	12	0.629
Tac	12	26	

Clinical Kidney Biomarkers and molecular changes

OS302 IDENTIFICATION OF ANTIBODY-MEDIATED REJECTION AFTER KIDNEY TRANSPLANTATION BY SPECIFIC MICRORNAS

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Background: Antibody-mediated rejection (ABMR) is the major cause for allograft failure, since a curative therapy is lacking and challenges in ABMR diagnosis still exist. The identification of specific microRNAs as biomarkers might reduce these crucial problems after kidney transplantation.
Methods/Materials: Total RNA from blood cells of 6 ABMR patients, of 6 matched patients with stable graft function (SGF) and of 4 patients with T-cell mediated rejection (TCMR) was isolated. The small RNA fraction was isolated and libraries were prepared for single end sequencing with 50 bp by HiSeq2500 Illumina Next Generation Sequencing Device. Raw data was mapped by the miRDeep2.0.0.8 algorithm script to detect the expression of microRNAs. Differentially expressed microRNAs were determined with deseq2 using the Wald test (p value<=0.05; fold change>=1.5). The identified candidates were validated with RT-PCR in patients with SGF (n = 56), UTI (n = 18), Banff3-BL (n = 24), Banff4-TCMR I (n = 21), Banff4-TCMR II/III (n = 27), Banff2-ABMR (n = 21) and IFTA (n = 30).
Results: From 301 detected microRNAs, 61 were differentially expressed between the three patient cohorts. The expression of 31 microRNAs distinguished ABMR from SGF, 18 differentiated ABMR from TCMR. Two microRNAs discriminated ABMR from SGF and from TCMR. 32 microRNAs were differentially expressed between SGF and TCMR, whereas 11 of these differentiated SGF from ABMR and TCMR. Eight specific microRNAs distinguished TCMR from ABMR and SGF. Ultimately the expression of 1 microRNA discriminated all three patient groups from each other. The differential expression of several promising candidate microRNAs could be confirmed by RT-PCR in patients with different pathologies.
Conclusion: The identification of ABMR specific microRNAs in blood allows the evaluation of these potentially diagnostic markers in studies including high numbers of patients with different etiologies like TCMR, infections and IFTA after kidney transplantation.

Translational Kidney Biomarkers and molecular changes

OS303 FP7 BIOMARGIN SHOWS THAT SMALL SETS OF URINARY PEPTIDES ARE GOOD BIOMARKERS OF ACUTE KIDNEY GRAFT REJECTION

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Background: FP7 Biomargin aimed at detecting and validating non-invasive biomarkers of kidney graft lesions. After untargeted screening of different – omics, candidate biomarkers were confirmed in independent patient groups, and their diagnostic performance evaluated in a larger trans-sectional study. All studies were approved by ethics committees, complied with the Helsinki declaration amended in 2008, and patients provided informed consent.

Methods/Materials: Urine samples were collected just before protocol or for-cause biopsies following a standardized procedure, and then retrospectively selected following a case-control (discovery and validation sets) or a trans-sectional (performance assessment) design.

For the first two steps, untargeted screening of natural urine peptides was performed using nano-liquid chromatography – high resolution QTOF mass spectrometry, while targeted micro-LC-QTOF was used for the third. Biomarker candidates were selected if they were significantly associated ($p < 0.05$ after FDR correction) with one of the 4 groups (normal, AbMR, TCMR or IF/TA), as assigned after centralized histological reading by expert pathologists, and had an AUC under the ROC curve >0.6. Finally, the most pertinent combinations of peptides were selected using SPLS-DA.

Sample Distribution:

	AbMR	TCMR	IF/TA	Normal	Others
Discovery set (n = 133)	34	42	49	37	0
Confirmation set (n = 128)	31	25	51	43	0
Trans-sectional study (n = 399)	43	20	116	225	40

Results: 343 natural urinary peptides were identified. A combination of 6 showed the highest diagnostic performance with respect to AbMR in the discovery set, and yielded AUCROC=0.862 and 0.787 in the independent confirmation set and trans-sectional study, resp. Another set of 12 peptides was able to best discriminate patients with TCMR, with AUCROC=0.822 and 0.807, resp. No efficient signature was found for IFTA.
Conclusion: We identified and validated very efficient urine peptide signatures of TCMR and AbMR. Their predictive performance is now being tested in BECS, the BIOMARGIN European prospective Cohort Study.

Clinical Kidney Biomarkers and molecular changes

OS304 REGULATORY T CELLS POPULATION AND GENE EXPRESSION EARLY AFTER TRANSPLANTATION INFLUENCES 1-YEAR KIDNEY TRANSPLANT OUTCOME

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We assessed T cell subsets (including Tregs and CD3 + CD8 + CD28- cells) and related gene expression in peripheral blood of prospectively included kidney transplant recipients (KTx) during the first year after Tx, as well as in long-term stable allograft recipients to find phenotypic and/or expression pattern prognostic of the kidney transplant outcome.
Material and Methods: The prospective analysis was performed in 36 KTx recipients followed for a year since transplantation (examined at 1st week, 1st, 3rd, 6th, 12th month) and in 21 long-term KTx recipients, compared to 18 healthy volunteers and 21 hemodialysis patients. The research involved flow cytometry assessment of T lymphocyte subpopulations and PBMC gene expression analysis of CD4, CD8, CTLA4, GZMB, FOXP3, IL10, IL4, ILR2A, NOTCH, PDCD1, PRF1, TGFB, TNFA genes on a custom designed low density array (TaqMan).
Results: Natural Tregs count at 1st month correlated positively with allograft function at all time-points (GFR 1st month: $r = 0.58$, $p < 0.001$, 3rd month $r = 0.45$, $p = 0.008$, 6th month $r = 0.42$, $p = 0.018$, 12th month $r = 0.48$, $p = 0.007$). The absolute Treg count at 3rd month correlated positively with 12th month allograft function (12th month GFR $r = 0.38$, $p = 0.035$).

FOXP3 1st month gene expression positively correlated with graft function in the 1st month ($r = 0.42$. $p = 0.012$), 3rd month ($r = 0.44$. $p = 0.008$), 6th month ($r = 0.52$, $p = 0.002$).

CD3 + CD8 + CD28- cells correlated with CD8, GZMB and PRF expression suggesting their cytotoxic properties (3rd month CD3 + CD8 + CD28-/ul: CD8 $r = 0.65$, $p < 0.001$; GZM $r = 0.35$, $p = 0.039$; PRF $r = 0.38$, $p = 0.023$).
Conclusion: The size of Treg population and regulatory FOXP3 gene expression in the early period after transplantation influences 1-year kidney transplant outcome and may be regarded as a useful diagnostic test in prediction of subsequent allograft function.

Translational Kidney Biomarkers and molecular changes

OS305 FP7 BIOMARGIN: URINARY PROTEIN BIOMARKERS OF RENAL GRAFT INJURIES IN KIDNEY ALLOGRAFT RECIPIENTS

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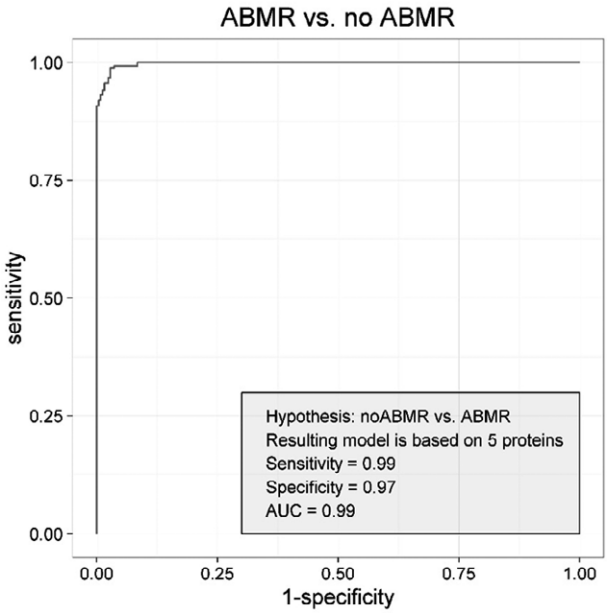
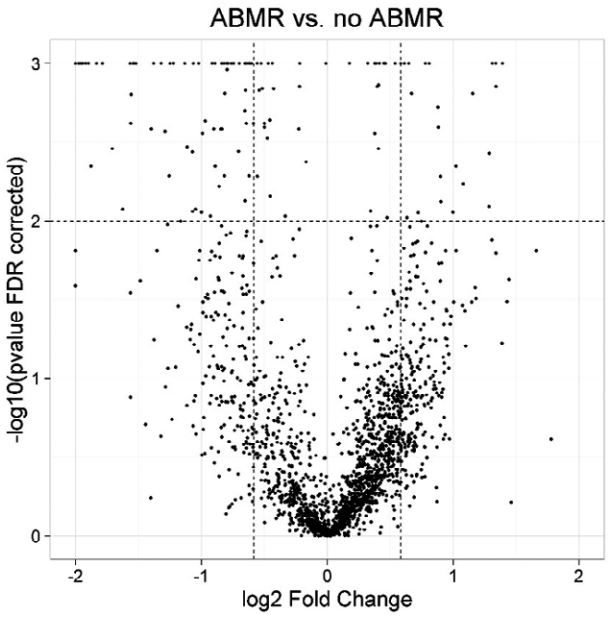
Background: In renal allograft recipients, histological examination of graft biopsies is the gold standard to confirm graft injuries, but biopsies are invasive and histological grading is not very robust. There is thus a need for robust, non-invasive methods to predict and diagnose acute and chronic graft lesions. The goal of the presented research is to discover urine biomarkers with good diagnostic performance for graft injuries.





Methods/Materials: In the discovery step, 245 urine samples with matched kidney allograft biopsies were analyzed from patients with different renal graft conditions (normal biopsy controls (NL), antibody-mediated rejection (ABMR), Interstitial Fibrosis/Tubular Atrophy (IFTA) and T-cell mediated acute rejection (TCMR)) using LC-MS²-based proteomics. Using in-house developed software, all missing peptide intensities in all samples were looked up in the MS1 data layer and verified using a decoy search. Five different hypotheses were tested using multivariate analysis. The FDR-corrected p-value was set <0.001 and the fold change (before log transformation) at least at 2. The generated model was first internally cross-validated. In a next validation step, 200 additional, independent samples were analyzed using the same proteomic pipeline.
Results: For every tested hypothesis, the statistically significant proteins were filtered by a Gene Ontology Analysis and a final model was generated based on a list of statistically & biologically relevant proteins that can classify patients based on the local and central biopsy reading. Unsupervised statistical models were used to check for outliers, due to errors in biopsy readings, to improve the models. Especially for the hypothesis no ABMR vs ABMR we have promising results (see figure 1 and 2). All models will be validated in an independent data set of 200 patients.
Conclusion: The generated models can help clinicians to improve patient treatment and long term graft survival.

OS306 USE OF PERIRENAL ADIPOSE TISSUE AS A NON-INVASIVE SOURCE OF DONOR ENDOTHELIAL CELLS ALLOWING MONITORING OF DELETERIOUS ALLOIMMUNE RESPONSES AFTER KIDNEY TRANSPLANTATION

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Background: Living donation and use of kidney from expanded-criteria donors (ECDs) is a perspective to overcome organ shortage. Donor-related comorbidity factors are known to affect graft survival. Our working hypothesis was that the perirenal adipose tissue (PR-AT), a surgical waste, can be a relevant source of donor-derived cells allowing assessment of kidney allograft endothelial « quality » and immunogenicity.
Methods/Materials: Perirenal (PR) adipose tissue was obtained from 23 kidney donors (7 living donors and 16 Multi Organ Retrieval donors with various comorbidities factors). Tissue slicing and collagenase digestion allowed isolation of the Stromal Vascular Fraction (PR-SVF). Multiparameter flow cytometry was used to characterize the PR-SVF CD45- CD34 + CD146 + endothelial cell compartment. CD144 + endothelial cells were purified from PR-SVF and expanded after cell culture. The PR-AT derived endothelial cells were tested for their capacity to bind transplant recipient circulating alloantibodies and evaluated in a cross match assay of alloantibody activity resulting from FcR-driven antibody dependent NK cell cytotoxicity (ADCC).
Results: The distribution of the endothelial cell subset within the PR-SVF (median 5.3%) was shown to be comparable in living and deceased donors. Endothelial cell surface expression of CD31 and CD144 endothelial markers tends to be higher in PR-SVF of ECD donors when compared to non-ECDs or living donors. We provide evidence that endothelial cells isolated from donor perirenal adipose tissue can be used as targets to evaluate the binding and cytotoxic alloreactive potential of donor specific antibodies (DSA) found in the serum of sensitized recipients.
Conclusion: We validated the feasibility of obtaining donor specific endothelial cells from the perirenal adipose tissue and provide evidence that such cells can be used in the individualized assay of donor-related factors that may further associate to allograft vasculopathy.

OS307 INCLUSION OF CD8 MONITORING IMPROVES THE PROGNOSTIC CAPACITIES OF THE KIDNEY TRANSPLANT FAILURE SCORE

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Background: Beside the classical monitoring of kidney graft function using serum creatinine or proteinuria levels, the assessment of other non-invasive biomarkers has been proposed to identify patients at-risk of kidney rejection. To reach a true clinical utility, the prognostic capacities of a biomarker have to be higher than other available metrics such as clinical-based scoring system. We have previously shown that an increase in terminally differentiated effector memory (TEMRA) CD8 T cells is associated with a 2-fold higher risk of long-term graft dysfunction. In this study, we evaluate if the monitoring of CD8-related biomarkers could improve the prognostic capacities of a clinical-based scoring system (Kidney Transplant Failure Score; KTFS).
Methods: 286 kidney-transplant recipients have been prospectively enrolled and followed for more than 8 years. At the end of the follow-up time, 51 patients returned to dialysis. Targeted analysis of 22 CD8 T cell subsets have been performed on blood samples retrieved 12 months post-transplantation.
Results: The frequency of effector memory (EM) and TEMRA CD8 measured at one year post-transplantation is correlated with the risk to return in dialysis during the 8 years follow-up. Moreover, we show that the prognostic capacity of the KTFS can be improved by the inclusion of the CD8 markers as the AUC of the biomarker-updated KTFS is 0.75 as compared to 0.71 a single predictor. Finally, when clinical based KTFS was used as inclusion criteria, we demonstrate that the use of one-year frequency of TEMRA CD8 allows the discrimination of patients that will lose their graft from those that will maintain stable graft function.
Conclusion: The combination of CD8-related biomarkers with clinical-parameters based KTFS allows to better predict patients at-risk of kidney graft failure and to target those with a more specific immunologic risk. Such score, after further validation on large external cohorts, could be us.

OS308 ACTIVATED NATURAL KILLER CELL TRANSCRIPTS PREDICT GRAFT OUTCOME IN KIDNEY TRANSPLANTATION: THE BIOMARGIN STUDY

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Background: Immune cells have been implicated in the graft failure after kidney transplantation. However, the best therapeutic target(s) among immune cells subtypes have been not identified yet. We aimed therefore to identify which immune cell subtypes possess the highest prognostic value for graft failure.
Methods: We recently described the role of activated NK cell transcripts in ABMR diagnosis and activity in BOMARGIN. Here, we applied an innovative deconvolution algorithm to estimate the relative fraction of immune cells subsets, using RNA transcripts expression of 547 genes in a dataset of 282 indication biopsy samples. These estimates were corrected for the global inflammation in each biopsy.
Results: Analysis of estimated immune cells subsets infiltration, based on deconvolution of transcriptomic data, showed that activated NK cells have the highest discriminative power in predicting graft failure at both 1 and 2 years post-biopsy in all biopsies; irrespective of rejection (AUC = 0.74; $p < 0.0001$ and AUC = 0.67; $p = 0.0006$, respectively), and within biopsies with rejection (AUC = 0.79 ($p = 0.002$) and AUC = 0.68 ($p = 0.03$), respectively). Cox proportional hazard analyses confirmed that activated NK cells were the cell type most robustly associated with graft failure (HR 3.60; $p < 0.0001$), especially in biopsies with acute rejection (HR 3.89; $p = 0.002$). We then evaluated individual NK cell transcripts expression in relation to graft failure. Using both the differentially expressed genes from the deconvolution algorithm and a literature-based NK-cell related transcript set, the prognostic performance of individual activated NK cell genes for post-biopsy kidney allograft failure was confirmed.
Conclusion: These findings, in addition the emerging role of NK cells infiltration in ABMR diagnosis and activity, offer promising new avenues for development of NK-cell targeted prognostic biomarkers and therapeutic strategies to prevent or attenuate graft failure.

OS309 ISCHAEMIA-INDUCED DNA HYPERMETHYLATION PREDICTS CHRONIC ALLOGRAFT INJURY IN KIDNEY TRANSPLANTATION: AN EPIGENOME-WIDE ASSOCIATION STUDY ACROSS MULTIPLE COHORTS

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Background: Ischaemia during kidney transplantation is a major cause of chronic allograft injury and adversely impacts outcome. We investigated whether DNA methylation underlies ischaemia-induced chronic allograft injury.
Methods: We profiled DNA methylation across >450 000 genome-wide CpG sites using 3 cohorts of brain-dead donor kidney allograft biopsies: a longitudinal cohort with paired biopsies at procurement ($n = 13$), after implantation and reperfusion ($n = 13$), and at 3 or 12 months after transplantation ($n = 5$ for both); a cohort with pre-implantation biopsies after cold ischaemia ($n = 82$); and a cohort with post-reperfusion biopsies ($n = 46$). Chronic allograft

injury was defined by a Chronic Allograft Damage Index (CADI) score >2 at 1 year after transplantation.
Results: DNA methylation levels of kidney allografts increased after ischaemia in the longitudinal cohort ($p < 0.001$). These changes were not transient, as DNA methylation was still increased up to 1 year after transplantation. In the pre-implantation cohort, longer cold ischaemia time directly correlated with the extent of DNA hypermethylation ($p < 0.001$). Hypermethylation preferentially affected genes involved in suppression of kidney injury and fibrosis. Based on the 66 CpG islands hypermethylated by ischaemia in both cohorts at FDR<0.05, a methylation risk score was developed, which in pre-implantation kidney biopsies predicted chronic injury at 1 year after transplantation (AUC 0.92). Of all 6 CADI score lesions, the score was highest for fibrosis and glomerulosclerosis. Independent validation in post-reperfusion biopsies confirmed that the methylation risk score predicted chronic injury, while outperforming baseline clinical variables (AUC 0.78 vs. 0.69), and also correlated with reduced allograft function at 1 year after transplantation in both cohorts ($p = 0.03$; $p = 0.009$).
Conclusion: Our results indicate a novel, epigenetic mechanism underlying ischaemia-induced chronic injury in kidney transplantation.

Translational Kidney Biomarkers and molecular changes

OS310 CELL-FREE DONOR DNA CIRCULATING IN RECIPIENT PLASMA: INDEL-POLYMORPHISMS AS NON-INVASIVE MARKER FOR ACUTE REJECTION IN KIDNEY TRANSPLANTATION

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Background: Donor-derived cell-free DNA (cf-DNA) can be found in the recipient's plasma following solid organ transplantation. In previous studies higher levels of donor-specific DNA were associated with acute rejection (AR). These studies were based on the detection of either Y-chromosomal cf-DNA in female recipients receiving male grafts, single nucleotide polymorphisms or HLA-specific molecular techniques. In this study, we investigated the usefulness of insertion-/deletion (indel) polymorphisms as non-invasive markers for AR.
Methods: Pre-transplant nucleic DNA of 20 donor/recipient pairs (8 with AR/12 without AR) was screened for informative indel markers (recipient negative/donor positive). The level of donor-derived DNA in the recipient's plasma was investigated in parallel to routine renal biopsies taken for diagnosis of potential AR between postoperative days 6–39 (mean 11.4). Informative indel markers were used for relative quantification of donor-derived cf-DNA in quantitative real-time PCR. The comparative Ct (cycle threshold) method was used to calculate the relative amount of donor-specific cf-DNA.
Results: The percentages of donor-derived cf-DNA in plasma differed significantly between recipients with and without biopsy-proven AR ($p = 0.010$; Mann–Whitney-*U*-Test). The cut-off values of 2% and 3% both resulted in a sensitivity of 0.88 and a specificity of 0.75 and 0.83, respectively (Table 1).
Conclusion: Our results demonstrate a high sensitivity and specificity using the relative quantification of donor-derived cf-DNA in recipient plasma for the diagnosis of AR. Therefore, we could identify donor-derived cf-DNA as a promising non-invasive marker for AR after kidney transplantation with the high potential to reduce the number of invasive postoperative biopsies.

cfDNA /AR by biopsy	+/+	+/–	–/+	–/–	total	PPV	NPV	Sensitivity	Specificity	Accuracy
Cut-off value 2%	7	3	1	9	20	0.70	0.90	0.88	0.75	0.80
Cut-off value 3%	7	2	1	10	20	0.78	0.91	0.88	0.83	0.85

Translational Kidney Rejection

OS311 CIRCULATING DONOR-SPECIFIC MEMORY B CELLS (MBC) DISCRIMINATES KIDNEY TRANSPLANT PATIENTS WITH HISTOLOGICAL LESIONS OF ABMR IN ABSENCE OF CIRCULATING DSA

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The diagnosis of chronic (c) ABMR requires both specific histological lesions and detection of donor-specific alloantibodies (DSA). However, a significant number of patients showing such lesions do not display detectable DSA. Importantly, circulating donor-specific (d-sp) memory B cells (mBC) may exist regardless the presence of DSA and be associated to ABMR after kidney transplantation (KT).
Methods: Cross-sectional analysis of 108 KT patients with different histological phenotypes following the Banff score classification: (i) aABMR with DSA ($n = 16$), (ii) cABMR with DSA ($n = 36$), (iii) cABMR without DSA ($n = 35$), (iv) IFTA lesions without inflammation and no DSA ($n = 8$) and (v) normal parenchyma (STA) ($n = 13$); assessment of d-sp mBc frequencies using an HLA-sp B-cell ELISPOT assay were investigated.
Results: While all STA and all but 2 IFTA patients did not show detectable alloreactive d-sp mBC frequencies, 54.5% of cABMR with DSA and 48.3% cABMR without DSA displayed circulating alloreactive d-sp mBC with similarly high mBC frequencies (0.23 ± 0.28 and 0.18 ± 0.21, respectively, $p = NS$), although lower than aABMR patients (0.38 ± 0.20 $p = 0.036$ and $p = 0.003$, respectively). Supernatants of stimulated mBC cultures in cABMR patients illustrated the lower Ab production of mBC as compared to aABMR individuals, strengthen by the higher detection sensitivity of the B–cell ELISPOT assay. All cABMR and aABMR patients showed similar APRIL and BAFF levels than STA and IFTA patients. Anti-donor TFH cell function as well as numbers of different B-cell subsets were not different between groups. Of note, PTC and C4d histological scores, as well as MFIs of detectable DSAs positively correlated with d-sp mBC frequencies ($r = 0.255$, $p = 0.031$; $r = 0.252$, $p = 0.021$; $r = 0.429$, $p < 0.001$, respectively).
Conclusion: Assessment of circulating mBC frequencies discriminates the immune effector mechanism of different chronic kidney allograft injuries, potentially guiding treatment decision-making.

OS312 LEVELS OF SERUM AND URINARY CXCL10 PREDICT FOR ACUTE REJECTION IN KIDNEY TRANSPLANTATION

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Background: he early diagnosis of acute rejection is crucial for graft survival after kidney transplantation. The aim of the study was to evaluate the prognostic value of serum and urinary levels of CXCL10 for predicting the onset of acute rejection and graft outcome.
Methods/Material: In the study, 65 living related donor kidney transplant recipients were included. Serum and urinary samples were collected pre-operatively, on post-operative days 1, 7, and 30, and 3 months after transplantation. Levels of serum and urinary CXCL10 were assayed for chemokine content using and enzyme-linked immunosorbent assay (ELISA). Clinical variables including rejection episodes and kidney function were monitored. Receiver operator characteristic (ROC) analysis was performed to determine their sensitivity and specificity, defined here as area under the curve (AUC).
Results: 9 patients (9/65 (13.8%)) had biopsy proven rejection during the follow-up period. Preoperative serum and urinary levels of CXCL10 were not differ the acute rejection group and non-acute rejection group. ($p = 0.149$). Serum levels of CXCL10 in acute rejection group were higher than non-acute rejection group on postoperative days 1 and 7 (149.26 ± 99.26 ng/ml; 62.40 ± 22.80 ng/ml and 153.84 ± 113.74 ng/ml; 75.16 ± 27.20 ng/ml respectively) ($p = 0.031$; $p = 0.021$) and resulted in an AUC of 0.92 and 0.87 respectively. At the same time, urinary levels of CXCL10 in acute rejection group were higher than levels observed for non-acute rejection group on

postoperative days 1 and 7 (148.55 ± 76.66 ng/ml; 65.58 ± 26.10 ng/ml and 138.21 ± 48.89; 72.16 ± 21.51 ng/ml respectively) ($p = 0.049$; $p = 0.003$) and resulted in an AUC of 0.90 and 0.92 respectively.
Conclusion: Monitoring of serum and urinary CXCL10 levels may be a useful for detection in acute rejection in kidney transplant recipients. Early detection of acute rejection by non-invasive method may be helpful for allograft survival.

Clinical Kidney Rejection

OS313 TREATMENT OF CHRONIC ANTIBODY MEDIATED REJECTION WITH INTRAVENOUS IMMUNOGLOBULINS AND RITUXIMAB: A MULTICENTRE, PROSPECTIVE, RANDOMIZED, DOUBLE BLIND CLINICAL TRIAL

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Background: Despite chronic antibody mediated rejection (ABMR) is a main cause for graft failure, there are no approved treatments. We conducted a multicentre, prospective, randomized, placebo-controlled, double blind clinical trial to evaluate efficacy and safety of intravenous immunoglobulins (IVIG) combined with Rituximab (RTX) (EudraCT 2010-023746-67).
Patients and methods: Patients with chronic ABMR defined as the presence of transplant glomerulopathy and anti-HLA donor-specific antibodies (DSA) were eligible. Patients with estimated glomerular filtration rate (eGFR) < 20 ml/min/1.73 m^2 and/or severe interstitial fibrosis/tubular atrophy were excluded. Patients were randomized to receive IVIG (4 doses of 0.5 g/kg every 3 weeks) and RTX (one single dose of 375 mg/m^2) or a wrapped isovolumetric saline infusion. Primary efficacy variable was the decline of eGFR at one year. Secondary efficacy variables included evolution of proteinuria, renal lesions and DSA at one year.
Results: Between March 2013 and November 2015, twenty-five patients were randomized (13 to the treatment group and 12 to the placebo group). There were no differences between the treatment and placebo groups in eGFR decline (−4.2 ± 14.4 vs. −6.6 ± 12.0 ml/min/1.73 m^2, p-value = 0.475), increase of proteinuria (+0.9 ± 2.1 vs. +0.9 ± 2.1 g/day, p-value = 0.378), Banff scores at one year and MFI of the immunodominant DSA. One patient in each group experienced graft loss. Safety was similar between groups.
Conclusion: Despite the recruited number of patients was lower than planned, our data suggest that the combination of IVIG and RTX is not useful in patients displaying transplant glomerulopathy and DSA.

OS314 IMPACT OF COMPLEMENT COMPONENT 3 SINGLE NUCLEAR POLYMORPHISMS ON RENAL TRANSPLANT RECIPIENTS WITH ANTIBODY-MEDIATED REJECTION

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Background: Antibody-mediated rejection (ABMR) is an important risk of allograft dysfunction in kidney transplantation. The complement 3 (C3) is considered to be associated with the generation of alloreactive antibodies and donor-specific antibodies. However, the association of C3 single nuclear polymorphisms (SNPs) with ABMR still remained unclear.
Methods: Blood samples of 199 renal transplant recipients containing 68 with ABMR and 131 with stable graft function were collected, and analyzed by next-generation sequencing with an established gene panel. High quality readout was obtained in 15 SNPs.
Results: After being adjusted with age, sex and immunosuppressive protocols, rs10411506 and rs2230205 were found to be significantly associated with ABMR in dominant model (rs10411506: OR = 2.73, 95% CIs: 1.16, 6.68, p = 0.028; rs2230205: OR = 2.52, 95% CIs: 1.07, 5.92, p = 0.034); rs10411506, rs2230205 and rs2230201 were found statistically different in HET model (rs10411506: OR = 3.05, 95% CIs: 1.22, 7.64, p = 0.017; rs2230205: OR = 2.90, 95% CIs: 1.20, 7.00, p = 0.018; rs2230201: OR = 2.41, 95% CIs: 1.03, 5.64, p = 0.042). The linkage analysis showed relatively low linkage disequilibrium among these SNPs.
Conclusions: Our study firstly identified the two SNPs (rs10411506 and rs2230205) in C3 gene were significantly correlated with ABMR in kidney transplantation. These findings may have implications for the diagnosis and prevention of ABMR.

OS315 BIOLOGICAL INTERPLAY BETWEEN CIRCULATING HLA-SP ALLOREACTIVE MEMORY B-CELLS AND LONG-LIVED PLASMA CELLS IN KIDNEY TRANSPLANT PATIENTS UNDERGOING CHRONIC ABMR

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Alloreactive humoral responses are one of the main causes of graft injury in kidney transplantation. Different biological compartments are involved in generation and maintenance of humoral alloreactivity through different B-cell subsets, showing a close interplay between them in order to orchestrate allograft rejection.
Methods: We investigated frequencies of HLA-specific (HLA-sp) memory B cells (mBc) both in peripheral blood (PB) and in bone marrow (BM) as well as Long Lived plasma cells (LLPC) residing in BM in a group of healthy individuals ($n = 6$), in highly sensitized patients in waiting list ($n = 3$) and in kidney transplant patients showing chronic humoral rejection (cABMR) with ($n = 4$) or without circulating DSA ($n = 8$). Comparison of HLA-sp mBc responses and HLA-sp Ab repertoire from sera or mBc cultures were investigated using a HLA B-cell ELISPOT assay and Luminex® platform, respectively.
Results: HLA-sp LLPC (CD138 +) responses from BM and circulating mBc frequencies were detectable in an important proportion of patients. All highly sensitized patients showed HLA-sp responses from both compartments. Most patients showed circulating HLA-sp mBc frequencies, regardless detectable circulating DSA. All cABMR patients without detectable DSA showed HLA-sp mBc frequencies in periphery. Conversely, cABMR patients with detectable DSA displayed HLA-sp frequencies from either circulating mBc or LLPC. Through a 6 days polyclonal stimulation within the CD138- fraction of BM, an ASC-like phenotype (CD20lowCD27-CD38 + +IgD-) appeared in some patients showing the same HLA-sp repertoire than that observed in PB, suggesting a replenishment mechanism between both compartments.
Conclusion: Different functional B-cell subsets residing in different compartments seem to be responsible for production and maintenance of circulating HLA-sp Ab detected in sera thus, having key implications regarding treatment decision-making in kidney transplant patients developing chronic ABMR.

Translational Kidney Rejection

OS316 COMPLEMENT-ACTIVATING ANTI-HLA ANTIBODIES: IDENTIFICATION OF SPECIFIC HISTO-MOLECULAR PHENOTYPE OF REJECTION FOR COMPLEMENT-TARGETING THERAPY

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We investigated whether circulating complement-activating donor-specific anti-HLA antibodies (DSA) induce specific rejection phenotype and influence response to complement-targeting treatment.

We prospectively enrolled 931 kidney recipients transplanted between 2011 and 2014, with systematic screening for circulating DSA in the first year post-transplantation. All patients underwent allograft biopsy at the time post-transplant DSA detection. The allograft rejection phenotypes were assessed by histopathology, immunochemistry and allograft gene expression (microarray). A model of fully MHC-mismatched male CBA (H-2k) kidneys transplanted into B6.RAG1−/− (H-2b) immunodeficient mice with adoptive transfer of complement and non-complement-activating DSA was studied. The effect of complement inhibition therapy (Eculizumab) on allograft injury phenotype was assessed in two prospective studies ($n = 116$).

The histo-molecular phenotype of C1q-binding DSA allograft rejection ($n = 44$) was characterized by increased microvascular infiltration by NK cells ($p < 0.001$), monocyte/macrophages ($p < 0.001$), greater prevalence of complement deposition ($p < 0.001$), and selective changes in gene expression including interferon-gamma and endothelial activation (CXCL11, CCL4, MS4A6A, MS4A7, GBP1; $p < 0.01$) as compared with patients with non-C1q-binding DSA ($n = 113$). This phenotype was distinct from that of patients with non-C1q-binding DSA and without DSA in unsupervised principal component analysis. Mice receiving complement-binding DSA reproduced the human complement-activating antibody-mediated histo-molecular rejection phenotype. Eculizumab specifically abrogated the histo-molecular phenotype induced by C1q-binding DSAs and showed no effect on allograft injury in patients with non-C1q-binding DSA.

Circulating complement-activating DSA induce a specific histo-molecular phenotype of kidney allograft rejection that can be reversed by complement inhibition.

OS317 IN THE ABSENCE OF HUMORAL ANTIBODY RESPONSES LONGTERM KIDNEY FUNCTION NOT ONLY STABILIZES BUT IMPROVES

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Background: While deterioration of long-term graft function due to insufficient control of humoral immune responses is a major focus of current research the typical evolution of kidney function in the patients without humoral immune activation is not well described. In the present longitudinal observational cohort study we analyzed the course of kidney function in patients stratified to those with a detectable antibody response and those without.
Methods: All kidney transplant patients at the University Hospital of Zurich between January 2006 and February 2015 were included and the course of kidney function was determined by slope of eGFR after CKD-EPI starting from 12 months after transplantation until the last follow up visit (at latest February 2016). Slope of eGFR was compared between patients without development of humoral allograft immune responses and patients with development of donor specific antibodies as determined by Luminex single bead assays, which were performed at least annually.
Results: Patients without humoral allograft immune responses present an improvement of kidney function in the long term follow up as reflected by a positive eGFR slope. Such a continuous improvement of graft function is still present even six years after transplantation, although less pronounced than in the first years after transplantation. In contrast, patients with donor specific antibodies show a decline in kidney function as reflected by a negative eGFR slope.
Conclusion: The kidney allograft, transplanted in a patient without development of humoral allograft immune response as determined by development of donor specific antibodies shows an adaptive hyperfiltration, which is maintained even in the long-term.

Clinical Kidney Immunology

OS318 REFRACTORY ACUTE ABMR: EFFECTIVE TREATMENT BY A NOVEL STRATEGY OF MEMBRANE FILTRATION PLUS IMMUNOADSORPTION FOR CLASSICAL COMPLEMENT INTERFERENCE IN ADDITION TO ANTIBODY DEPLETION

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Background: Apheresis for IgG depletion represents an effective strategy for the prevention and treatment of antibody-mediated rejection (ABMR). We have earlier shown that membrane filtration (MF), added to the circuit of conventional immunoadsorption (IA), may specifically interfere with alloantibody-triggered complement activation, by eliminating C1q, the key component of the classical pathway (CP). Here we report on the effect of combined apheresis in four cases of severe refractory C4d-positive ABMR.
Methods: For IA we used a semiselective double-column device (146-GAM peptide adsorber; 2–3 plasma volumes per session). For combined apheresis, a porous membrane filter (MONET®) was connected to the extracorporeal circuit. ABMR was classified and scored according to the Banff 2013 update.
Results: Four kidney allograft recipients (transplantation between 2014 and 2016; two re-transplants, two female recipients, age 47–71 years, pre-Tx CDC-PRA 0–44%) were transplanted across preformed donor-specific antibodies (DSA, HLA class I and/or II) using a local standard protocol of peri-transplant IA and ATG induction. Despite desensitization, studied patients developed severe acute/active ABMR (g+ptc score: 2–4; TMA in 2 cases) 14 to 17 days after transplantation (two of the patients were dialysis-dependent). Signs of intragraft CP activation (diffuse C4d staining in all four cases) prompted us to add MF to IA treatment. Upon 2–8 combined treatment sessions, recipients showed reversal of rejection, two within the first week. Remarkably, follow-up allograft biopsies showed marked morphological improvement (g+ptc: 0–2, no TMA), with negative C4d staining in three cases. Last serum creatinine 3–20 months post-Tx was 1.42 mg/dl (median; range: 0.97–3.1).
Conclusion: Our findings illustrate that MF as an add-on to IA may be an effective strategy to reverse refractory acute ABMR, presumably as a result of CP interference.

OS319 TREATMENT OF ACTIVE CHRONIC ANTIBODY-MEDIATED REJECTION: DANGEROUS AND USELESS?

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Background: Chronic antibody-mediated rejection (cABMR) and transplant glomerulopathy (TG) are main features associated with long-term graft loss.
Methods/Materials: Sixty-four patients with TG and active cABMR diagnosis between 2006 and 2015 were analyzed retrospectively. Twenty-two patients were treated with Rituximab (RTX) in combination with IVIG and plasmapheresis and two received only RTX; while the others 40 were not treated or only intensified maintenance immunosuppression. The efficacy and safety of the therapy was analyzed.
Results: Treated and untreated patients had similar Charlson comorbidity indexes (CI); however RTX treated patients were younger (43 vs. 53 years, $p = 0.01$). Time on dialysis prior to transplant, glomerular filtrate rate and proteinuria at diagnosis of cABMR were similar in both groups.

At diagnosis acute inflammatory and chronic lesions related with cABMR and TG were similar in both groups (Banff 2013). Only C4d deposition was more frequent in RTX patients ($p < 0.001$). Six patients in the untreated group presented concomitant acute cellular rejection.

The mean dose of RTX was 985.9 ± 351 mg and the mean number of doses was 1.79 ± 0.41. RTX treatment began from 1 to 3 weeks after cABMR diagnosis. Graft survival censoring death was equal in both groups (Log Rank 0.74). At 24 months, 9 and 13 patients lost their grafts in RTX treated and untreated groups, respectively ($p = 0.68$). Infections requiring hospitalization within one year after treatment were more frequent in RTX patients, 0.62 vs. 0.25 infections/patients (OR = 4, $p = 0.012$). Four patients died in the treated group (2 by sepsis). A CI of 3 was associated with more infectious complications in the untreated group ($p = 0.017$), but not in the treated patients ($p = 0.14$).
Conclusion: RTX therapy, alone or in combination with IVIG and plasmapheresis, was not effective in cABMR treatment and was associated with an important increase in serious infectious complications.

OS320 SAFETY AND ACTIVITY OF ANTI-C1S HUMANIZED MONOCLONAL ANTIBODY TNT009 IN LATE ANTIBODY-MEDIATED KIDNEY ALLOGRAFT REJECTION – RESULTS OF A FIRST-IN-HUMAN PHASE 1 TRIAL

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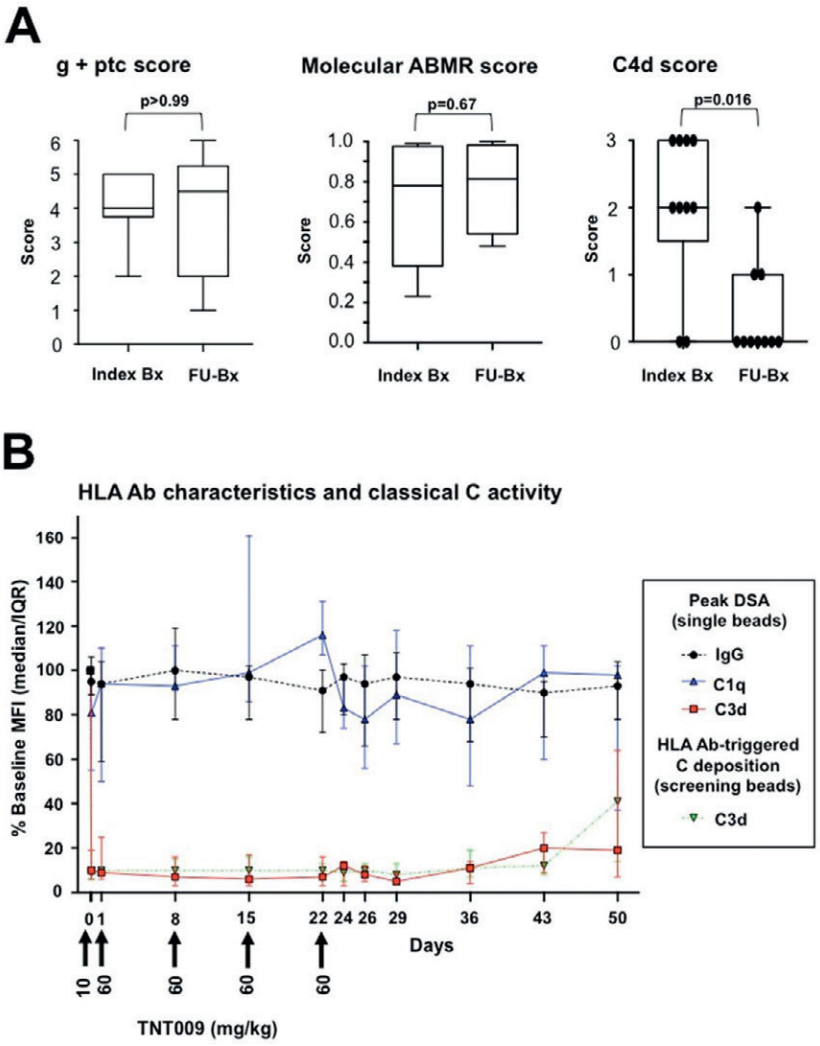
Study purpose: The classical pathway (CP) of complement may significantly contribute to antibody-mediated rejection (ABMR). Blockade of CP key component C1 may be a promising strategy to counteract rejection. In this first-in-human phase 1 trial (NCT02502903), we evaluated the safety and activity of TNT009, a humanized monoclonal antibody against C1s, in late ABMR.
Methods: We enrolled 10 kidney transplant recipients with late ABMR [median time to index biopsy (Bx): 4.3 years]. Major inclusion criteria were (i) an involvement of CP activation (capillary C4d and/or C1q/C3d-fixing DSA), (ii) a g+ptc score $\geq$2, and (iii) a molecular ABMR score $\geq$0.2. Patients received TNT009 (IV) at an initial test dose of 10 followed by 60 mg/kg at 4 weekly doses. After the last infusion, a follow-up (FU) Bx was performed.
Results: TNT009 was well tolerated without SAEs. Median C4d scores decreased from 2 to 0 in FU-Bx ($p = 0.016$), whereby 5 of 8 C4d+ cases turned completely negative (Figure 1A). A limited course of treatment, however, did not affect g+ptc or molecular ABMR scores (Figure 1A). While Ab-triggered solid phase C3d fixation was profoundly inhibited (patient sera as CP source), there was no change in IgG MFI and fixation of recombinant C1q (Figure 1B). Renal parameters did not change during the study period.
Conclusion: We demonstrate that TNT009 is safe and well-tolerated in transplant recipients. This trial shows that TNT009 can effectively prevent intragraft CP activation, and provides a valuable basis for future studies designed to investigate the effect of prolonged C1s blockade in the treatment of ABMR.



OS321 ANTI-HLA ANTIBODY-MEDIATED REJECTION IN ABO-INCOMPATIBLE (ABOI) LIVING DONOR KIDNEY TRANSPLANT (KT) PATIENTS

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Antibody-mediated rejection (AMR) in ABOi KT patients can either be due to donor-specific anti-HLA antibody (DSA) or anti-blood group antibody (anti-ABO). The relative frequency and possible differential clinical features of these two types of AMR in ABOi KT patients has not been investigated.

Among 91 ABOi KT patients between 2007 and 2016 in our center, 11 (12.1%) patients developed clinical acute AMR. Since there is no histologic distinction between DSA- and anti-ABO-induced AMR, we assumed the causative antibody in each case based on anti-ABO level and DSA, measured in serum collected at the time of AMR. DSA was determined by luminex single antigen beads assay.

Of these 11 cases of AMR, 5 were attributable to anti-ABO since anti-ABO titer was 16 or higher and DSA was undetectable at the time of rejection. Three cases were attributable to DSA since DSA was detectable and anti-ABO was low (≤8) during rejection. Another 2 cases with low (2) anti-ABO titer and undetectable DSA were assumed to be DSA-induced, since this low level of anti-ABO is unlikely to cause rejection and DSA can be undetectable in DSA-induced AMR by adsorption of Ab on graft, as frequently seen in ABO-compatible patient. One case with anti-ABO 8 and no detectable DSA was regarded as undetermined. The onset of AMR was within 2 weeks in all cases and comparable between two types of AMR. Initial anti-ABO titer was also not statistically different; median (range) 256 (64-4096) in ABO-AMR and 64 (16–256) in DSA-AMR. All the 5 patients with ABO-AMR had negative PRA before KT, whereas 4 of 5 patients with DSA-AMR had positive PRA before KT, and one DSA-AMR patient had persistent DSA before KT and at the time of AMR. All the AMR were recovered by treatment and no graft was lost to rejection.

We conclude that a significant proportion of AMR in ABOi KT are caused by DSA, and clinical features and possible differential therapeutic approach of these 2 types of AMR needs to be explored by further studies.

OS322 COMPOSITE PROGNOSTIC SCORE IMPROVES CLINICAL BENEFIT IN KIDNEY RECIPIENTS RECEIVING STANDARD OF CARE THERAPY FOR ANTIBODY-MEDIATED REJECTION

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There is a substantial heterogeneity in antibody-mediated rejection (AMR) patients' prognosis after standard of care (SOC) including plasma exchange (PE) and intravenous immunoglobulin (IVIG). We investigated whether the use of a prognostic score in kidney recipients receiving AMR SOC therapy improves clinical-decision making.

We prospectively enrolled 2666 kidney recipients transplanted between 2004 and 2012 and included those diagnosed with active AMR who received standardized treatment with PE (×4) and high-dose IVIG (2 g/kg every 3 weeks ×3). Patients were assessed at diagnosis and 3 months post-treatment for clinical and histological characteristics, and donor-specific anti-HLA antibodies (DSA) by SAB. An AMR prognostic score was derived from the multivariate Cox model for allograft loss. The net clinical benefit of the prognostic score was assessed by decision curve analysis.

We included 284 patients with biopsy-proven active AMR who received SOC treatment. The independent predictors of graft loss were: GFR (HR, 0.93; 95% CI, 0.90–0.95; $p < 0.001$) and presence of IF/TA (HR, 2.44; 1.36–4.37; $p = 0.003$) at AMR diagnosis, and change in GFR (HR, 0.24; 95% CI, 0.16–

0.35; p < 0.001), ptc Banff score (HR, 1.50; 95% CI, 1.16–1.93; p = 0.002) and DSA level after treatment (HR, 1.30; 95% CI, 1.11–1.52; p = 0.001). The AMR prognostic score showed good discrimination (C-statistic, 0.84). Decision-making after AMR SOC based on the prognostic score provided greater net clinical benefit than considering patients on the same risk level. The initiation of a second-line therapy based on the prognostic score would lead to treat 11 patients who will lose their graft in the absence of clinical intervention per 100 patients receiving SOC while not treating patients who will not lose their graft.

The use of an accurate composite prognostic score based on clinical, histological and immunological parameters in kidney recipients receiving SOC therapy for AMR improved clinical decision-making.

OS323 EARLY ANTIBODY-MEDIATED REJECTION C4D STATUS REMAINS A MARKER OF PROGNOSIS IN HLA-INCOMPATIBLE KIDNEY TRANSPLANTATION

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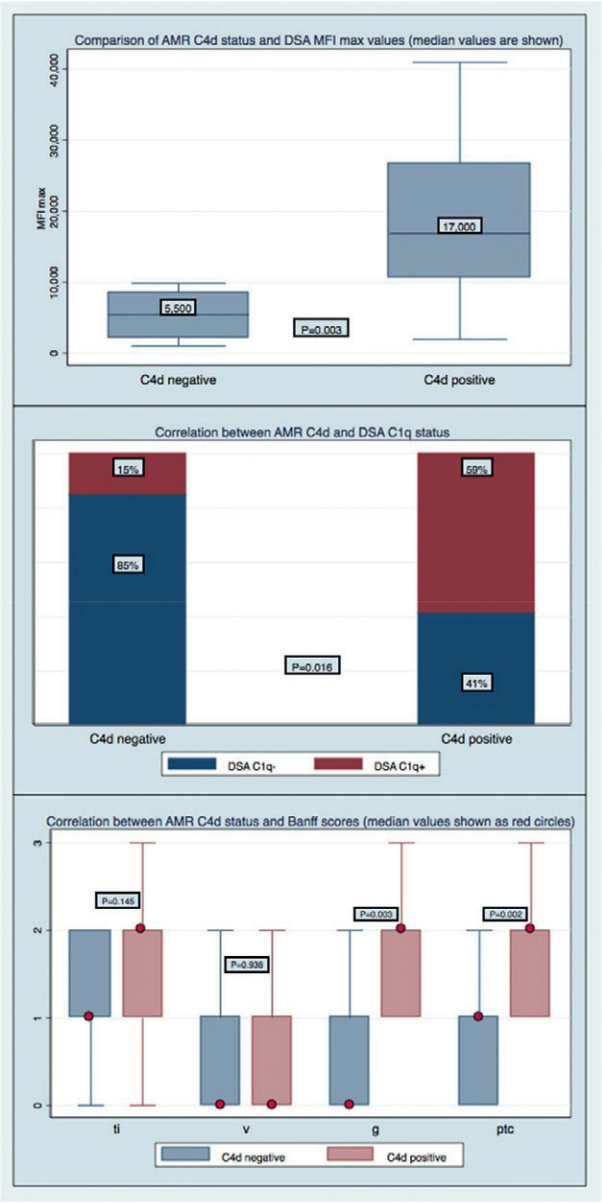
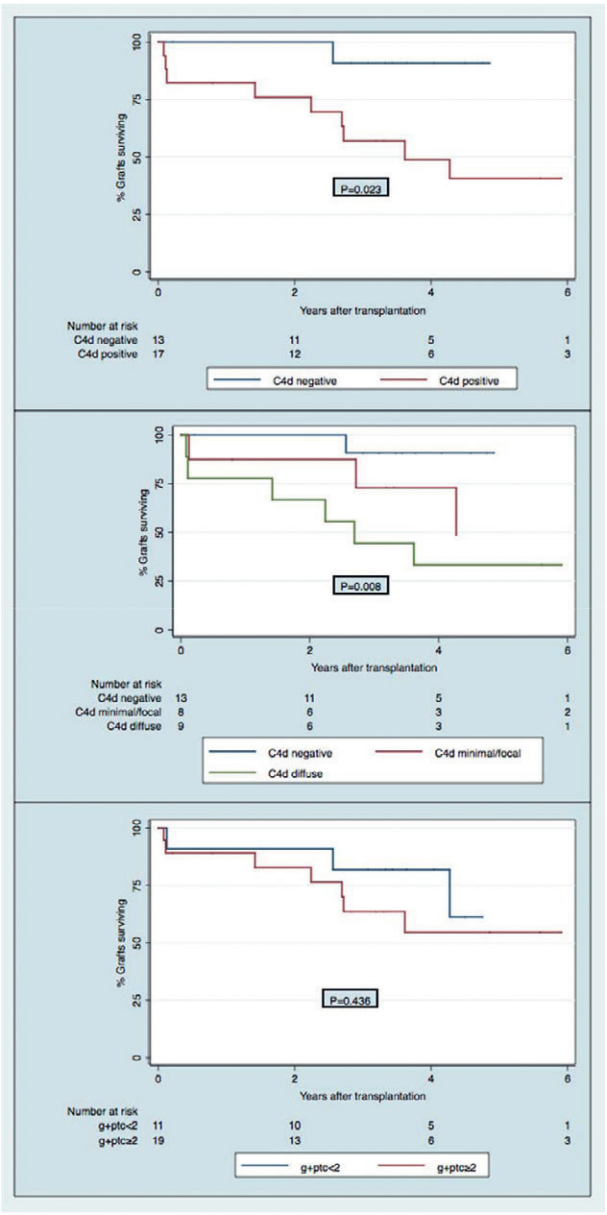
Banff criteria for the diagnosis of antibody-mediated rejection (AMR) in kidney transplantation (KT) was recently updated to include the entity of C4d negative AMR, if moderate microvascular inflammation (MVI, g+ptc≥2) is detectable. Nevertheless, its clinical impact in the setting of early AMR remains unclear.





Thirty recipients experiencing early AMR after HLA-incompatible KT were studied. Median days to AMR: 13 (IQR 9–31). C4d was detected in frozen tissue samples by immunofluorescence. We aimed to analyze the relationship between C4d status, DSA and other histological characteristics. Furthermore, we sought to evaluate the impact of AMR C4d status, C4d and MVI Banff scores in graft survival.

Comparison of clinical characteristics according to AMR C4d status:

	C4d − (*n* = 13)	C4d + (*n* = 17)	p
Previous kidney transplant (%)	39	59	0.269
HLA mismatch, mean	3.92	4.18	0.678
Peak CDC-PRA, median	24	50	0.165
ATG induction, %	69	77	0.698
Pretransplant desensitization with PP+IvIg, %	23	41	0.440
Pretransplant desensitization with PP+IvIg+Rituximab, %	15	29	0.427
DSA I, %	85	71	0.427
DSA II, %	62	77	0.443
DSA number, median	2	3	0.180
Days to AMR, median	12	11	0.526
AMR treatment with PP+IvIg+Rituximab, %	31	100	<0.001

Censored graft survival curves according to AMR C4d status, C4d and MVI Banff scores:

C4d+ AMR was associated with stronger and C1q-binding DSA. It correlated significantly with MVI scores. However, graft survival was significantly lower in patients experiencing C4d+ AMR, while AMR-defining MVI score was not associated with poorer graft survival. C4d remains a powerful marker of prognosis in early AMR.

OS324 LONG-TERM OUTCOME OF ANTIBODY-MEDIATED REJECTION DUE TO PRE-EXISTING VS. DE NOVO DSA IN KIDNEY ALLOGRAFT RECIPIENTS

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Background: Antibody-mediated rejection (ABMR) can occur in patients with pre-existing anti-HLA donor-specific antibodies (DSA) or in patients who develop *de novo* DSA. However, how these processes compare in terms of kidney allograft outcome has not been addressed.
Methods: From a cohort of 771 kidney biopsies, we included all patients with a diagnosis of ABMR. We used an integrative analysis strategy comprising a systematic assessment of clinical-biological parameters, transplant characteristics, histopathology, immunohistochemistry, type of treatment and circulating DSA assessment.
Results: Among the 205 patients with ABMR, 103 were related to pre-existing DSA while 102 were related to *de novo* DSA. ABMR due to *de novo* DSA displayed increased proteinuria and transplant glomerulopathy lesions, lower glomerulitis, but similar peritubular-capillaritis Banff scores and C4d-deposition than patients with ABMR due to pre-existing DSA. Graft survival was superior in patients with pre-existing DSA ABMR compared to patients with *de novo* DSA ABMR (graft survival at 8 years post ABMR of 63% vs. 35% respectively, $p < 0.001$). We identified *de novo* DSA ABMR (HR = 1.82 compared to pre-existing DSA ABMR); low (<30 ml/min/1.73 m^2) eGFR at diagnosis (HR = 3.27; $p < 0.001$); ≥0.30 g/g proteinuria/creatinine ratio (HR = 2.44; $p < 0.001$); and presence of cg-lesions (HR = 2.25; $p = 0.002$) as the main determinants of allograft loss independently of type of treatment, time of diagnosis and degree of allograft injury and atrophy scarring at the time of diagnosis.
Conclusion: We found that these diseases have distinct prognosis with an acceptable and superior allograft survival in patients with pre-existing/persisting DSA related ABMR. This supports the transplantation of highly-sensitized patients but also encouraging efforts to monitor patients for *de novo* DSA and avoidance of minimization strategies.

OS325 REMOTE ISCHAEMIC PRECONDITIONING (RIPC) LEADS TO SUSTAINED IMPROVEMENT IN ALLOGRAFT FUNCTION FOLLOWING LIVE DONOR (LD) KIDNEY TRANSPLANTATION: 5 YEAR FOLLOW UP IN THE REPAIR STUDY

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Background: Ischaemia reperfusion (IR) injury at transplantation contributes to damage that limits allograft longevity, RIPC may protect against this injury. The REPAIR study demonstrated a trend towards improved iohexol GFR (adjusted mean difference 3.08 ml/min/1.73 m^2; $p = 0.13$), and a significant improvement in eGFR (4.98 ml/min/1.73 m^2; $p = 0.011$) at 1 year in patients undergoing early RIPC prior to LD kidney transplantation. We analysed eGFR and graft loss/mortality data up to 5 years.
Methods: 406 adult live donor/recipient pairs were randomised by factorial design to: sham RIPC/early RIPC (immediately pre-surgery)/late RIPC (24 h pre-surgery)/dual RIPC (early+late RIPC). The primary outcome was iohexol GFR at 12 months. eGFR (CKD-EPI) up to 60 months was an important secondary outcome, as was graft loss and all-cause mortality.
Results: eGFR data demonstrated a sustained benefit of early RIPC – adjusted mean differences between control & early RIPC groups were 3.94 ($p = 0.052$), 5.16 ($p = 0.015$), 5.55 ($p = 0.039$) & 5.05 ($p = 0.104$) ml/min/1.73 m^2 at 2,3,4 & 5 years (100% completed 3 years, 4 & 5 year follow up ongoing), Figure 1.

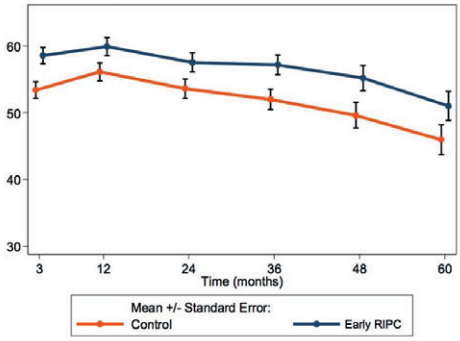

Figure 1: Adjusted mean differences in eGFR (ml/min/1.73m^2) between control & early RIPC groups: 1 year - 3.77 (p=0.049), 2 years - 3.94 (p=0.052), 3 years - 5.16 (p=0.015), 4 years - 5.55 (p=0.039), 5 years - 5.05 (p=0.104). Overall, eGFR difference between early RIPC and control: 4.82; 95% CI 1.60 to 8.03; p=0.003. All patients have completed 3 years of follow up.

There was no strong evidence for an effect of late RIPC on allograft function. There were no clinically significant/prolonged adverse effects.

There was also a trend towards a reduction in all-cause mortality and graft loss in the preconditioned groups.

At the time of presentation we anticipate that the majority of patients will have completed 5 years of follow up, and this updated dataset can be presented.
Conclusion: RIPC, a safe and virtually cost-free intervention, resulted in sustained improvement in eGFR post LD transplantation, reaching 13% by 5 years. This is expected to translate into increased graft longevity, and with longer follow up, RIPC might also reduce mortality & graft loss. Given the resultant clinical, economic & quality of life implications, we recommend that RIPC is adopted into routine care for these patients.

Clinical Kidney Ischemia-reperfusion and preservation

OS326 THE GOLDEN HOUR: LENGTH OF COMBINED WARM ISCHEMIA TIME PRESAGES DEVELOPMENT OF SEVERE ACUTE KIDNEY INJURY AFTER DCD LIVER TRANSPLANTATION

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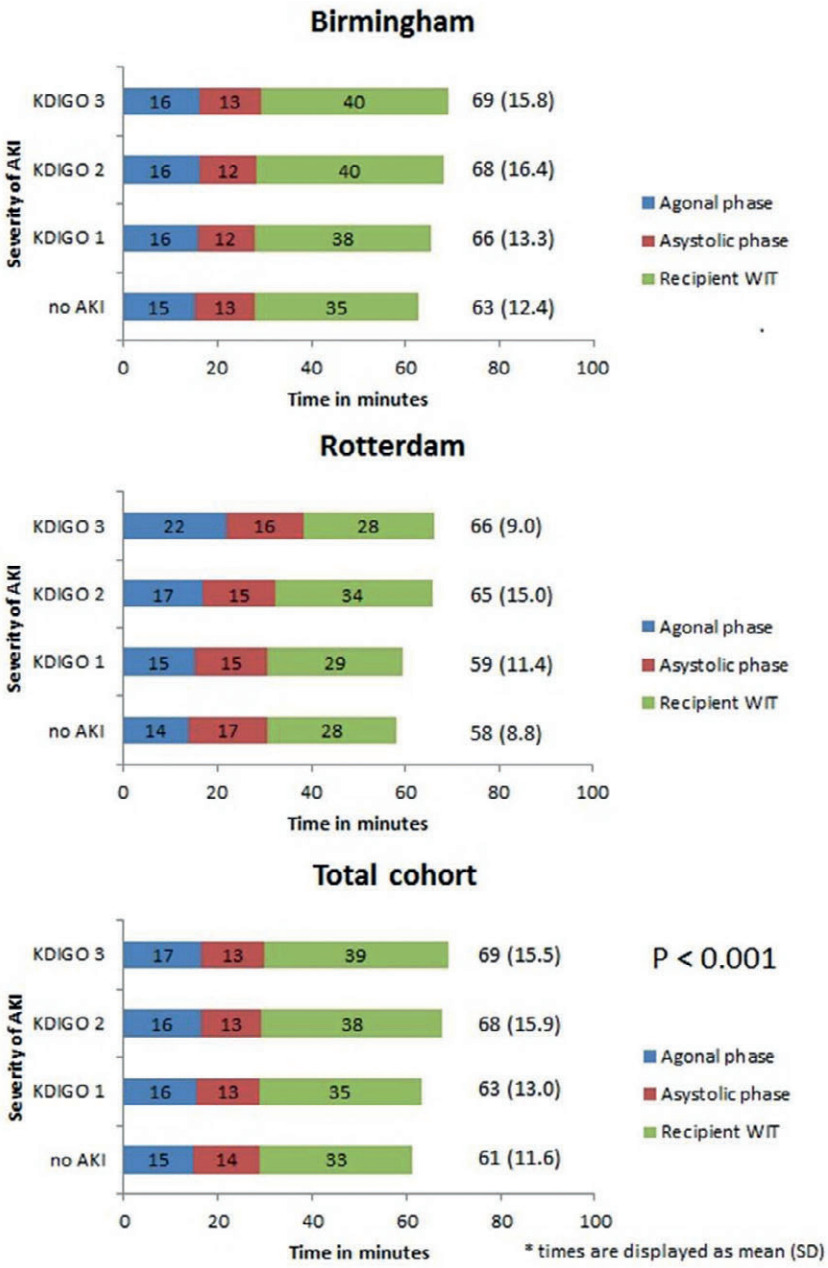
Background: Acute kidney injury (AKI) is more frequently observed in DCD liver transplantation. The donor warm ischemia time (DWIT) aggravates hepatic ischemia/reperfusion injury and thereby enhances renal impairment. Our aim was to analyse the impact of all ischemia periods on development of AKI after DCD liver transplantation.
Methods: Retrospective two centre study of all DCD liver transplants (2008–2016). AKI was defined according to KDIGO criteria and KDIGO stage 2 & 3 was considered as severe AKI. DWIT was divided into two periods: the agonal phase (donor treatment withdrawal–circulatory arrest) and asystolic phase (circulatory arrest–cold perfusion). The sum of DWIT and recipient warm ischemia time (RWIT) before reperfusion was defined as combined warm ischemia time (combined WIT).
Results: A total of 368 patients were included. 239 recipients developed AKI (65%), including 151 severe AKI (41%). The relation between warm ischemia and AKI was different between centres: in Birmingham RWIT was longer in recipients with severe AKI (40 vs. 36 minutes; $p = 0.003$), while in Rotterdam agonal phase was longer in recipients with severe AKI (19 vs. 15 minutes; $p = 0.028$). Analysis of the entire cohort showed that the combined WIT increased with severity of AKI (figure 1): 61 minutes in recipients without AKI up to 69 minutes in recipients with AKI stage 3 ($p < 0.001$). Multiple logistic regression identified length of combined WIT as a factor associated with severe AKI (OR 1.03; 95% CI 1.01–1.05; $p < 0.001$). On the contrary, cold ischemia time did not correlate with development of severe AKI (OR 0.98; 95% CI 0.84–1.15; $p = 0.822$).
Conclusion: The extra donor warm ischemia time in DCD liver transplantation exposes grafts to more warm ischemia upon the warm ischemia period prior to reperfusion. Subsequently, the length of combined WIT is associated with development of severe AKI and should ideally not exceed 60 minutes.



Clinical Liver Ischemia-reperfusion and preservation

OS327

THE RECOVERY STATUS FROM DELAYED GRAFT FUNCTION CAN PREDICT LONG-TERM OUTCOME AFTER DECEASED DONOR KIDNEY TRANSPLANTATION

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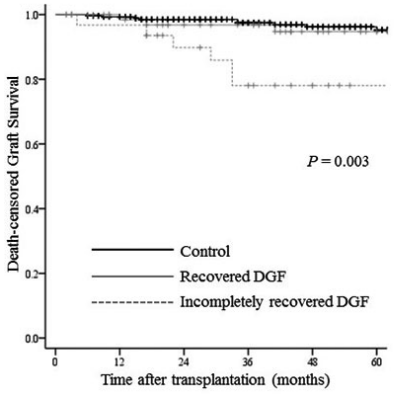
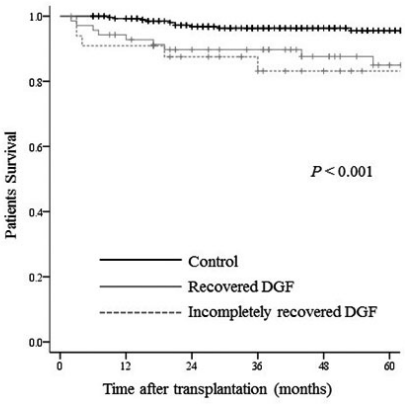
Background: The effect of delayed graft function (DGF) recovery on long-term graft outcome is unclear. The aim of this study was to examine the association of DGF recovery status with long-term outcome.
Methods: We analyzed 385 recipients who underwent single kidney transplantation from brain-dead donors between 2004 and 2014. Patients were grouped according to renal function at 1 month post-transplantation: control (without DGF); recovered DGF (glomerular filtration rate [GFR] ≥30 ml/min/1.73 m^2); and incompletely recovered DGF group (GFR < 30 ml/min/1.73 m^2).
Results: DGF occurred in 104 of 385 (27%) recipients. Of the DGF patients, 70 recovered from DGF and 34 incompletely recovered from DGF. Death-censored graft survival rates for control, recovered DGF, and incompletely recovered DGF groups were 95.3%, 94.7%, and 80.7%, respectively, at 5 years post-transplantation ($p = 0.003$). Incompletely recovered DGF was an independent risk factor for death-censored graft loss (hazard ratio, 3.053; 95% confidence interval, 1.085–8.590). DGF was associated with increased risk for patient death regardless of DGF recovery status. Patient survival rates were 95.6%, 85.0%, and 83.2%, respectively, at 5 years ($p < 0.001$). Mean GFRs at 5 years were 65.5 ± 20.8, 62.2 ± 27.0, and 45.8 ± 15.4 ml/min/1.73 m^2 for control, recovered DGF, and incompletely recovered DGF groups, respectively ($p < 0.001$). Incidences of acute rejection at 12 months were 10.3%, 17.1%, and 23.5% for control, recovered DGF, and incompletely recovered DGF groups, respectively ($p = 0.02$).
Conclusions: Control group and recovered DGF patients had similar renal outcomes. However, DGF was associated with increased risk for patient death regardless of DGF recovery status.





Clinical Kidney Ischemia-reperfusion and preservation

OS328

INTRA-ABDOMINAL COOLING SYSTEM PREVENTS ISCHEMIA-REPERFUSION INJURY DURING ROBOTIC-ASSISTED RENAL TRANSPLANTATION

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Background: Robotic-assisted kidney transplantation allows a minimally invasive approach yet it lengths operative time in which long warm ischemia is a concern. We developed a novel intra-abdominal cooling system has been designed to intra-operatively cool the donor kidney. Here we investigate the efficacy of this new intra-abdominal cooling system in the robotic-assisted versus standard open renal transplantation in a porcine model.
Methods: Porcine kidneys were procured by standard procurement technique via laparotomy. Donor kidneys were flushed with 4°C IGL-1 prior to being auto-transplanted. Groups were as follow: Robotic renal transplantation with (n = 11) and without a continuous intraabdominal cooling system (n = 6) and conventional open technique with intermittent 4°C saline solution cooling (n = 6). Renal cortex temperature, MRI and histology were analyzed.
Results: Robotic renal transplantation required a longer operative time, with and without cooling system, compared to open approach (70.4 ± 17.7 min and 74.0 ± 21.5 min vs. 49.4 ± 12.4 min, p-values<0.050). The temperature was lower in the robotic group with cooling system compared to the open approach group (6.5 ± 3.1°C vs. 22.5 ± 6.5°C; p = 0.002) or compared to the robotic group without cooling system (28.7 ± 3.3°C; p = 0.133). MRI parenchymal heterogeneities and histologic ischemia reperfusion lesions were more severe in the robotic group without any cooling system compared to the two other groups.
Conclusion: Robotic-assisted kidney transplantation prolongs warm ischemia time of the donor kidney. We developed a new intra-abdominal cooling system that allowed to minimize the warming of donor kidneys during transplantation and prevented ischemia-reperfusion injuries.

Basic Kidney Ischemia-reperfusion and preservation

OS329

COMBINED CALORIE AND PROTEIN RESTRICTION IN LIVE KIDNEY DONORS IMPROVES KIDNEY FUNCTION IN BOTH DONORS AND TRANSPLANT RECIPIENTS

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Introduction: Ischemia-reperfusion injury (IRI) negatively impacts on transplant outcome. Short-term dietary and protein restriction protects against IRI in mice. Previously, we showed that preoperative combined calorie and protein restriction (CCPR) is save in kidney donors and adherence to the diet was shown by compliance markers. Here, we investigated the effects of CCPR on outcome in live kidney donors and their recipients.
Methods: Thirty-five live kidney donors were randomized into either the CCPR (n = 15) or control (n = 20) group. The CCPR diet contained 30% fewer calories and 80% less protein for five days prior to donation; the control group had no restrictions. Effects of CCPR were assessed via metabolic parameters and postoperative kidney function of donors and recipients using percentage of serum creatinine compared to values preoperatively and percentage of acute tubular necrosis (ATN) determined by a MAG3 scan. Gene expression analysis was performed on biopsies taken before and after IRI.
Results: All patients complied to the CCPR, while no changes in metabolic parameters occurred due to the diet. From postoperative day (POD) 2 (p = 0.011) up until 1 month postoperatively (p = 0.036) kidney function of the donors was significantly better in the CCPR group. Kidney function of their recipients improved significantly from POD 4 (p = 0.020) up until POD 14 (p = 0.019). Partial ATN on POD 1 occurred in 1/15 of the CCPR donors and 6/20 in the control group (p = 0.06). CCPR inhibited immune regulation pathways and anti-inflammatory regulator NFKB1A.
Conclusions: Five days of a preoperative calorie and protein restriction diet in live kidney donors reduces the incidence of ATN, ameliorates kidney function in both donors and their recipients, and suppresses the immune response in the kidney on a transcriptional level. These results are the first to successfully translate the beneficial effects of short-term dietary restriction on postoperative outcome into the clinic.

Clinical Kidney Ischemia-reperfusion and preservation

OS330

EVALUATION OF A NOVEL MITOCHONDRIA-TARGETED ANTI-OXIDANT THERAPY FOR ISCHAEMIA REPERFUSION INJURY IN A MODEL OF PIG AND HUMAN KIDNEY TRANSPLANTATION

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Introduction: Ischaemia reperfusion injury (IRI) makes a major contribution to graft damage during kidney transplantation. As mitochondria play a central role in the generation of reactive oxygen species during IRI, we examined the efficacy of the novel mitochondria-targeted antioxidant MitoQ in amelioration of renal IRI using porcine and human kidneys.
Methods: MitoQ uptake by warm and cooled pig and declined human kidneys was measured when preserved in cold static storage or by hypothermic machine perfusion. Pairs of pig kidneys were exposed to 10 min of warm ischaemia, flushed and stored ±MitoQ (50 nm–250 μM) at 4°C for 10 h and underwent *ex-vivo* normothermic perfusion (EVNP) with oxygenated autologous blood. Pairs of declined human kidneys were flushed and stored ±MitoQ, stored at 4°C for 6 h and underwent EVNP with ABO group-matched blood.
Results: Stable and concentration-dependent uptake of MitoQ was demonstrated for up to 24 h in pig and human kidneys. Pig renal blood flow and urine output were significantly higher in the 50 μM MitoQ-treated group compared to controls (115 ± 15 vs. 33 ± 7 ml/min/100 g, p = 0.001 and 678 ± 208 vs. 309 ± 112 ml/100 g; p = 0.007 respectively; n = 5 pairs). Compared to controls, 50 μM MitoQ-treated human kidneys demonstrated a numerically higher urine output and creatinine clearance after 3 h of EVNP but the difference did not reach statistical significance (196 ± 139 vs.74 ± 90 ml/100 g; p = 0.054, 4.0 ± 4.1 vs. 1.5 ± 2.1 ml/min/100 g, p = 0.152 respectively; n = 7 pairs).

Conclusion: Our data suggest that treating kidneys with MitoQ during cold preservation ameliorates the detrimental effects of IRI and can potentially improve graft and patient outcomes after kidney transplantation.

Translational Kidney Ischemia-reperfusion and preservation

OS331 HYPOTHERMIC MACHINE PERFUSION FOLLOWING STATIC COLD STORAGE IN DONATION AFTER CARDIAC DEATH CADAVERIC KIDNEYS: A UK POPULATION-BASED COHORT STUDY

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Background: Previous systematic reviews have demonstrated the reduction in delayed graft function (DGF) rates when hypothermic machine perfusion (HMP) is used to preserve kidneys prior to transplantation. However, heterogeneity in design of randomised controlled trials, such as the timing of the start of HMP, may explain why reduction in DGF rates in a Eurozone population were not demonstrated in a UK study in Donation after Cardiac Death (DCD) donors.

The aim was to assess the outcome of DCD donor kidneys which undergo a period of HMP following SCS compared to those which are preserved with SCS alone.

Methods: A population based cohort study was performed using prospectively collected data from the National Health Service Blood and Transplant service in the United Kingdom. All adult recipients of single organ DCD kidneys transplanted between 2007 and 2015 were included.

Results: A total of 4529 DCD kidneys were included in the study with HMP used in 19.1% of cases ($N = 864$). HMP usage was found to be in decline over the period of the study ($p < 0.001$), from 25.6% of transplants in 2007–2010, to 14.4% of transplants in 2014–2015. Cases where HMP was used had significantly longer CIT than SCS organs (median: 14.8 vs. 14.1 h, $p < 0.001$), and HMP was most commonly used in organs that were reperfused with the recipients' blood during the daytime (8:00–16:59, $p < 0.001$).

The rate of DGF was found to be significantly lower in organs where HMP was used, compared to SCS (34.2% vs. 41.9%, $p < 0.001$). This remained significant after accounting for potentially confounding factors in a multivariable analysis, with an odds ratio of 0.64 (95% CI: 0.53–0.78, $p < 0.001$) for HMP vs. SCS. Neither patient ($p = 0.610$) nor graft ($p = 0.664$) survival were found to differ significantly between the HMP and SCS cohorts.

Discussion: Our UK population-based study demonstrates the incidence of delayed graft function can be significantly reduced by a period of HMP in DCD kidneys, even after a period of SCS.

OS332 EVALUATION OF OUTCOMES IN RENAL TRANSPLANTATION USING MACHINE PERFUSION FOR THE PRESERVATION OF KIDNEYS FROM EXPANDED CRITERIA DONORS

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Introduction: The shortage of kidney grafts led to retrieve organs from old donors with one or more co-morbidities, considered as "expanded criteria donors" (ECD). In France, since 2012, the Agency of biomedicine (ABM) has recommended the use of machines perfusion (MP) to preserve kidneys from this donor population to improve kidney preservation and the transplantation outcomes, with the creation of a specific lump sum financing the additional costs of this strategy. This study evaluates the impact of MP vs. cold storage (CS), for the period 2011–2014 with kidneys from ECD.

Methods: From the ABM database (Cristal), the effect of MP on the delayed graft function (DGF) was analyzed using a multivariate logistic model excluding pre-emptive transplants and primary non functions (PNF). In addition, transplants from the same donor, whose one kidney preserved by MP and the other by CS (population of twins), were analyzed using a mixed model.

Results: Co-morbidities of recipients are more frequent and the age of donors and recipients is significantly higher for kidney preserved by MP ($n = 801$) vs. CS ($n = 3515$). With 16% of DGF for MP vs. 29% for CS, MP has a protective effect on the DGF (OR adjusted = 0.45, CI [0.36, 0.56]). In the population of the twins (84 pairs, 168 grafts), we observed 7% of DGF for MP vs. 33% for CS and an adjusted OR 0.19 (CI [0.06; 0.58]). The durations of hospitalization and dialysis after transplantation are shorter with fewer sessions of dialysis.

Discussion: Our results confirm the reduction in the incidence of the DGF of ECD kidneys preserved by machines, with 2.2 times less risk despite a population more at risk in this group, and a lower 5.2 times risk in the population of the kidneys "twins". It remains to assess the impact of the DGF in the long term survival and measure the cost effectiveness of this strategy.

Clinical Kidney Ischemia-reperfusion and preservation

OS333 EXTENDED EX-VIVO NORMOTHERMIC HUMAN KIDNEY PERFUSION USING AN ARTIFICIAL OXYGEN CARRIER

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Background: Hypothermic machine perfusion (HMP) is commonly used in kidney preservation, providing some advantage over static cold storage. However, the low temperature offers little opportunity to improve organ quality or to obtain functional data. We therefore established an oxygenated normothermic machine perfusion (NMP) system to investigate the possibility of rescuing discarded kidneys.

Methods/materials: Pressure and temperature controlled NMP with an enriched media and Hemopure (bovine hemoglobin-based oxygen carrier) was used to perfuse 9 human kidneys deemed un-transplantable by all transplant centers. The average cold ischemia time (CIT) was 21 h. The grafts were discarded for different reasons, including poor performance on the HMP pump, concerning biopsy results, poor flush, fail to allocate the organ, and surgical damage to the hilum. Organs from donation after circulatory and brain death were accepted. Kidneys were perfused for up to 12 hrs. Different metabolic markers, functional parameters and macroscopic assessment measurements were recorded throughout the perfusion session.

Results: Renal artery flow/resistance showed a sustained improvement throughout the perfusion period. The maintenance of a relatively physiologic pH/bicarbonate level and the arterio-venous oxygen difference showed evidence of significant metabolic activity. Only the last three kidneys in our series produced significant amounts of urine; this correlated with removing the albumin aiming to assess the implications of decreasing the oncotic pressure of the perfusate.

Conclusions: Our ongoing series results are notable for a significant metabolic activity, favorable functional parameters and macroscopic characteristics; in addition to urine production suggesting that some of these kidneys could have been used for transplantation. ATP and pathology results are pending, which will likely add more information for us to more accurately catalog these grafts and theorize which ones could be implanted.

Translational Kidney Ischemia-reperfusion and preservation

OS334 DEVELOPMENT OF AN AUTOMATIC REGULATED NORMOTHERMIC KIDNEY PRESERVATION DEVICE FOR LONG-TERM PERFUSION

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Background: Normothermic kidney perfusion for a period of 24 h or longer could offer significant clinical advantages. It would enable clinicians to investigate the condition of renal parenchyma during the warm preservation period and provide a platform for repairing kidneys that are currently discarded. This would enlarge the donor pool and enable more successful renal transplants.

Methods: We have established an automated closed circuit normothermic kidney perfusion (NKP) prototype, with the objective of perfusing human kidneys for 24 h.

Results: Twenty-one discarded human kidneys from DBD (donation after brain death) and DCD (donation after cardiac death) donors were perfused and functional parameters were proven stable and physiological. Median perfusion time was 15 h (1.5–24.4). Eight kidneys were perfused for 24 h. Cold ischemia time (CIT) was significantly longer in DCD compared to DBD; $p = 0.033$. Median CIT was 25.3 h (8.1–106). DCD kidneys (601.7 $\pm$ 150 ml) produced more urine than DBDs (285 $\pm$ 95.74 ml) but this was not significant; $p = 0.17$. Urinary output was significantly correlated with warm ischemia time in DCD; $p = 0.018$. Measured biochemical parameters included glucose, lactate, NGAL, KIM-1 and L-FABP. All but one perfused kidneys showed clear

evidence of glucose consumption. Delta L-FABP was significantly less with shorter CIT; p = 0.027 and significantly less in DBDs; p = 0.011. Kidney biopsies showed that the frequency of acute tubular injury did not differ between the pre- and post-perfusion biopsies, p = 0.22. These data suggest that NKP does not cause acute tubular injury.
Conclusion: Automated NKP for at least 24 h was shown to be feasible, with the ability to measure biomarkers that might reliably indicate viability in otherwise marginal donor organs. Clinical translational studies are now needed to demonstrate the clinical utility of this technology.

OS335 IMPACT OF PULSATILE MACHINE PERFUSION ON POSTOPERATIVE OUTCOMES IN KIDNEY TRANSPLANT RECIPIENTS FROM STANDARD CRITERIA DONORS

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Introduction: Delayed graft function (DGF) has a negative impact on kidney transplant (KT) outcomes. This study aimed to assess the impact of pulsatile machine perfusion (MP) in KT performed in a Brazilian region where transplants with standard criteria deceased donors (DD) are predominant.
Methods: Prospective cohort including 110 KT performed from Jan/15 to Dec/16, who received paired kidneys from 55 DD in which one kidney underwent MP following static cold storage (CS) preservation (MP group) and the other underwent only static cold storage (CS Group). The decision for MP or CS was at discretion of transplant staff. The primary end-point was DGF (requirement for dialysis in the first week after KT) incidence and duration.
Results: Donors were young (31 ± 12 years), mixed race (84%), non-hypertensive (93%), non diabetic (100%), overweigh (BMI 26 ± 4 kg/m^2), who died due to traumatic brain injury (69%), with final serum creatinine of 1.3 ± 0.7 mg/dl. 94% were standard criteria donors and the mean KDPI and KDRI were 33 ± 21% and 0.86 ± 0.2, respectively. Demographic characteristics of the KT recipients were similar in both groups: males (60%), young (42 ± 18 years), mixed race (86%), with chronic kidney disease of unknown etiology (38%), and 45 ± 45 months on dialysis. However, patients on MP group were more sensitized: panel reactive antibodies (PRA) 19 ± 32 vs. 9 ± 25% (p = 0.066) and pre-transplant donor specific antibodies (DSA) 18 vs. 2% (p = 0.008). The total cold ischemia time (TIF) was 29 ± 6 vs. 21 ± 4 h (p < 0.001), and dynamic CIT was 13 ± 6 h. MP significantly reduced the incidence of DGF (39 vs. 61%, p = 0.035), and there was no difference on the duration time of DGF (16 ± 20 vs. 13 ± 18 days, p = 0.516).
Conclusion: Machine perfusion is beneficial in reducing DGF even when standard donors are utilized. Despite higher immunological risk, patients who received MP kidneys presented lower incidence of DGF. This cohort will be followed to assess the impact of DGF reduction on long-term outcomes.

Clinical Kidney Ischemia-reperfusion and preservation

OS336 NORMOTHERMIC EXTRACORPOREAL PERFUSION IN SITU IN DECEASED ORGAN DONORS WITH IRREVERSIBLE CARDIAC ARREST AND ONE HOUR OF ASYSTOLE: 5-YEARS OUTCOMES OF KIDNEY TRANSPLANTATION

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Background: The global shortage of deceased organ donors caused increasing interest to the use organs from the donors with a sudden irreversible cardiac arrest (DCD). Ischemia-reperfusion injury (IRI) is a key problem that limits the use of such organs. Our clinical study was intended to determine the acceptability of kidney transplants (KTx) derived from the DCD using ECMO «in situ» after 60 min of asystole.
Materials and methods: In 2009–2014, St Petersburg Organ Procurement Organization (OPO) obtained kidneys from 29 DCD with critically expanded warm ischemic time (WIT). The design of this study was approved by the Ethics Committee of the State Institute for Emergency (№7/0615/09). In case failed advanced CPR the death of patient was declared and initiated the protocol of abdominal ECMO, thrombolytics and LD. The procedures were established by the authorized OPO team which had arrived with perfusion equipment in 30–40 min after declaration of donors' death. Mean WIT was 58.1 (19.39) min. Resuscitated grafts were transplanted into 58 recipients. The outcomes of Tx of resuscitated kidneys were compared to outcomes of 112 KTx from 115 brain death donors (BDDs).
Results: IGF was observed in 28 (48.3%) of the 58 recipients. There were 4 cases of PNF. By the end of the first post-transplant year there was an acute rejection rate of 12.1% (9 episodes) in the DCD group versus 23.2% (26) in the BDD group (p < 0.05). The actuarial 5-year graft survival rate was 82.8% (*n* = 48) in DCD, and 87.5% (*n* = 98) in BDD (p > 0.05). Creatinine levels at the end of the 5 year were 0.094 (0.06) and 0.103 (0.07) mmol/l in DCD and BDD groups, respectively (p > 0.05).
Conclusions: Kidneys from DCDs with critically WIT could be successfully used for Tx if "resuscitation" perfusion in situ procedures are included into procurement protocol. The 5-years outcomes meet the generally accepted criteria grafts and recipient's rates of survival and functioning. This approach could expand the organ donors' pool.

Clinical Kidney Donation and donor types

OS337 KIDNEY DONOR RISK INDEX IS A GOOD PROGNOSTIC TOOL FOR PREDICTION OF EARLY POST-TRANSPLANT KIDNEY FUNCTION AND GRAFT SURVIVAL IN KOREAN POPULATION

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Background: Kidney donor risk index (KDRI) is used in the United States to estimate the deceased donor kidney. However, KDRI is not yet used in Asian population. We tried to validate KDRI in assessment of deceased donor kidney in a large number of Korean population group.
Methods: The data of Korean Organ Transplantation Registry (KOTRY) between 2009 to 2012 was used in the analysis. Among 1924 deceased donor kidney transplantation, 1582 cases in which KDRI score could be calculated were included in this study. We investigate the impact of KDRI on the graft function and graft survival.
Results: We divided the donors by KDRI tertile (T1: range, 0.6432–1.17025, T2: range, 1.17057–1.48566, T3: range, 1.48630–3.80629). The recipients of T1 were younger and had less diabetes. Mean estimated glomerular filtration rate at post transplant 1 year of each group was 76.1 ± 21.0, 64.7 ± 20.3, 55.5 ± 21.0 ml/min/1.73 m^2 respectively. In the Cox regression analysis, KDRI showed good association with death censored graft survival, of which median follow up duration was 24.6 months (hazard ratio 1.778, 95% confidence interval 1.087–2.906, p = 0.022).
Conclusion: KDRI is a good tool for estimation of early post-transplant outcomes in Korean population.

OS338 VALIDATION OF THE PROGNOSTIC KIDNEY DONOR RISK INDEX (KDRI) SCORING SYSTEM OF DECEASED DONORS FOR RENAL TRANSPLANTATION IN THE NETHERLANDS

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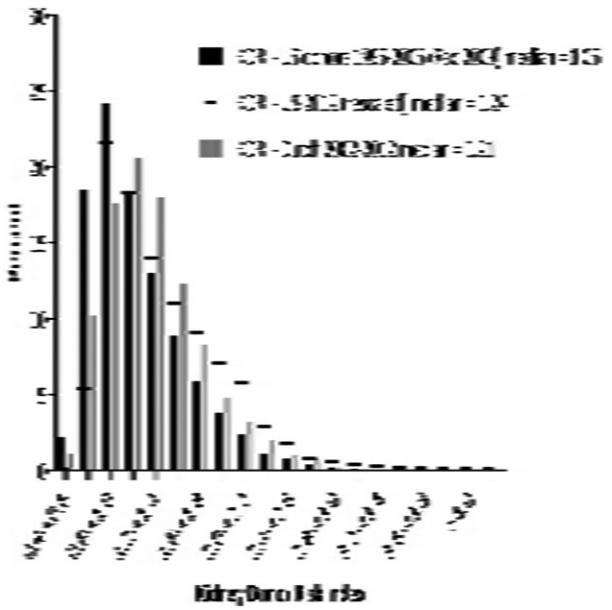
Background: The prognostic Kidney Donor Risk Index (KDRI)—developed and internally validated in the US—is a widely-used tool to predict transplant outcome of a deceased donor kidney. The KDRI has not been externally validated in many other countries.
Methods: We aimed to externally validate the KDRI as proposed by Rao et al. (2009), containing 10 donor factors ($KDRI_{donor\text{-}only}$) and one with 4 additional transplant factors ($KDRI_{full}$), with stratification on recipient age and diabetes. We used the Dutch Organ Transplantation Registry to include 3201 adult recipients transplanted from 2002 to 2012, and followed them till September 2015. Outcome was graft survival.
Results: The median Dutch KDRI was increased to 1.21 compared with the median of 1.0 reported by Rao et al. in 2009, and comparable with the year 2012 in the US (1.24). Kidneys in the lowest $KDRI_{full}$ quintile (0.45-<0.79) had a 5-year-graft survival of 87.3% if transplanted in nondiabetic recipients aged between45- < 55 years, whereas the lowest quintile (<0.79) showed a survival of 71.2%. The calibration-slope was 0.98 and 0.96 for the $KDRI_{full}$ and $KDRI_{donor\text{-}only}$, respectively, indicating that—on average—predictions of the KDRI on graft failure were almost identical. The discriminative ability (Harrell's C) of the $KDRI_{full}$ was 0.63 (95% CI 0.62–0.64) at 5 years, and slightly lower for the $KDRI_{donor\text{-}only}$ 0.62 (95% CI 0.61–0.63). We found misspecification of the following donor factors: age (p = 0.002), weight (p = 0.017), and cold ischemia time (CIT) (p < 0.001). Possibilities to improve the KDRI include the use of



inotropic drugs prior to donation (p = 0.040), and interaction of prolonged CIT and circulatory-death donor kidneys (p = 0.059).
Conclusion: The KDRI scoring system for deceased donors shows equivalent but modest discrimination and similar accuracy as compared within the US. An updated Dutch-KDRI may contribute to a standardized uniform policy to meet the growing demand of donor kidneys in the Eurotransplant region.

Clinical Kidney Allocation

OS339

SATISFACTORY OUTCOME OF VERY HIGH KDPI KIDNEYS IN ELDERLY KIDNEY TRANSPLANT RECIPIENTS IN EUROPE

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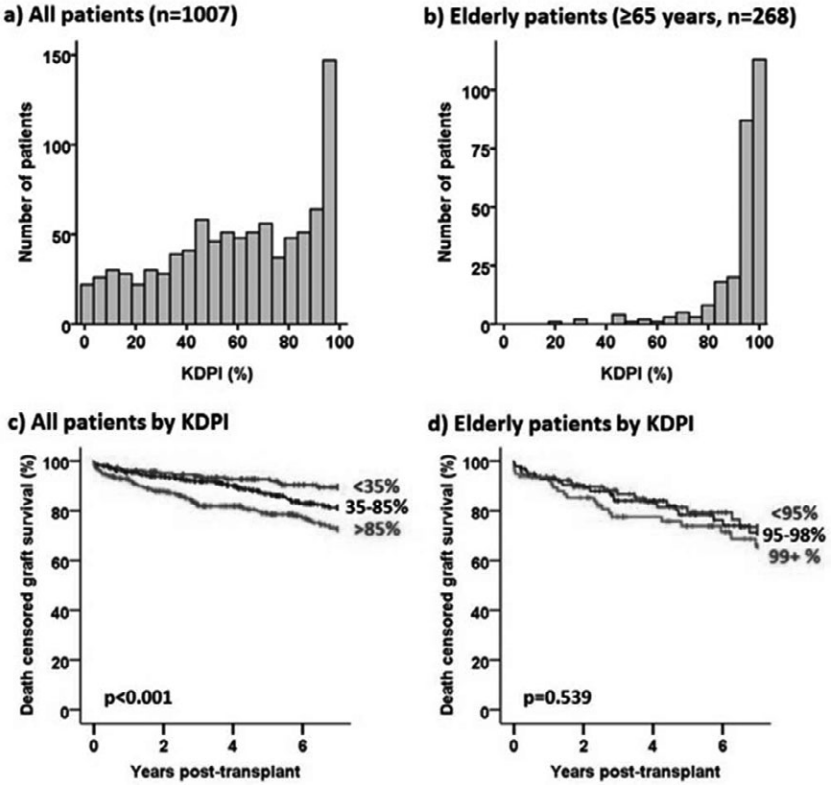
Background: Limited data exist on long-term outcomes of very high KDPI kidneys in elderly (≥65 years) kidney transplant recipients (KTR). Discard rates of donor organs with a KDPI > 95% were 72% in the US 2012–2014.
Methods: This retrospective single center study included 1007 adult KTR who received a deceased donor kidney 1995–2015. KDPI was calculated using the US OPTN data as reference. Post-transplant outcomes were assessed over a maximum period of 21 (mean 7.4) years.
Results: Elderly KTR received significantly older donor organs, spend less waiting time on dialysis, had shorter cold-ischemic time and more HLA mismatches. The median KDPI in the study cohort was 67% (Fig. 1a). Elderly KTR (n = 268) mostly received organs with a very high KDPI (median 97%, Fig. 1b). Categorization of all KTR by donor KDPI (<35%, 35–85%, >85%) confirmed significantly poorer survival of grafts with higher KDPI ($p < 0.001$; Fig. 1c). The groups of elderly recipients with a very high donor KDPI of 95–98% (n = 97, mean KDPI 96.7%) or even 99 + % (n = 78, mean KDPI 99.4%) showed no significant difference in terms of graft survival compared to elderly KTR with donor KDPI <95% (n = 93, mean KDPI 81.4%) (p = 0.539; Fig. 1d). Even the category of KDPI 99 + kidneys showed satisfactory graft survival (73.9% after 5 years). Donors in this category had an unfavorable risk profile (mean donor age 76 years, 90% cerebrovascular death, 80% hypertension, 36% diabetes, mean donor cGFR 62 ml/min). Mean death censored graft survival in elderly KTR was 10.1 years (CI 9.2–11.0), mean life expectancy 8.5 years (CI 7.7–9.4) indicating a good functional match between very high KDPI kidneys and elderly recipients in this cohort.
Conclusions: In Europe elderly KTR frequently receive high and even very high KDPI (99 +) kidneys (mostly discarded in the U.S.) nevertheless resulting in satisfactory graft survival rates. Efforts can be made to increase utilization of those donor organs for elderly kidney transplant candidates.

Figure 1.



Clinical Kidney Donation and donor types

OS340 COMPARISON OF COMBINATIVE IMPACT OF HIGH KIDNEY DONOR PROFILE INDEX (KDPI) AND PRESENCE OF SCLEROSIS ON POST-TRANSPLANT OUTCOMES IN KIDNEY TRANSPLANTATION

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Background: Initial kidney allograft condition is impacted by factors analysed by Kidney Donor Profile Index (KDPI), as well as by the presence of interstitial and glomerular sclerosis in "zero" biopsy. The aim of this study was to analyse separate and combinative impact of these two factors on post-transplant outcomes.
Methods/materials: Study included all consecutive kidney transplantations from deceased donors performed in period from 01.01.2004 till 31.12.2007, where donor's kidney zero biopsies were performed and patients were available for 8-year follow-up ($n = 101$, male/female = 53/48, mean age 46.9 $\pm$ 14.0 years). All cases were divided into 4 groups according to KDPI and presence of sclerosis in biopsy: group A (KDPI > 50 and sclerosis), group B (KDPI > 50, no sclerosis), group C (KDPI < 50 and sclerosis) and group D (KDPI < 50, no sclerosis). Groups were compared for post-transplant outcomes and 8-year graft and patient survival.
Results: Presence of higher KDPI (>50) was associated with higher rate of delayed graft functions (DGF, 31.3% vs. 14%). Presence of sclerosis in zero biopsy was associated with higher DGF (55.3% vs. 33.3%) and lower graft survival ($p = 0.045$).

Comparison of posttransplant complications showed higher incidence of delayed graft functions in groups A, B and C compared to group D (32.6%, 25%, 21.2% and 0%, respectively), and more frequent acute rejections in group A. Incidence of surgical complications and recipient serum creatinine at discharge and at the end of follow-up showed no statistical differences between groups. Group D showed higher 8-year patient survival and lower graft survival (figure 1).
Conclusion: Both high KDPI and presence of sclerosis had negative impact on posttransplant outcomes, especially when combined. Early post-transplant results in cases of separate presence of sclerosis were comparable with results in cases of absence of both factors, however late results

OS341 VARIATIONS IN RISK-APPETITE BETWEEN UK KIDNEY TRANSPLANT CENTRES AND IMPACT ON PATIENT AND GRAFT OUTCOMES

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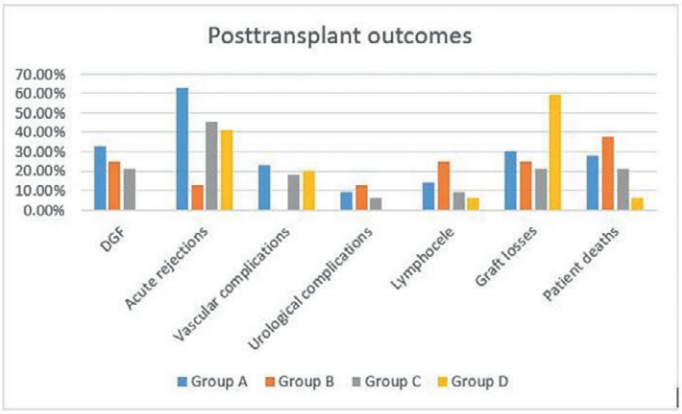
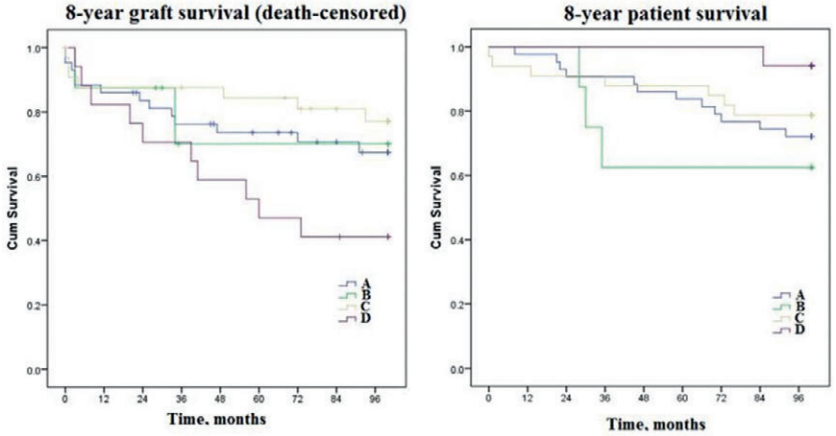
Background: Risks associated with deceased donors may be donor-related (e.g. transmission of disease), organ-related (e.g. poor graft survival), or both. Variations between individual transplant centres in the risks they are prepared to accept ('risk profile'), and the impact on patient and graft outcomes have hitherto been poorly characterised. This UK registry analysis aims to address these issues.
Methods: Adult recipients of deceased donor kidney transplants (DDKTx) between 2006 and 2015 were identified. Nine donor and operative variables perceived to be associated with increased risk (donor hypertension, diabetes, age >70 years, malignancy, increased risk behaviour for blood-borne viral diseases, meningitis / encephalitis, UKKDRI > 1.60, DCD donor, and dual transplantation) were compared between units. Novel risk scores were developed based on centre quartiles and centre ranking for each variable. Centres were compared over the entire study period, and in early and late 5-year eras. They were divided into four groups based on risk score over the 10-year period. Logistic regression analyses were performed to examine interactions between centre risk and patient outcomes.
Results: Over 10 years, 14 619 DDKTx were carried out from 8632 deceased donors. The proportion of DDKTx carried out from the above donor risk groups varied widely between centres, and some centres markedly increased their 'risk profile' from early to late eras. Patients were significantly more likely to receive a transplant if they were listed at a 'high risk' centre versus a 'low risk' centre (odds ratio 2.1 (95% CI 1.9–2.2), $p < 0.001$). No difference in unadjusted 5-year first kidney graft survival was apparent between 'low risk' centres or 'high risk centres' (85.8% vs. 86.6%, $p = 0.43$). Patient





survival from listing appeared to be no worse in 'high risk' than lower risk centres.
Conclusions: UK kidney transplant centres display wide variation in their appetite for risk.

OS342 PROPENSITY SCORE-BASED COMPARISON OF THE GRAFT FAILURE RISK BETWEEN KIDNEY TRANSPLANT RECIPIENTS OF STANDARD AND EXPANDED CRITERIA DONOR GRAFTS: TOWARDS INCREASING THE POOL OF MARGINAL DONORS

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A recent meta-analysis demonstrated the lack of external validation for the Expanded Criteria Donor (ECD), a classification still used in renal transplantation to allocate marginal organs. From a prospective and multicentric French cohort, we propose such a validation study based on 4833 kidney recipients transplanted for the first time between 2000 and 2014 from deceased donors. Estimating a *subject-specific* effect by a multivariable Cox regression, we confirmed a 1.71-fold (95% CI from 1.49 to 1.96, $p < 0.0001$) increase in graft failure risk if a given patient received an ECD graft compared to a graft from a Standard Criteria Donor (SCD). But, given the recent developments in causal inference, we additionally estimated the *population-average* association using propensity scores. We estimated a 1.34-fold (95% CI from 1.09 to 1.64, $p = 0.0049$) increase in graft failure risk among patients receiving an ECD graft compared to the situation of the same recipients had received a SCD graft. In terms of absolute effect, at 10 years post-transplantation, we observed a decrease of the mean time to graft failure estimated at 8 months (95% CI from 2 months to 14 months) between ECD and SCD groups. In conclusion, we described that the excess in the graft failure risk due to the ECD organs seemed overestimated due to methodological pitfalls of previous studies. Regarding the increase in the quality of life related to transplantation compared to dialysis, the perspective of our study is to increase the pool of expanded donors, as the loss of chance in term of mean survival time due to ECD transplantation compared to SCD may be considered as reasonable.

Clinical Kidney Allocation

OS343 ABSENCE OF INDEPENDENT AND ADDITIONAL PREDICTIVE ABILITY OF PREIMPLANTATION KIDNEY ALLOGRAFT BIOPSIES FOR LONG-TERM OUTCOME: POPULATION BASED STUDY

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Background: A significant number of kidneys are discarded worldwide. The mean cause is the result of the preimplantation biopsy without clear evidence that its results are associated with long-term allograft survival.
Methods: We included patients who underwent kidney transplantations from a deceased donor in 2 French referral centers between 2004 and 2011 where preimplantation are routinely performed. All the patients with preimplantation biopsy were included. A systematic assessment of donor, recipient, and transplant clinical characteristics, a preimplantation biopsy and an evaluation of baseline circulating donor-specific anti-HLA antibody (DSA) levels were performed.
Results: A total of 882 patients were included in the study. A total of 352/882 (40%) transplantations were performed using ECD kidneys and a total of 143/882 (16%) had an anti-HLA DSA at the day of transplantation. The mean follow-up time after transplantation was 6.56 ± 2.37 years. After adjusting for donor, recipient, and transplant characteristics as well as for preimplantation biopsy findings (including the atrophy-fibrosis, percentage of sclerotic glomeruli, arteriosclerosis and arteriolar hyalinosis scores) and baseline immunological parameters, we identified the KDRI score (HR = 2.17; $p = 0.002$) and the presence of circulating anti-HLA DSA on the day of transplantation (HR = 2.89; $p < 0.0001$) as the main independent determinants of long-term allograft loss. None of the preimplantation biopsy findings showed independent association with the kidney allograft survival.
Conclusion: Preimplantation biopsy assessment does not provide independent and additional predictive ability for long-term allograft outcome at a population level in deceased donor program. The current practice of discarding kidneys based on preimplantation biopsy findings may not be optimal for decision-making and is a barrier to the decrease in the rate of discarded kidneys.

Clinical Kidney Donation and donor types

OS344 DELAYED GRAFT FUNCTION AND LONG-TERM GRAFT SURVIVAL IN DBD AND DCD KIDNEY RECIPIENTS

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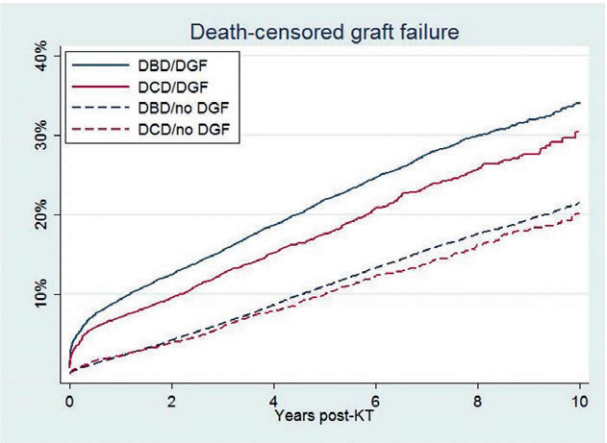
Background: Several single-center studies have recently suggested that delayed graft function (DGF) is not associated with increased risk of graft loss in recipients of donation after cardiac death (DCD) kidneys. Given the strong association between DGF and graft loss in general, we were surprised by these reports and suspected type II error. The goal of this study was to investigate these findings in a large registry powered to answer this question.
Methods: Using US national registry data 2005–2015 on 76 114 adult, first-time, kidney only deceased donor kidney transplant (DDKT) recipients, we studied the association between DGF and death-censored graft failure (DCGF) among recipients of donation after brain death (DBD) and DCD kidneys, using Cox regression and adjusting for recipient characteristics and kidney donor profile index (KDPI).
Results: DGF was higher among DCD recipients than DBD recipients (41.4% vs. 23.3%, $p < 0.001$). DCGF was higher in recipients who experienced DGF, both among DBD recipients (cumulative incidence at 10 years = 34.0% vs. 21.5%) and DCD recipients (30.4% vs. 20.1%) (Figure). Among DBD recipients, DGF was associated with 3.9-fold higher risk of DCGF in the first year post-transplant (aHR $= {}_{3.57}\,3.86\,{}_{4.18}$, $p < 0.001$); this association attenuated over time but remained significant at >5 years post-transplant (aHR $= {}_{1.09}\,1.21\,{}_{1.33}$, $p < 0.001$). Among DCD recipients, increased risk associated with DGF was slightly attenuated in the first year (aHR $= {}_{2.78}\,3.22\,{}_{3.73}$, $p < 0.001$, interaction $p = 0.02$) but comparable to risk for DBD recipients thereafter (interaction $p = 0.3$).



Conclusion: DGF was associated with substantially higher risk of DCGF among recipients of both DBD and DCD kidneys, particularly in the first year post-transplant. DCD organs should not be viewed differently in terms of the impact of DGF.

OS345 THE IMPACT OF DONOR-RECIPIENT AGE DIFFERENCE ON GRAFT FUNCTION AND SURVIVAL AFTER DECEASED-DONOR KIDNEY TRANSPLANTATION

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Background: Donor-recipient age difference is one of the reasons that patients in waiting list refuse to receive the donated kidneys. However, the impact of donor-recipient age difference on graft function and survival is still controversial in deceased-donor kidney transplantation (DDKT).
Methods: From June 2005 to May 2014, 153 recipients received a first-time DDKT in our hospital were enrolled. Recipients were divided into two groups by donor-recipient age difference (DRAD): group 1 ($n = 74$), donors are younger than recipients; group 2 ($n = 79$), donors are the same age or older than recipients. In group 2, it was divided into three subgroups based on the DRAD: $0 \leq$ DRAD <10 ($n = 35$), $10 \leq$ DRAD <20 ($n = 32$), DRAD ≥ 20 ($n = 12$). Outcome measures included delayed graft function (DGF), acute rejection, estimated GFR at 3 months, 1, 2 and 5 years after transplantation as well as graft and patient survivals.
Results: Compared with kidneys from younger than recipients, kidneys from the same age or older than recipients showed no significant differences in the incidence of DGF, acute rejection, graft and patient survivals. Although estimated GFR until 2 years were significantly higher in recipients received grafts from younger than themselves, there was no significant difference at 5 years. In subgroups of group 2, categorized in detail according to DRAD, there were no significant differences in the incidence of DGF, acute rejection, patient survival as well as estimated GFR until 5 years among subgroups. However, graft survival in subgroup of DRAD $\geq$20 was significantly decreased compared with subgroup of $10 \leq$ DRAD <20 ($P < 0.05$).
Conclusions: Even though donors are the same age or older than recipients, it showed acceptable graft function and survival in DDKT. However, because DDKT from donors over 20 years older than recipients showed decreased graft survival, it might be important to consider this point in donor-recipient matching of DDKT.

OS346 EXTRACTION TIME DURING ORGAN DONATION IS ASSOCIATED WITH GRAFT LOSS AFTER KIDNEY TRANSPLANTATION: A EUROTRANSPLANT COHORT STUDY

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Background: While the consequences of prolonged cold ischaemia time for kidney transplant outcome have been extensively studied, the effect of ischaemia time during organ procurement in the donor (extraction time) on graft survival has hardly been investigated.
Methods: We investigated the relationship between extraction time and graft survival in 13 973 recipients of single adult to adult first-time deceased-donor kidneys transplanted in the Eurotransplant region (2004–2013). Cox regression analyses were corrected for donor, preservation, and recipient variables. Extraction time was defined as the time between aortic clamping and nephrectomy.
Results: Median extraction time was 58 minutes (interquartile range 43–72 minutes). Extraction time was longer in thoracic-abdominal donation, multi-abdominal organ donation, dual versus single kidney donation, donation after circulatory death (DCD), standard-criteria versus extended-criteria donation, and younger donors without hypertension or diabetes (Wilcoxon test $p < 0.01$ for all comparisons). Because the fitter the donor, the more organs procured, and the longer the extraction time, the unadjusted survival analysis failed to demonstrate an effect of extraction time on death-censored graft survival ($p = 0.61$). However, when adjusted for these and other transplant-related variables, extraction time did influence graft loss (adjusted HR 1.02 per 10-minute increase, 95% CI 1.00–1.05; $p = 0.04$). Interestingly, when DCD and DBD transplants were considered separately, the effect remained only in DCD transplants (adjusted HR 1.04 per 10-minute increase, 95% CI 1.00–1.08; $p = 0.04$), and failed to influence graft loss in DBD transplants ($p = 0.35$).
Conclusion: Extraction time in DCD donation is associated with worse graft survival after kidney transplantation.

Clinical Kidney Allocation

OS347 KAS IMPLEMENTATION IN THE US REDUCES RACIAL DISPARITIES IN KIDNEY TRANSPLANT ACCESS: A MULTISTATE MODELING APPROACH USING TIME-VARYING PRA STATES AND ACTIVITY STATUS

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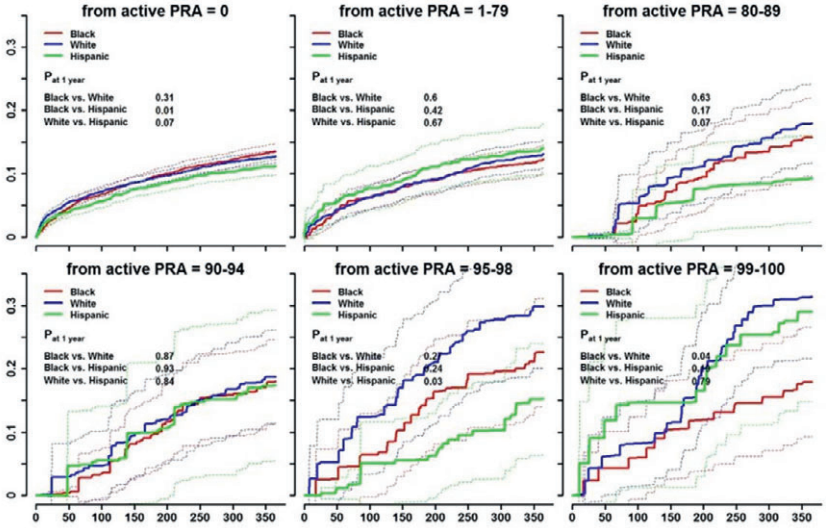
Background: Highly sensitized kidney transplant candidates are at higher risk of death on the waiting list. Policy change 8.3 (Kidney Allocation System, (KAS) increases transplant rates for these patients. As time-varying covariates, the level of sensitization (PRA state) and waitlist activity status can be used in a multistate modeling framework for predicting the probability of receiving a transplant and evaluating the impact of KAS.
Methods: Two retrospective cohorts of adult kidney transplant candidates were created from the UNOS database–pre-KAS (10/01/2009-12/04/2013) and after its implementation (12/04/2014-06/17/2015). The combination of PRA state and waitlist activity status was used to create intermediate states. Using a multistate framework, we estimated transition probabilities between intermediate states and the following competing risks: transplant (living), transplant (deceased), death, or other/well. We evaluated the impact of KAS on new listings by comparing these cohorts specifically for the cumulative probability of receiving a deceased donor transplant. Then we relaxed event censoring after KAS implementation to analyze the impact of KAS on the pre-KAS cohort.
Results: Pre-KAS, there were statistically significant racial differences in the probabilities of receiving a deceased donor transplant between whites, blacks and Hispanics across all PRA states ($p < 0.001$). Post-KAS, these established racial disparities were largely eliminated across most PRA states



(Figure below). However, there continued to be a higher probability of transplant for whites over blacks in the PRA 99–100% group.
Conclusion: Multistate modeling shows how time-varying PRA states and waitlist status impact transplant outcomes. Since the implementation of KAS, established racial disparities in access to kidney transplant have largely been eliminated. Continued advantages of whites in the highest PRA state is consistent with larger pool of white haplotypes.

OS348 THE NEW KIDNEY ALLOCATION SYSTEM IN FRANCE RESULTS IN A SIGNIFICANT INCREASE IN TRANSPLANT ACCESS RATE, AGE AND HLA DR-QD MATCHING FOR YOUNG ADULTS

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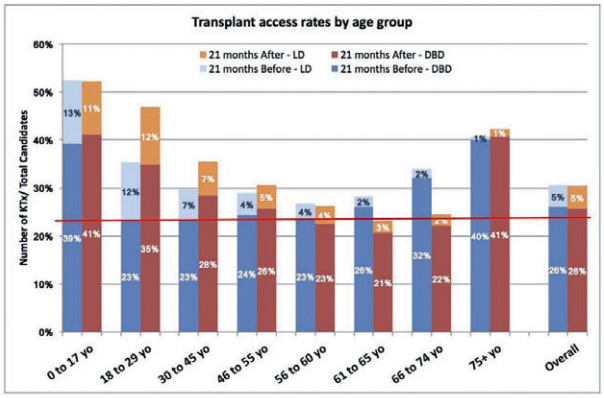
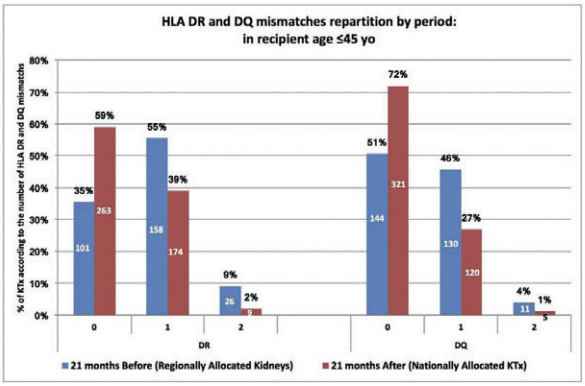
Introduction: A new Kidney Allocation System (KAS) was introduced in France as of February 2015, after a 3 years-simulation study in interaction with KTx advisory committee and patients' associations. The objectives of the new KAS were to increase transplant access rates and to maximize donor-recipient age and Class II HLA matching for young adults, as to prevent any further sensitization.
Methods: In addition to existing national allocation priorities for urgencies (no more possibility for dialysis), sensitized patients (full match, acceptable mismatch program) and children, a new scoring system was built, taking into account dialysis duration, time on the waiting list, recipient age, donor-recipient HLA and age matching, recipient's matched donor potential (an indicator of low access to well matched donors, counterbalancing the weight given to HLA matching) and travel time between procurement and transplant centers.
Results: At 21 months from its implementation, 5011 KTx were performed from DBD donors, allocated according to national priorities and programs (22%) and new allocation score at national level (32%) or local level (46%). Results compare the 21 months periods before and after new KAS implementation.

Figure 1 shows changes in transplant access rates according to recipient's age and figure 2 changes in HLA-DR and DQM mismatch in young adults between the 2 period. Results conformed to simulated and previously targeted results.
Conclusion: Although progressive decline of transplant access rates with age may raise ethical debate according to the societal background of each country, age and HLADR/DQ matching increase in young adults is indeed an ubiquitous relevant target, as a tribute to DSA appearance prevention and possibility to get a second KTx on the long run.





Clinical Liver Surgical technique

OS349 TECHNICAL ASPECTS OF LIVER TRANSPLANTATION – A SURVEY-BASED STUDY WITHIN THE EUROTRANSPLANT, SWISSTRANSPLANT, SCANDIATRANSPLANT AND BRITISH TRANSPLANTATION SOCIETY NETWORKS

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Background: Orthotopic liver transplantation (OLT) has emerged as the mainstay of treatment for end-stage liver disease. Technical aspects of OLT are still subject of ongoing debate and are widely based on personal experience and institutional protocols. Aim of the present study was to obtain an overview of technical aspects of OLT within the European transplant community.
Methods: In February 2017, an online-survey with 22 open-ended multiple-choice questions was sent to all centers of the Eurotransplant (ET; $n = 37$), Swisstransplant (ST; $n = 3$), Scandiatransplant (SCT; $n = 5$) and British Transplantation Society (BTS; $n = 7$) networks. The survey sought information on center-specific OLT case-load, techniques used for vascular- and biliary-reconstruction, modes of vascular reperfusion, intraoperative control of hemodynamics and usage of intraoperative drains. Both qualitative and quantitative methods were used for data-analysis.
Results: At 40-days follow-up, 41/52 (79%) centers responded. 49% percent of the centers reported piggyback (PB) and 41% total cava-replacement (TCR) as their standard technique respectively. No differences were found between the centers case-load and OLT-technique implemented ($p = 0.09$). In 61% of all centers, venovenous bypass (VVB) or temporary portacaval shunt (PCS) is not applied during OLT. VVB for TCR is routinely implemented in 12% and temporary PCS for PB in 10% respectively. Portal vein first reperfusion is used in 61%, followed by simultaneous portal vein and artery (15%), and retrograde reperfusion (12%). End-to-end choledocho-choledochostomy without biliary drain (85%) was the most common performed method of biliary reconstruction. 73% percent of the respondents believe that the above-detailed technical issues of OLT are not evidence-based and 81% would participate in randomized controlled trials (RCT).
Conclusion: Techniques of OLT vary widely among European centers. Well-designed multicenter RCTs are urgently needed.

OS350 BACK-TABLE HEPATIC ARTERY RECONSTRUCTION IN ORTHOTOPIC LIVER TRANSPLANTATION -INFERIOR OUTCOMES?

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Background: With an incidence of 20–50% variations on the anatomy of the hepatic artery are common. In the context of orthotopic liver transplantation (OLT) these variations often necessitate meticulous back-table hepatic artery reconstruction (HAR). Herein, we analysed our recent experience with back-table HAR in adult liver transplant recipients.
Methods: We performed a retrospective analysis of all consecutive adult OLT performed between January 1st, 2007 and December 31st, 2013 and analysed the correlation between requirement of arterial reconstruction on the incidence of arterial and biliary complications as well as its impact on patient and graft long-term survival.
Results: In total, we included 374 patients in our analysis, of which 30 patients required back-table HAR prior to implantation. Patients with jump-grafts on the abdominal aorta or unknown arterial anastomosis were excluded. Using the Spearman′s rank correlation our data revealed only one statistically significant weak positive correlation, the one between back-table HAR and arterial dissection of the hepatic artery (correlation coefficient = 0.146; $p = 0.005$). There were no other statistically significant correlations between HAR and the remaining analysed arterial and biliary complications such as arterial stenosis and thrombosis or bile duct leakage, bile duct anastomotic and non-anastomotic strictures. Requiring HAR resulted in 80% and 70% 1- and 5-year graft survival, respectively, versus 87% and 76% in the group without HAR ($p = 0.11$). In the HAR group 1- and 5-year patient-survival were 83% and 76%, respectively, versus 90% and 81% in the group not requiring HAR ($p = 0.31$).
Conclusion: Despite no statistically significant differences in patient- and graft survival there was a tendency towards inferior graft survival in livers requiring back-table HAR. This might reflect the observed weak correlation between back-table HAR and arterial dissection.

OS351 LIVER TRANSPLANTATION FOR INCURABLE HEPATIC ALVEOLAR ECHINOCOCCOSIS: FORTY-FOUR CASES FROM AN ENDEMIC REGION

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Hepatic alveolar echinococcosis (HAE) is a parasitic disease caused by Echinococcosis multilocularis. Symptoms are mostly non-specific. HAE is incidentally detected in more than one-third of patients. Treatment is surgical. In cases with biliary sepsis, portal hypertension, invasion of both liver lobes, and Budd-Chiari syndrome liver transplantation (LT) is indicated. We present here our HAE cases treated with LT.
Patient methods: Patients undergoing LT in for HAE in our institution between April 2011 and December 2016 were investigated retrospectively. The age, sex, symptoms, laboratory and radiological findings were collected.
Results: A total of 44 patients underwent LT for HAE. Fifteen were male. Mean age was 41 years (range 13–72 years). Most common indication for transplantation was hilar invasion. Thirty-five patients received living (LDLT) and 9 deceased donor liver transplantation (DDLT). The right lobe was used as the graft in all LDLTs. Inferior vena cava (IVC) resection was performed in 11 patients, 7 were replaced with cadaveric aortic grafts and 4 with bovine graft. Four patients underwent right hemidiaphragm resection. Portal vein was resected because of invasion in 2 patients and both were revised using bovine grafts. The bile duct was anastomosed duct-to-duct in 15 patients, whereas hepaticojejunostomy was performed on 29 patients. Hepatic artery anastomosis was done with microsurgery in all cases of LDLT.

Major complications included arterial thrombosis in 1 patient and bile leakage in 6 other. Two patients with bile leakage underwent biliary reconstruction with hepaticojejunostomy. The histopathological investigations revealed AE in all patients with chronic hepatitis B in 2.

Mean follow-up time was 16.1 months (range, 6–62 months). No recurrence in the graft occurred in any patient during follow up. However, AE was detected in the brain of 2 patients one year and 3 years after transplant and vertebral bones in one. Thirteen of the 44 patients (29.5%) died.

OS352 THE USAGE OF LIVE DONOR GRAFTS WITH MULTIPLE BILE DUCTS DOES NOT NEGATIVELY IMPACT PATIENT OUTCOME IN LDLT

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Background: It has been previously reported that the use of live donor (LD) liver grafts with multiple bile ducts (BD) increases the risk of BD related complications after liver donor liver transplantation (LDLT). The aim of this study was to evaluate the impact of multiple BD in LD grafts on the outcome following LDLT.
Methods: Between 2000–2015, 510 patients received adult-to-adult right-lobe LDLT at the Toronto General Hospital. Outcome-parameters of patients receiving grafts with ≥2 BD ($n = 190$) and those receiving grafts with one BD ($n = 320$) were compared.
Results: Demographic variables and disease severity were similar between both groups. Roux-y-reconstruction was significantly more common in the ≥2 BD-group (77.9% vs. 38.6%, $p < 0.001$). No difference was found in biliary complication-rates after LDLT (1 BD: 23.4% vs. ≥2 BD: 22.6%, $p = 0.914$). In the ≥2 BD-group, 98/190 (51.6%) patients were reconstructed with ≥2 anastomoses. The number of anastomoses did not impact on biliary complication-rates. Recipients' major complication-rate (Clavien ≥ 3b) was similar between both groups (1 BD: 41.6% vs. ≥2 BD: 44.7%; $p = 0.517$). In addition, the 1-(90% vs. 91%) and 10-year (70% vs. 68%) graft-survival was comparable between both groups ($p = 0.588$). However, patients who developed a biliary leak ($n = 53$) and additionally belonged to the ≥2 BD-group ($n = 20$) showed significantly worse graft-survival than the single BD-group ($n = 33$) (10-year graft-survival 89.6% vs. 68.4%, $p = 0.024$). There was no significant difference in the 1- and 10-year patient survival between both groups (1 BD: 92%, 75% vs. ≥2 BD: 94%, 78%, respectively; $p = 0.84$). Furthermore, patients receiving a graft with 3 BD ($n = 21$) showed similar graft survival compared to those with ≤2 BD ($n = 492$) (≤2 BD: 90%, 80%, 60% vs. 3 BD: 94%, 87%, 75%; $p = 0.745$).
Conclusion: This study demonstrated that selected LD grafts with multiple BD can be used safely and without negatively impacting on biliary complication

OS353 IMPACT OF ABERRANT LEFT HEPATIC ARTERY LIGATION ON THE OUTCOME OF LIVER TRANSPLANTATION

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Abstract:
Background: During LT (liver transplant), the graft is more exposed to ischaemic injury than the native liver because of the presence of a terminal circulation not replaceable by perihepatic arterial supply. The reconstruction of aberrant LHA (left hepatic artery) during LT ensures optimal vascularization of the left liver but can also be considered a risk factor for HAT (hepatic artery thrombosis). In contrast, the ligation of the aberrant LHA may lead to hepatic ischaemia with a potential risk of graft dysfunction and biliary complications. The aim of the study is to prospectively analyse the impact of ligation of aberrant LHA versus its reconstruction on patient outcomes after liver transplantation (LT). The study also aimed to describe a novel diagnostic algorithm to determine whether the aberrant LHA is an accessory or a replaced artery.
Methods/Materials: From 8/2005 to 12/2016, 419 LTs were performed in 402 patients. Five parameters were evaluated to determine whether the aberrant LHA was an accessory or a replaced artery. Based on our decision algorithm, aberrant LHA was ligated during surgery when assessed to be accessory, and it was preserved when assessed to be replaced.
Results: There were 138 anatomical variants of the hepatic arterial vascularization in 120/419 (28.6%) grafts. Overall, the incidence of aberrant LHA was 15.03% (63/419) of all transplanted patients. The LHA was ligated in 33 patients (52.4%) and preserved in 30 patients (47.6%). After a mean follow-up of 54.6 ± 37.3 months, there were no statistically significant differences in terms of hepatic artery thrombosis, primary non-function, early allograft dysfunction, biliary stricture or leaks between the two groups.
Conclusions: Ligation of an accessory LHA did not produce any significant clinical differences compared to the patients where the dominant LHA was preserved. The dominant LHA should be preserved in the absence of other evidence.

OS354 OUTCOME FOLLOWING RIGHT-EXTENDED SPLIT LIVER TRANSPLANTATION IN THE RECENT TRANSPLANT ERA

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Background: In case of appropriate donor quality and allocation of the liver to a small child classic liver graft splitting is performed with consecutive transplantation of the right-extended graft in an adult. Based on organ quality data a clearly superior outcome following split liver transplantation (LTX) has to be expected, especially in contrast to the decreasing donor quality in Europe since implementation of the MELD allocation system. However, literature data show an almost comparable outcome with a possibly higher complications risk compared to whole organ LTX.
Methods: We analysed our recipients of right-extended split liver grafts (2007–2015). Special regard was given to the splitting procedure (in-house liver graft splitting by the own team vs. external liver graft splitting by a different team with subsequent graft shipping).
Results: We found excellent donor data with young (28 ± 13 years) and hemodynamic stable donors (short ICU stay (3 ± 3 days), low max. catecholamine level (0.2 ± 0.2 µg/kg/min), low reanimation rate (23%)) with normal or at most slightly elevated liver enzymes. Recipient characteristics were comparable between patients with in-house vs. external liver graft splitting. However, cold ischemic time was significant longer in external liver graft splitting (14 ± 2 vs. 12 ± 2 h). Interestingly, there was a significant reduced patient and a clear trend to a reduced graft survival in patients with external liver graft splitting. Likewise the rate of biliary/vascular complications was higher in patients with external vs. in-house liver graft splitting (21/12% vs. 8/0%).
Conclusion: The outcome following right-extended split LTX is disappointing against the background of excellent organ quality. We found a negative impact of external liver graft splitting on the outcome and surgical complication rate. This may related to the prolonged cold ischemic time due to twofold transportation and the ignorance of the detailed splitting procedure and related pitfalls.

OS355 REDUCING TRANSFUSION REQUIREMENTS IN LIVING DONOR LIVER TRANSPLANTATION: DO WE NEED POINT OF CARE COAGULATION MANAGEMENT?

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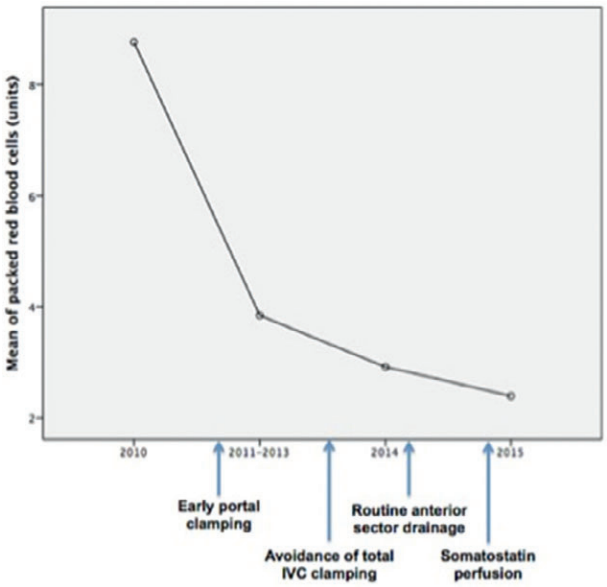
Introduction: Blood transfusion has been shown to be an independent predictor of outcome after liver transplantation (LT). Therefore, minimizing blood loss and reducing transfusion requirements are key goals in LT surgery. In this retrospective single-center cohort study, we reviewed the developments in our surgical technique and intraoperative management since 2010 and analyzed their impact on transfusion requirements during adult living donor LT (LDLT).
Material/Methods: We analyzed 468 adult patients who underwent right lobe LDLT between January 2010 and December 2015. The main advancements in this era were the introduction of early portal clamping during recipient hepatectomy and avoidance of total inferior vena cava clamping in 2011, routine anterior sector drainage using Dacron grafts and splenic artery ligation for portal flow modulation in 2014, and avoidance of fresh frozen plasma and use of somatostatin infusion during hepatectomy in 2015. During this time period, neither point of care (POC) coagulation tests nor coagulation factor concentrates were available for routine use in our institution.

Transplant year	Number of patients	Mean MELD score	Red blood cell (units)	Fresh frozen plasma (units)	Patients without transfusion	90-day mortality	1-year survival
2010	60	18.5 ± 8.1	8.7 ± 8.6	9.8 ± 4.1	10.2%	18.3%	73.3%
2011	73	16.9 ± 6.9	4.7 ± 6.0	8.3 ± 3.4	6.3%	5.5%	87.8%
2012	95	15.5 ± 5.1	3.6 ± 3.7	6.8 ± 2.8	27.0%	6.3%	88.6%
2013	88	16.8 ± 6.4	3.4 ± 3.4	4.8 ± 2.5	27.8%	5.7%	90.1%
2014	72	15.4 ± 5.2	2.7 ± 3.0	3.8 ± 1.7	25.0%	2.7%	93.1%
2015	77	15.2 ± 5.1	2.3 ± 3.1	2.6 ± 3.0	40.3%	3.9%	94.3%



Results: Mean pre and post-transplant hematocrit levels were 29.7 ± 6.0 and 30.2 ± 3.8, respectively. Starting from 2011, each innovation resulted in a significant reduction in transfusion requirement (ANOVA, $p < 0.001$), as well as a significant improvement in post-transplant survival (Log rank, $p = 0.006$). Intraoperative transfusion requirement showed significant correlation with both pre-transplant MELD score (Spearman's rho = 0.297, $p < 0.001$) and post-transplant 90-day mortality (Spearman's rho = 0.248, $p < 0.001$).
Conclusion: In LDLT, a number of intraoperative strategies are available to significantly decrease transfusion requirements without the use of POC coagulation monitoring.

Clinical Liver Ischemia-reperfusion and preservation

OS356 ANASTOMOSIS TIME DURING LIVER TRANSPLANTATION IMPAIRS TRANSPLANT SURVIVAL

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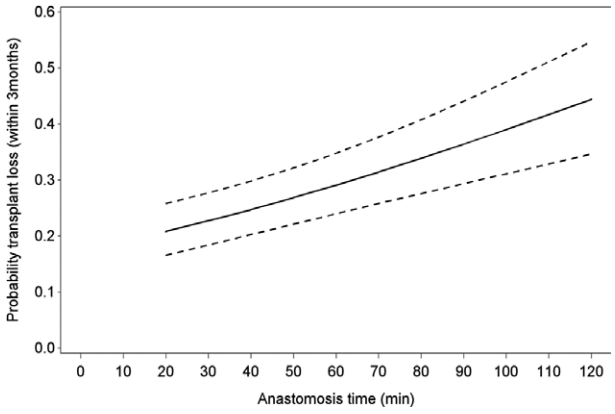
Background: Warm ischemia sustained during implantation might harm the liver graft.
Methods: We investigated the relationship between anastomosis time (AT) and transplant survival in 5223 recipients of deceased-donor livers transplanted in Eurotransplant (2004–2013). Cox regression analyses were corrected for donor, preservation, recipient variables. Transplant center was included as a random effect as it impacted outcome. AT lasted from graft leaving ice until portal reperfusion. Transplant survival represents all-cause graft failure.
Results: Median follow-up was 4.5 years (IQR 2.4–6.8). Median AT was 41 min (IQR 43–51). AT independently associated with transplant loss (adjusted hazard ratio 1.04 for every 10 min increase, 95% CI 1.01–1.07; $p = 0.007$). Other independent risk factors were donor/recipient age, donor terminal sodium, donation after circulatory death (DCD), split liver, cold ischemia time, lab MELD, acute liver failure, retransplant, and year of transplant. The magnitude of the AT-effect was comparable to the effect of each hour of additional cold ischemia time (adjusted hazard ratio 1.03, 95% CI 1.02–1.05; $p < 0.0001$). The AT-effect was most pronounced early post-transplant when the effect was allowed to differ between <3 months, 3–6 months, 6–12 months, >12 months in the multivariable model. The form of the relation between AT and risk did not suggest a clear cut-off after which the risk for transplant loss increases exponentially. The Fig. depicts the probability for transplant loss within 3 months in this cohort as a function of AT. The increased risk for transplant loss in DCDs could be attributed to donor warm ischemia time. There was no evidence that DCD livers are more susceptible to AT (no interaction between AT and DCD status), but there were only 208 DCDs in this cohort.



Conclusion: AT associates with inferior liver transplant outcome. The detrimental effect is most pronounced early post-transplant. Minimizing warm ischemia during implantation by reducing AT or keeping the graft cold might improve outcome.

Clinical Liver Surgical technique

OS357 ENDOSCOPIC TREATMENT OF EARLY BILE LEAKAGE FOLLOWING ORTHOTOPIC LIVER TRANSPLANTATION – A WORD OF CAUTION?

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Introduction: Biliary complications remain common following orthotopic liver transplantation (OLT) and are known to jeopardise graft survival. They can be managed either non-operatively via interventional stenting or by surgical treatment. Herein, we analysed our experience with adult patients suffering from early bile leakage following OLT.
Methods: We performed a retrospective analysis of all 1035 OLTs performed between January 1st, 2000 and October 1st, 2016. OLTs with biliodigestive reconstruction were excluded from the analysis. Early bile leakage was defined as leakage occurring within 30 days following OLT.
Results: In the analysed period, we identified 80 patients experiencing an early bile leakage. Our patients displayed the following characteristics: 63 recipients were males (78.7%) and 17 were females (21.3%), median recipient age at transplantation was 59 years (range 25–73) and the median labMELD score was 16 (range 6–40). The donor collective consisted of 49 (61.2%) male and 30 (37.5%) female donors (1 unknown) with a median age of 50 years (range 14–80); the median donor GGT was 51 IU/l (range 4–853 IU/l) and the median cold ischemia time was 8.8 h (range 3.9–18.2).

31 patients (38.3%) underwent endoscopic treatment, 49 patients (61.2%) surgical treatment. 5-year patient and graft survival rates following OLT in this cohort were 72.8% and 57.4%, respectively. Using cox regression donor GGT ($p = 0.008$) could be identified as a risk factor for worse graft survival while patient survival was not influenced by any of the analysed factors. Interestingly interventional treatment tended to be associated with inferior graft survival ($p = 0.094$) compared to the operative approach whereas both therapy options had similar patient survival rates.
Conclusion: Early bile leakage is associated with worse 5-year graft survival following OLT. The observed tendency for inferior graft survival in patients receiving endoscopic treatment should be further analysed.

OS358 IMPACT OF SIMULTANEOUS SPLENECTOMY IN LIVING DONOR LIVER TRANSPLANTATION ANALYZED BY PROPENSITY SCORE MATCHING

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Background: Simultaneous splenectomy is indicated in living donor liver transplantation (LDLT) for portal flow modulation, especially when small graft was used. There has been no prospective randomized trial to elucidate its impact. The aim of this study was to investigate the impact of simultaneous splenectomy in LDLT by propensity score matching analysis.
Methods: Data from 517 patients who underwent LDLT were collected retrospectively. Patients were divided into two groups according to the performance of simultaneous splenectomy as follows: 315 patients with splenectomy and 202 without splenectomy. Propensity score matching analysis was used to overcome selection biases.
Results: Among 517 eligible patients, 211 patients were discarded after propensity score matching; 153 patients in each group were remained. There was no significant difference in recipient age, recipient gender, donor age, donor gender, presence of HCV RNA in recipient, graft type, graft weight-standard liver weight ratio, ABO compatibility, MELD score, pre-LDLT white blood cell count, or platelet count between two groups. Total bilirubin (4.9 vs. 9.1 mg/dl, $p < 0.001$), drainaged ascites (347 vs. 762 ml, $p = 0.001$), or PT% (83 vs. 70, $p < 0.001$) on 14 post-operative day was significantly better in the splenectomy group. Acute cellular rejection less occurred in the splenectomy group (13.2% vs. 23.5%, $p = 0.03$). Graft survival rate 6-month after LDLT was significantly better in the splenectomy group (94.8% vs. 86.2%, $p = 0.01$). Among 153 patients, splenectomy-related complication, such as pancreatic fistula, portal thrombus, bleeding from surgical stump or portal thrombus occurred in 13 patients, 3 patients, 1 patient, or 4 patients, respectively.
Conclusions: Simultaneous splenectomy in LDLT improves survival rate and achieves a lower risk of graft dysfunction after LDLT. Technical refinement to avoid splenectomy-related surgical complication is required.

OS359 SURGICAL OUTCOMES OF LIVING DONOR LIVER SURGERY: TECHNICAL KNACK FOR ZERO MORBIDITY

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In living donor liver surgery, safety and minimal invasiveness should be the most essential. Though practical donor surgery consists of basic surgical procedure, there would be room for improvement for zero-morbidity. We demonstrate the knack and pitfalls of living donor surgery with case-review.
Knack & Pitfalls: 1. Safety: The precise vascular anatomy and liver volumetry should be identified by preoperative imaging. Basically, all procedure should be appropriately performed by gentle handling.

2. Liver transection: CUSA & soft coagulation system can be mainly used for resection. These can work for resection and hemostasis in parallel. The intervention of Pringle maneuver could depend on blood loss. The glissonian branch should be ligated, especially in the area adjacent to hepatic hilus. And the hanging maneuver is useful for dorsal liver resection.

3. Control of outflow system: Hepatic vein pressure would be a key factor of blood loss. Accordingly, keeping low CVP and lifting the cut surface could contribute to blood loss reduction.

4. Biliary complication: Basically, problematic bile leakage can occur from bile duct stump or caudate lobe. Precise bile duct transection and suturing should be indispensable. In case of right lobe graft, a stump could be covered by ligament of teres hepatis.

VIDEO case: Right lobe graftectomy. Anterior liver parenchyma was widely transected along the Rex-Cantlie line. Subsequently, MHV trunk was exposed at cut surface. And V5/V8 could be preserved till graftectomy by tape repositioning for hanging maneuver (No Pringle, OR time 4:50, blood loss 50 ml).

Clinical overview: 131 living donor ('08–'15) were divided into the 1st group ($n = 91$) and the 2nd group ($n = 40$). Concerning the surgical outcomes, the 2nd group showed the improvement in blood loss (664 ml vs. 240 ml, $p = 0.0014$), and morbidity (C-D > grade II, 9.9% vs. 7.5%, NS).

Conclusion: Promising intervention and surgical innovation could improve the surgical outcome of living donor surgery.

Clinical Pediatric transplantation Donation and donor types

OS360 PEDIATRIC LIVING DONOR LIVER TRANSPLANTATION USING PURE LAPAROSCOPIC DONOR HEPATECTOMY: A COMPARATIVE STUDY

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Objectives: To evaluate outcomes and complication with pediatric living-donor liver transplant, especially performed with laparoscopic donor hepatectomy

Introduction: There were some papers about the CO2 gas which using it during laparoscopic surgery has adverse effect on survival of graft. Then we want to evaluate the effect of laparoscopic circumstance on the aspect of transplantation surgery.

Materials and methods: Between May 2008 and June 2014, there were 27 children age $\leq$ 17 years who received a liver transplant.

Demographic characteristics, patient survival, rejection episodes, and complications were recorded.

Statistical methods included simple descriptive analysis and Kaplan-Meier method. Statistical significance was defined by $P \leq 0.05$

Results: The mean patient age was 1.6 $\pm$ 1.61 and was 11 male (39.3%) and 16 female (57.1%). Mean total bilirubin was 13.8 $\pm$9.5 and mean INR was 1.44 $\pm$ 0.57. Biliary atresia was the most common cause of end-state liver disease and mean PELD score was 14.5 $\pm$ 7.3. 24 patients were performed Laparoscopic Left lateral sectionectomy and 3 patients were performed Laparoscopic Left hepatectomy. The most common cause of complication was acute cellular rejection (25.9%). Mean follow-up period was 59.2 months (range 4.2–93.1)

There were not reported on In-hospital mortality and all patients were survived until end of follow-up date. (Dec. 2015).

Conclusions: Laparoscopic donor hepatectomy was feasible and safe tool for living-liver transplantation and may provide excellent graft outcomes in children.

The circumstance of laparoscopic surgery has not adverse effect on recipient of living donor liver transplantation.

Clinical Kidney Immunology

OS361 PREFORMED DONOR HLA-DP SPECIFIC ANTIBODIES INFLUENCE THE RISK OF ANTIBODY MEDIATED REJECTION IN SENSITIZED PATIENTS WITHOUT ANY OTHER PREFORMED DONOR HLA SPECIFIC ANTIBODIES

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Background: The clinical relevance of preformed (PF) HLA-DP donor specific antibodies (DSA) on antibody mediate rejection (AMR) is still controversial, especially when present solely. Our aim was to determine the impact of PF DSA and non-DSA anti HLA-DP antibodies (Abs) on incidence of AMR, 1 and 2 years graft function and delayed graft function (DFG).

Methods: Retrospective analysis of HLA antibodies was conducted in 456 patients transplanted between 1/2012-1/2016. All pretransplant CDC crossmatches were negative. HLA antibody screen was performed by Luminex using Lifecodes LSA Class I and Class II (SAB) kits (Immucor, USA), setting positivity at MFI > 1000. Clinical data were analysed for a total of 80 patients including all with anti-HLA-DP Abs and two control groups selected randomly. Immunosuppression (IS) consisted of induction therapy and triple IS protocol.

Results: Among 456 renal recipients, 123 had anti HLA Abs (27%), among them 32 (7% of all patients; 26% of immunized patients) had anti HLA-DP Abs. The analysis revealed that 12 patients (10% of immunized patients) had PF HLA-DP DSAs. Final analysis was conducted on 26 patients with PF DP Abs (DP group), 26 patient with PF non-DP-anti-HLA Abs (Imm group) and 28 non-immunized patients (NonImm group). Patients with PF DSA anti HLA-DP had AMR more frequently compared to those in Imm group (17% vs. 4.5%, $p = 0.028$) and compared to Imm group and NonImm group taken together (17% versus 1.5%, $p = 0.01$). Furthermore, DP group had highest DGF rates compared to Imm and NonImm group (55.6%, 43.3%, 12.5% respectively, $p = 0.005$) and anti-DP Abs were an independent predictor of DGF (OR 7.3 [1.6, 34.1]). There were no differences in 1 and 2 year graft function between the studied groups ($p > 0.05$).

Conclusion: This study indicates that PF HLA-DP DSAs, without presence of any other anti HLA DSAs have impact on incidence of AMR and DGF but without influence on 1 and 2 years graft function.

OS362 DISTINCT USEFULNESS OF PRETRANSPLANT ENDOTHELIAL CELL CROSSMATCH AND ANGIOTENSIN II TYPE 1 RECEPTOR ANTIBODIES TO PREDICT GRAFT FUNCTION AND ALLOGRAFT REJECTION IN KIDNEY TRANSPLANTATION

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Background: Anti-endothelial cell antibodies (AECAs) and anti-angiotensin II receptor 1 antibodies (anti-AT1R) have been known to play a role in allograft rejection. The aim of this study was to evaluate the impact of both tests on post-transplant outcome in low risk living donor kidney transplantation (LDKT) recipients.

Methods/Materials: We prospectively included 94 consecutive low risk LDKT recipients who were ABO compatible, negative CDC crossmatch for T and B donor cells with no pre-transplant donor-specific antibody (DSA), and less than 50% cPRA. We determined the presence of AECAs using a flow cytometric endothelial cell crossmatch (ECXM) test, XM-ONE assay (Absorber AB, Stockholm, Sweden) and measured the concentration of anti-AT1R antibodies (Onelambda Inc., Luckenwalde, Germany) in pretransplant sera which acquired at the same time for CDC crossmatch.

Results: Rejections occurred in 40 recipients (42.6%) between day 7 and day 1035 post-KT. AECAs were detected in 22 recipients (23.4%), and the results of anti-AT1R antibodies were that 49 were $\geq$10 U/ml (52.1%) and 45 were < 10 U/ml (47.9%). There were no significant differences in occurring rejection between positive and negative ECXM. However ECXM+ group had a significantly higher creatinine and lower eGFR at 6 months ($p = 0.0016$; $p = 0.0168$) and 12 months ($p = 0.0001$; $p = 0.0066$) compared to 1 month post-transplant. The change pattern for creatinine levels of ECXM+ between 1 month and 12 months post-transplants were different significantly compared to that of ECXM- group ($p = 0.0225$). Multivariate analysis showed that anti-AT1R $\geq$10 U/ml was an independent predictor of allograft rejection (HR = 2.031).

Conclusion: We found that the presence of pretransplant anti-AT1R antibodies and AECAs detected by ECXM test have different impact on post-transplant KT outcomes. Therefore, it may be prudent to consider both tests as pretransplant immunological work up for optimizing post-transplant outcome in KT recipients.

OS363 COST EFFICACY OF SIMULTANEOUS IMMUNE ADSORPTION AND HAEMODIALYSIS IN ABOI RENAL TRANSPLANTATION

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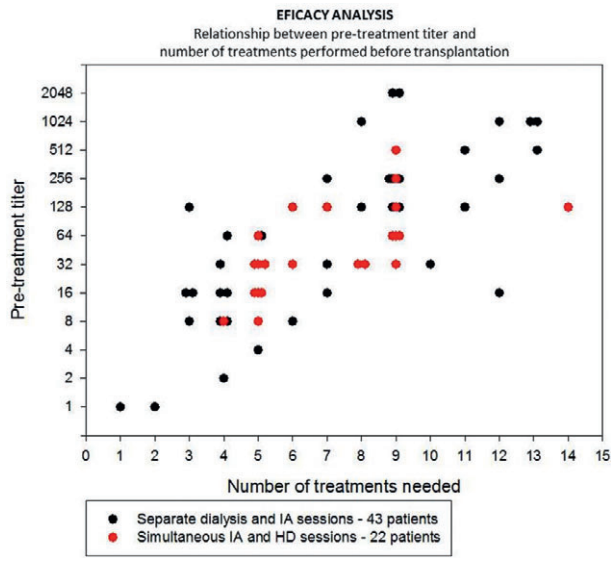
Background: Immune adsorption (IA) sessions for removal of isoagglutinins to allow for ABO incompatible renal transplantation are costly. In haemodialysis (HD) patients regular HD sessions are needed on top of the IA sessions. Fitting an IA column on a standard HD machine by the use of two standard infusion pumps makes it possible to perform simultaneous IA and HD potentially save time and money.

Methods: We compared the efficacy and cost of IA on a Fresenius Art Universal equipped with a Glycorex column (IA group; 43 patients) with



combined IA and HD on a Gambro AK-200 HD machine also fitted with a Glycorex IA column (IA+HD group; 22 patients)
Results: Maximum plasma flow in IA+HD sessions with two pumps was 40 ml/ml compared to 50 ml/min on IA sessions (column maximum). In the 22 IA+HD patients only 1 in-between HD sessions was needed. We found no differences between groups regarding pre-treatment titers or sessions needed before reaching level needed for transplantation (figure). Furthermore, no difference in biochemical parameters for pre- and post-treatment values for haemoglobin, lactate dehydrogenase or thrombocyte count or in treatment related hypotensive episodes.

An IA session on a standard Gambro AK-200 saved approximately 493 Euro per session in fittings and tubing compared to IA on a Fresenius Art Universal.
Discussion: Simultaneous IA+HD on a standard HD machine are efficacious and save time and money.

Clinical Kidney Histology

OS364 THE PROGNOSTIC VALUE OF INDIVIDUAL HISTOLOGIC LESIONS AND COMPOSITE SCORES IN BASELINE BIOPSIES FOR SHORT-TERM KIDNEY ALLOGRAFT FUNCTION

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Zaporizhzhia Medical Academy of Post-Graduate Education Ministry of Health of Ukraine, Ukraine

Background: We aimed to study the association of individual and composite histologic lesions in 0-biopsies with short-term kidney graft function.
Methods/Materials: Pre- and 30 minutes postimplantation biopsies were taken in the recipients of cadaver ($N = 101$) and living ($N = 29$) kidney. Scoring was performed jointly in two biopsies, except for acute tubular injury (ATI). We assessed individual lesions, Banff scores for indication (ind-Banff) and 0-biopsies (0-Banff), Remuzzi score, donor damage score (DDS), chronic damage score (CDS), and chronic allograft damage index (CADI). Serum creatinine was measured daily up to 7th day; GFR was estimated at discharge and at 3 and 6 months. We used multinominal logistic regression to evaluate predictors of slow graft function (SGF, i.e., serum creatinine on day $7 \geq 300$ μmol/L) and delayed graft function (DGF, i.e., ≥1 dialysis during first week posttransplant). Binary regression was applied for predictors of low GFR at discharge, and negative monthly slope of GFR up to month 6.
Results: Chronic ischemic glomerulopathy (CIG) predicted SGF but not DGF in multivariate analysis (OR = 1.24, $P < 0.05$). CADI, DDS, CDS, chronic and total ind-Banff and 0-Banff scores predicted lower, below median (49 ml/min) GFR at discharge ($P < 0.05$), however, none of them remained significant after adjustment for clinical variables. ATI in preimplantation biopsies, glomerulosclerosis, atherosclerosis, arteriolar hyalinosis individually predicted lower GFR at discharge. ATI remained significant (OR = 14.94) after adjustment for clinical variables. Median monthly GFR slope was +3.11 ml/min. 17.7% of patients demonstrated negative slope, which was predicted by glomerular thrombi (GT) in multivariate analysis (OR = 3.70, $p < 0.05$). Composite scores were not associated with DGF, SGF and negative slope of GFR.
Conclusion: Worse early kidney allograft function can be significantly predicted by CIG, ATI, and GT in baseline biopsies.

OS365 PREDICTIVE ABILITY OF IMPLANTATION BIOPSY FOR SLOW GRAFT FUNCTION AFTER KIDNEY TRANSPLANTATION

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Background: Delayed graft function (DGF) has an impact on long-term renal transplant outcomes in registry studies. However, an association between renal histology and DGF including slow graft function is unclear.
Methods: We investigated associations between clinical data and biopsy findings from 256 patients who underwent deceased kidney transplantation between November 2009 and January 2015. Associations of slow graft function on the basis of creatinine reduction ratio between days 1 and 2 (CRR2) and three histological scoring systems were examined. Patients were divided into three groups according to CRR2: IGF (immediate graft function; CRR2 > 30%), ND-DGF (non-dialysis-requiring DGF; CRR2 < 30%), and D-DGF (dialysis-requiring DGF). Banff classification, Remuzzi score and Maryland Aggregate Pathology Index (MAPI) were used in histological evaluation.
Results: IGF, ND-DGF, and D-DGF accounted for 81, 82, and 93 patients respectively. Recipient age, donor age, and donor type, tubular atrophy, fibrous intimal thickening, arteriolar hyaline thickening, Remuzzi score, and MAPI were significantly different between three groups. However, all parameters in ND-DGF and D-DGF did not significantly differ except donor type ($p = 0.0005$). By multivariate logistic regression analysis, arteriolar hyaline thickening ($p = 0.0054$; OR = 1.66 [1.17–2.39]), and MAPI ($p = 0.0084$; OR = 1.13 [1.03–1.24]) were independent risk factors for DGF. And arteriolar hyaline thickening ($p = 0.0320$; OR = 1.56 [1.03–1.53]), fibrous intimal thickening ($p = 0.0292$; OR = 1.45 [1.05–2.05]), Remuzzi score ($p = 0.0255$; OR = 1.25 [1.03–1.53]), and MAPI ($p = 0.0235$; OR = 1.12 [1.02–1.24]) were independent risk factors for ND-DGF/D-DGF.
Conclusion: Implantation biopsy was highly predictive of DGF. We recommend MAPI and arteriolar hyaline thickening scoring system as an appropriate tool for future studies and clinical decision making about minimizing calcineurin drugs in immediate post-transplant setting.

Clinical Kidney Rejection

OS366 INTERIM RESULTS OF THE PRISM (PREDICTION OF REJECTION IN SENSITIZED PATIENT BLOOD SAMPLES) TRIAL

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kSORT is a novel PBMC biomarker that detects clinical and sub-clinical acute rejection (AR) with high sensitivity (Roedder *et al*, Crespo *et al*), using the following risk scores for rejection: High-(HR), Low-(LR), Indeterminate-(IR) risk. We evaluated serial kSORT performance to predict AR and borderline (BL) graft inflammation in high immunologic risk pts in the first 6 months after kidney tx.
Methods: 78 patients with a cPRA > 50% were followed for 6 months after tx when they underwent a protocol kidney biopsy (bx). Blood for kSORT was obtained pre-tx, post-tx at 2 wks, 1 mo, 2 mo, 3 mo, 6 mo and at AR. Patients received Thymoglobulin induction and TAC/MMF/steroids.
Results: Data is on 69 evaluable pts. 58% pts had cPRA ≥ 90%, with mean cPRA= 87.64 ± 14.98%. 78% of pts had biopsies ($n = 54$) for a total of 69 bx (28 clinical for cause bx and 41 protocol bx).

Pre-tx kSORT predicted HR in 22% ($n = 10$), LR in 70% ($n = 32$), and IR in 6% ($n = 4$) pts. Having a pre-tx LR score had an 80% confidence for remaining rejection free in the first 6 mo after tx, with an NPV of 0.81 for AR and 0.76 for BL. Post-tx kSORT scores were correlated with bx results ($p = 2 \times 10^{-8}$): post-tx kSORT-HR predicted AR in all 12 cases of either AR ($n = 7$) or BL ($n = 5$) rejection and none of the non-rejection samples (NPV of 0.8 for both AR and BL rejection). LR-kSORT was only associated with NR (88%; $n = 28$) and 58% of BL ($n = 7$) phenotypes. Post-tx kSORT-IR was seen in 24% ($n = 15$, distributed as 5 AR, 6 BL and 4 NR). A sub-analysis of the 41 protocol bx shows that of the 23 patients with normal pathology, all were LR-kSORT.
Conclusion: kSORT has utility in the management of highly sensitized tx pts. A LR kSORT score pre-tx can predict absence of AR and BL in the first 6 mo after tx with 80% certainty. Serial kSORT could be used for used for Precision Medicine management to optimize outcomes of sensitized renal tx recipients.

OS367 LONG-TERM RESULTS OF DESENSITIZATION PROTOCOL WITH AND WITHOUT RITUXIMAB IN HIGHLY SENSITIZED KIDNEY TRANSPLANT RECIPIENTS

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The introduction of Rituximab has been a promising agent added to desensitization protocols allowing transplantation of high risk patients with anti HLA-Abs. However its long term effect is still unclear. We sought to determine the long term results after kidney transplantation using desensitization protocol with and without Rituximab in patients with anti-HLA Ab.
Patient and methods: We preformed a retrospective analysis of our group of patients (n = 37) undergoing desensitization with (17) and without Rituximab (20) between 12/2006-12/2012. The desensitization protocol was instituted in patients with anti-HLA Abs having a negative serological NIH-CDC crossmatch. The protocol included plasmapheresis X3 and IVIG (0.5 g/kg). In patients with high DSA (>7500 MFI) Rituximab, a single dose of 500 mg was given 2 weeks before transplant. We analyzed the incidence of cellular and antibody-mediated rejection (AMR) as well as graft and patient survival at 1 &5 yr. for the whole cohort and for the two groups with and without Rituximab.
Results: The mean age of the cohort was 43 yr. (10–65 years. The mean PRA was 71.8% (10–100%). There were 18 recipients of a 1st, 16 a 2nd, two a 3rd and 1 a 5th transplant. The Mean MFI at base-line and after treatment before transplant were 8404 and 3029, respectively. There were 3 episodes of AMR in the no-Rituximab and one in the Rituximab group. Nine patients lost their graft due to the following reasons: chronic rejection (6), recurrent disease (1) and death with a functioning grafts (2). Graft survival for 1 &5 years were 100% and 87.4.1%, for the Rituximab group and 100% and 80% for the no-Rituximab group (p = 0.88).
Conclusions: The results after desensitization protocol in highly sensitized patients undergoing kidney transplantation are good but the long-term outcome may be hampered by early development of chronic rejection. The addition of Rituximab to desensitization protocol seems to protect against AMR in the high MFI group.

Clinical Kidney Immunology

OS368 C3D NEGATIVE HLA-SPECIFIC DSA PRE-TRANSPLANTATION DOES NOT HAVE ADVERSE OUTCOME FOLLOWING DIRECT TRANSPLANTATION DESPITE POSITIVE CROSS MATCH AGAINST THE DONOR

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Characteristics	C3d negative HLA-DSA	C3d positive HLA-DSA	p Value
Age (mean)	43.5	39	0.010
Gender (% female)	73	51	0.012
Previous kidney Transplantation (mean no.)	0.73	1.0	0.015
Duration of ESRD (years, mean)	9.35	12.56	0.026
DR mismatch (mean)	0.9	1.05	0.119
Total HLA mismatch (A,B,DR; mean)	2.8	3.3	0.046
CDC positive crossmatch (%)	15.56	36.36	0.005
Highest MFI IgG DSA	4438	13158	<0.0001

Introduction: Complement activating characteristic of donor specific antibodies (DSA) may be an important factor that predicts long term renal allograft outcome. The objective of this study is to study the complement activation properties of the donor HLA specific antibodies in a cohort of patients who have undergone HLA incompatible renal transplants.
Methods: 146 cases from four University Hospitals in UK, who were either complement dependent cytotoxicity (CDC) or Flow Crossmatch positive at preconditioning and underwent direct transplantation after desensitisation protocol were selected (Baseline characteristics shown in Table). C3d (Immucor) assay was performed at preconditioning and peak IgG post transplantation, results were correlated with early antibody mediated rejection (EAMR) (within first 30 days) and death censored allograft survival (DCGS). Statistical analyses performed using IBM SPSS software.
Results: C3d positive DSAs were present in 55 (38%) cases out of 146 at preconditioning. Median follow-up was 46 months (interquartile range = 19–73 months). Presence of C3d positive DSAs was not predictive of EAMR (p = 0.12) and rejection free survival in first 30-days was not significant (p = 0.089). The relative risk of EAMR was 1.396 (0.95–2.06) and odds ratio was 1.778 (0.90–3.52). C3d DSA presence correlated significantly with poor graft survival (p = < 0.001) (Figure). The relative risk of DCGS was 2.95 (1.68–5.18) and odds ratio was 4.58 (2.1–9.98) (p < 0.0001). The risk of graft failure was highest if there was persistent C3d DSA with relative risk of 4.3 (2.08–8.91) and Odds ratio of 8.93 (2.97–26.86) (p < 0.0001) (Figure).
Conclusion: Presence of pre-transplant cross match due HLA-DSA IgG antibodies that are non-complement activating (C3d) does not effect mid-term allograft survival. This finding may enable the differentiation of IgG antibodies of varying pathogenicity and the potential role of C3d as additional biomarker in pre-transplant workup.

Clinical Kidney Histology

OS369 IMPACT OF THE BASELINE ANTI-A/B ANTIBODY TITER IN ABO-INCOMPATIBLE LIVING KIDNEY TRANSPLANTATION

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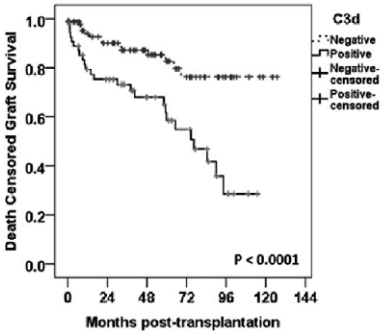
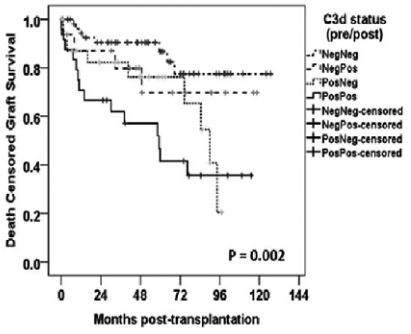
Background: We investigated the impact of the baseline anti-A/B antibody titer on the clinical outcome in ABO incompatible living kidney transplantation (LKT).
Methods: We included 73 patients who had undergone ABO incompatible living kidney transplantation (LKT) at our hospital between 2009 and 2016. 24 patients with a baseline titer of ≥1: 256 were assigned to the high-titer group and 49 patients with a baseline titer of ≤1: 128 were assigned to the low-titer group. We compared the clinical outcomes of the two groups. Retrospective





analysis included blood group; baseline and post operative isoagglutinin titer; number of pretransplant plasmapheresis; and clinical outcomes including postoperative serum creatinine and glomerulitis plus PTCitis score on post operation 1 hour protocol biopsy
Results: Preoperatively, rituximab administration and plasmapheresis were performed until the titer was reduced to ≤1:16. high titer group needs more pretransplant plasmapheresis than low titer group (3.8 vs. 6.6). The mean serum creatinine at 1 (0.9 mg/dl vs. 1.0 mg/dl), 3 (1.0 mg/dl vs. 1.1 mg/dl) months did not differ significantly between low and high titer group. Also, number of rejection (2/49 vs. 2/24 cases) and graft loss (3/49 vs. 2/24 cases) and patient loss (0/49 vs. 1/24 case) did not differ significantly between low and high titer group. Glomerulitis plus PTCitis score on postoperative 1 hour protocol biopsy shows no difference between low and high titer group (0.5 vs. 0.0).

Table 1. Clinical variables after renal transplantation

Variable	Low titer(n=49)	High titer(n=24)	P
POD 1month			
1)Anti-AB titer	5.93	6.37	NS
2)Serum Cr(mg/dl)	0.89	1.02	NS
POD 3 months			
1)Serum Cr	1.04	1.10	NS
1hour biopsy			
1)g+ptc score	0.46	0.00	NS
Rejection	2	2	NS
Graft loss	3	2	NS
Patient loss	0	1	NS

Conclusion: There is no correlation between high and low baseline anti-A/B antibody titers and the results of ABO-incompatible LKT was seen after rituximab and optimal pretransplant plasmapheresis with optimal immunosuppressant.(tacrolimus, mycophenolate mofetil, steroids, IL-2 blocking agent (Simulect)) application

Clinical Kidney Rejection

OS370 ASSOCIATION OF REPEATED HLA MISMATCHES WITH GRAFT SURVIVAL IN KIDNEY TRANSPLANTATION: DATA FROM THE DUTCH TRANSPLANT REGISTRY

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Background: Kidney re-transplantation is a risk factor for decreased allograft survival. Among other factors, repeated mismatched (RMM) HLA antigens potentially trigger an alloimmune memory response against the graft, resulting in antibody mediated rejection or chronic allograft nephropathy.
Objective: To evaluate the risk of a RMM (on the A, B or DR locus) on kidney allograft survival in the Dutch transplant registry.
Methods: Between 1994 and 2014 records of 1698 re-transplants were found in the Dutch transplant registry. Of 160 transplantations no clinical data were available and of 517 transplantations there were missing HLA data of a (previous) transplantation, leaving 1021 transplantations available for the analyses. The primary end point was graft failure with a potential immunological cause. Cox regression analysis was performed to calculate hazard ratios (HR) in RMM transplantations. Adjustments were performed for donor and recipient characteristics, year of transplant and PRA. Multiple imputation with 5 repetitions was performed to account for missing covariates.
Results: 919 transplantations (90%) were performed with a kidney without a RMM and 102 transplantations (10%) had a RMM on the A,B or DR locus (or both). Baseline characteristics were comparable between the groups. 299 death-censored graft failures were registered of which 192 (64%) were classified as graft failures with a potential immunological cause. Of these graft failures, 19 occurred in the RMM group. After a median follow-up of 5.9 years, a significant decreased death-censored graft survival was observed for a DR RMM. Further analysis revealed an adjusted hazard ratio for immunological graft failure of 2.42 (1.32–4.42) for a HLA-DR RMM and 0.85 (0.43–1.68) for a HLA-A or HLA-B RMM.
Conclusion: A HLA-DR, but not HLA-A or -B RMM confers a substantial increased risk for graft failure. The risk of a HLA-DR RMM has to be weighed against the risk of staying on dialysis.

Translational Kidney Rejection

OS371 PRETRANSPLANT EXPRESSION OF CD45RC ON BLOOD T CELLS TO PREDICT ACUTE ALLOGRAFT REJECTION AND CANCER IN KIDNEY TRANSPLANTATION: A LONG-TERM ANALYSIS

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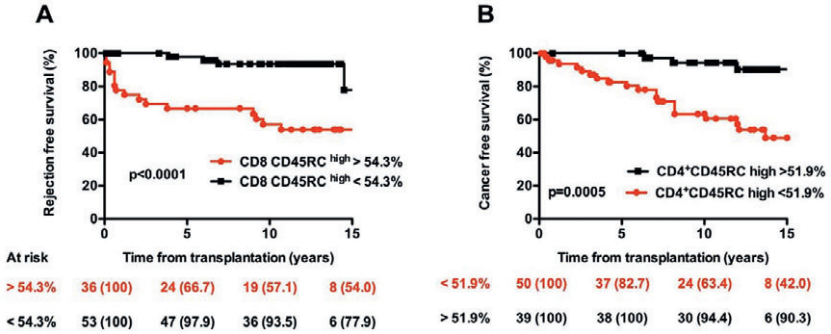
We previously reported that pretransplant expression of CD45RC, expressed on CD8+ T cells is associated with the risk of developing acute rejection (AR) at five years of follow-up in a cohort of kidney transplant recipient (KTR) [1]. The objective of the present study was to analyze the relationship between pretransplant CD45RC expression on T cells and the post-transplant outcomes, including AR and cancer in the long-term follow-up.

Pre-transplant expression of CD45RC on CD4+ and CD8+ circulating blood T cells was determined in a cohort of 89 consecutives, first time KTR. AR, cancers and deaths were retrospectively registered and characterized. The relationship between frequencies of both CD4+ and CD8 + CD45RC T cells subsets and posttransplant events was analyzed.

AR, cancer and patient death occured in 20 (22.5%), 25 (28.1%) and 14 (15.7) patients, respectively after a mean follow-up of 11 years. Pre-transplant frequency of CD8 + CD45RChigh T cells >54.3% was strongly associated with AR conferring a 4–7 fold increased risk after adjustment on classical risk factors. Cancer was associated with a decreased proportion of CD4 + CD45RChigh T cells, with a frequency < 51.9% conferring a 3.5–5.5 increased risk of malignancy. Figure 1 A&B represents AR and cancer free survivals according to predetermined cell subset frequencies, respectively. Frequencies of CD4+ and CD8 + CD45RChigh T cells were positively correlated ($p < 0.0001$) suggesting that recipients at high AR risk display a low cancer risk.

As a conclusion, pre-transplant T cell expression of CD45RC is strongly associated with AR and cancer development in KTR. Thus, our results suggest that CD45RC appears as a double-edged sword biomarker of promising interest to assess both AR and cancer risk before kidney transplantation.

Figure 1 (A) Acute rejection and (B) cancer free survival according to frequencies of CD45RC subsets. Kaplan-Meyer analysis, comparisons were done using log-rank test.



Clinical Kidney Immunology

OS372 PREDICTIVE VALUE OF PRE-TRANSPLANT CROSS-MATCH TECHNIQUES ON LIVING DONOR KIDNEY TRANSPLANT OUTCOMES

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Background: Despite the availability of multiple sensitive immune tests assessing the risk of rejection prior to Living-donor kidney transplantation (LDKT), their precise predictive value is still not well characterized. We aim at investigating the impact on main clinical outcomes of the different cross-match techniques and their combination in a cohort of LDKT.
Methods: Retrospective study including 342 LDKT recipients from 2 transplant centres in Barcelona (Spain) and 902 LDKT as external validation cohort from San Francisco (CA, USA). LDKT were AB0 compatible with negative CDC-crossmatch. Mean follow-up: 69 months. We evaluated: B/T-cell Flow-cytometry-crossmatch (FCM), Solid-phase assay (SpDSA) and complement binding DSA (DSAC3d+) test.
Results: In the first cohort, 30/342 (9%) were SpDSA+(9 class I, 12 II, 9 I+II; mean MFI 8873 ± 6273); 17 (5%) FCM+ and 18 (5%) DSAC3d+. Out of 30 SpDSA+patients, 14 (46%) displayed FCM+(anti-T and B), with no difference in mean SpDSA MFI compared to FCM-group.

70/902 (8%) LDKT of the external cohort showed spDSA+(mean MFI 6034 ± 5583): 23 class I, 41 II, 6 I+II. 24/72 (33%) showed FCM+(4 anti-T, 7 B, 13 T+B) no differences regarding SpDSA MFI. DSAC3d+ showed significantly higher SpDSA MFI (mean 12414 ± 5884, $p < 0.001$), a cut-off of 6192 predicted C3d positivity (AUC = 0.84).

Multivariate analysis predicting acute rejection (AR), revealed that DSAC3d+(OR 7.25, $p = 0.027$) and DSAMFI > 6190 (OR 8.26, $p = 0.026$) were the only independent predictors.

At univariate COX regression all the tested techniques and previous AR were associated to graft loss, while at multivariate analysis previous AR (HR 6.66, $p < 0.001$) was the only parameter independently predicting outcome.
Conclusions: Preformed DSAC3d+ or high MFI SpDSA are best predictors of AR, which in turn is the solely independent variable predicting high risk of graft loss. A virtual cross-match using SpDSA seems to be the most useful immune tool to predict AR and thus, patients at increased risk of premature graft loss.

Clinical Ethics / law / psychosocial / public policy Donation and donor types

OS373 RECORD-BREAKING TRENDS IN DECEASED ORGAN DONATION AND TRANSPLANTATION IN THE UK

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NHS Blood and Transplant, United Kingdom

Introduction: The number of donors after brain death (DBD) in the UK declined gradually for many years, leading to the British Government establishing an Organ Donation Taskforce in 2006 to recommend solutions to increase the number of transplants performed. The recommendations were implemented and aimed to increase the number of donors by 50% over 5 years.
Results: Over recent years, due at least in part to significant investment in a new organ donation infrastructure, the number of deceased organ donors in the UK has risen markedly, and did increase by 50% in the first five years after the Task Force recommendations were implemented.

The increase has been sustained and over the last 10 years there has been almost a 4-fold increase in DCD donors (to 579 in 2015/16), and the number of DBD donors has increased by 24% to 785 last year. The UK donor rate per million of population (pmp) was 21.0 last year (12.1 pmp DBD, 8.9 pmp DCD), a record high for the UK.

Acceptance criteria for organ donors have changed markedly: in 2006/7, 17% of deceased organ donors were aged over 60 years (including 3% ≥ 70), compared with 36% in 2015/16 (13% ≥ 70). While other organ waiting lists have grown, these changes have led to a 27% fall in the number of people in the UK waiting for a kidney transplant: 7190 at its highest in 2009 to 5275 in 2016. Median waiting time to kidney transplant has fallen from over three years for patients registered in 2005–2009 to 2" years for patients registered more recently.
Conclusions: Major initiatives coupled with a change in donor acceptance criteria have led to an increase in the number of deceased organ donors in the UK over recent years such that the number of people receiving a deceased donor organ transplant in the UK has increased by 48% in the last 10 years with a 19% fall in median waiting time to kidney transplant.

Translational Ethics / law / psychosocial / public policy Other

OS374 SELF-SUFFICIENCY ON ORGAN DONATION AND TRANSPLANTATION

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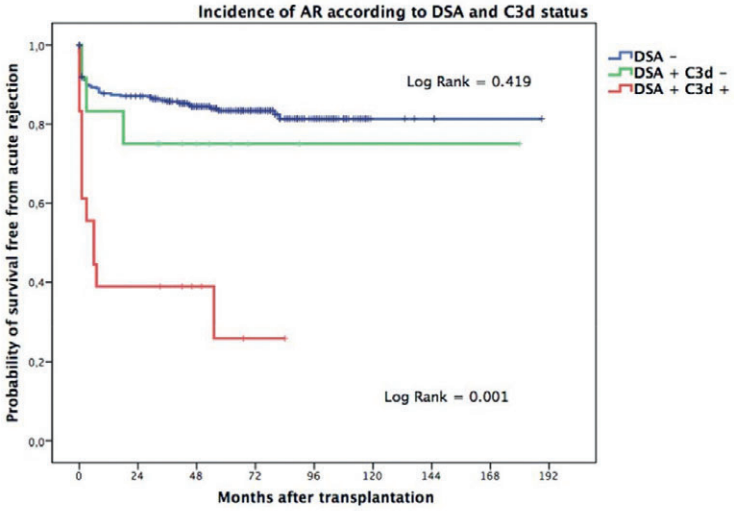
Background: Participants to the third WHO Global Consultation on Organ Donation and Transplantation urged for self-sufficiency. Far from that, about sixty thousand European citizens were waiting for an organ or composite tissue transplant by the end of 2014, out of which eleven died every day due to organ scarcity.



N° at risk									
DSA -	312	263	194	114	46	5	2	1	0
DSA + C3d -	12	9	5	2	1				
DSA + C3d +	18	7	4	1					

Methods: The study analyses the impact of two combined factors on self-sufficiency in nine different countries:

Public national and/or regional organ procurement organizations or competent authorities (and delegated bodies), as referred to in the EU Directive 2010/53/EU, that encompass the functions required to authorize, organize and monitor the donation and transplantation process

Continuous medical education of health care professionals about to join or already involved in the process.

Results: Six European countries (Croatia, France, Italy, Portugal, Slovenia, Spain), two from Asia (China, Thailand) and 1 from Middle East (Iran) were compared over a period of five to twenty years. Some of the countries enlisted took measures to improve their organ donation system even earlier. Steady increase in deceased donors per million population (pmp) was reported in all countries as following: Croatia from 4.3 (1996) to 38.6 (2016), France from 15.1 (1996) to 27.5 (2015), Italy from 11 (1996) to 24.3 (2016), Portugal from 21.2 (1996) to 32.6 (2016), Slovenia from 11 (2000) to 20.3 (2016), Spain from 26.9 (1996) to 43.4, Thailand from 0.7 (2005) to 3.2 (2015) and Iran from 0 (1999) to 11.5 in 2016.

As for China, the number of organs donated almost doubled from 2015 (2766) to 2016 (4080), as a result of building the organ donation system, optimizing the legal system, banning the organ procurement from executed prisoners in 2015, and implementing continuous medical education.

Conclusion: Continuous multifactorial approach leads to a steady increase of donation rates and better self-sufficiency.

Clinical Ethics / law / psychosocial / public policy Donation and donor types

OS375 FAMILY OVERRULE OF REFUSAL TO DONATE: ETHICAL ANALYSIS BY THE ELPAT WORKING GROUP ON DECEASED DONATION

David Shaw[1], Penney Lewis[2], Denie Georgieva[3], Tineke Wind[4], Bernadette Haase[5], Nichon Jansen[5], Undine Samuel[6], Dale Gardiner[7], Rutger Ploeg[8]
[1]Institute of Biomedical Ethics, University of Basel, United Kingdom; [2]Dickson Poon School of Law, King's College London, United Kingdom; [3]Dutch Transplant Foundation, The Netherlands; [4]Department of Surgery, Maastricht University Medical Centre, Maastricht, The Netherlands; [5]Dutch Transplant Foundation, Leiden, The Netherlands; [6]Eurotransplant, The Netherlands; [7]Nottingham University Hospitals, United Kingdom; [8]University of Oxford, United Kingdom

Background: It is well known that families frequently overrule the wishes of dying patients who had previously expressed a wish to donate their organs. Various strategies have been suggested to reduce the frequency of these 'family overrules'. However, the possibility of families overruling a patient's decision not to donate has not been discussed in the literature. In this paper we provide an ethical analysis of attempts by family members to overrule their relative's refusal to donate.

Methods: Ethical and legal analysis based on literature review.

Results: The ethical landscape of overruling refusal to donate reflects the topography of overruling consent to donate to some extent. Genuine overrule of refusal to donate is unethical, but there are circumstances in which a recorded refusal could and should be superseded. If new, more recent evidence of consent is offered by family or friends, donation should proceed. If information provided by family or friends suggests that donation would be in the patient's best interests, donation could proceed, with the caveat that any such assessment should not be based purely on a hypothetical refusal.

Conclusion: Despite some ethical asymmetries between overruling consent and overruling refusal, there are some cases in which refusal can be disregarded. Genuine family overrule of refusal to donate is unethical *per se*, but families should be able to provide new evidence of consent to donate.

OS376 CONSCIENTIOUS OBJECTION TO ORGAN DONATION: ANALYSIS BY THE ELPAT WORKING GROUP ON DECEASED DONATION

David Shaw[1], Dale Gardiner[2], Tineke Wind[3], Nichon Jansen[4], Bernadette Haase[4], Denie Georgieva[4], Rutger Ploeg[5], Penney Lewis[6], Undine Samuel[7]
[1]Institute of Biomedical Ethics, University of Basel, United Kingdom; [2]Nottingham University Hospitals, United Kingdom; [3]Department of Surgery, Maastricht University Medical Center, The Netherlands; [4]Dutch Transplant Foundation, The Netherlands; [5]University of Oxford, United Kingdom; [6]Dickson Poon School of Law, King's College London, United Kingdom; [7]Eurotransplant, The Netherlands

Background: Conscientious objection (CO) in medicine allows healthcare professionals (HP) to excuse themselves from participation in provision of a treatment or service that they find problematic for moral or religious reasons. It is most well-known with regard to religious objection to abortion, contraception and assisted dying. Clinical experience indicates that some nurses and doctors object to organ donation for various reasons. This paper explores the case for and against permitting conscientious objection to organ donation by health care professionals.

Methods: Ethical and legal analysis based on literature review.

Results: Conscientious objection is a long-standing concept in medicine. In limited circumstances, it allows HP to step back from practices to which they hold a genuine moral or religious objection. But CO in general has recently faced a great deal of criticism for being unprofessional and this seems particularly true in the context of organ donation. There is some merit in the argument that temporarily permitting CO enables dialogue with HP that will ultimately result in greater support for OD, and some professionals may have religious objections to the concept of brain death. However, dialogue is also a more plausible alternative to CO to organ donation, in most cases.

Conclusion: It may be contrary to professional obligations to refuse to take part in organ donation, as HP have a duty not just to a patient who wishes to donate but to those who need organs. With a few rare exceptions relating to genuinely held religious reasons for objection, those seeking to exercise CO to organ donation are morally complicit in risking patient's lives.

OS377 DIVERSITY IN DIAGNOSING BRAIN DEATH IN CHILDREN ACROSS EUROPE

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University Hospital Freiburg, Germany

"Brain death" (BD) is a rare event in PICU/NICU. Although the concept is widely accepted, surveys show diversity in establishing the clinical diagnosis. Diagnosing BD in children differs age-dependently from the diagnostic work-up in adults. Our comparative analysis focuses on diagnosing BD in children stipulated by national guidelines.

Guidelines from 9 European countries (A,B,CH,D,DK,ES,F,H&UK) were analysed using a pre-defined questionnaire.

The concept of "whole BD" is almost uniformly accepted (except UK); diagnostic hallmarks are persistent unconsciousness, absent brainstem reflexes and apnoea.BD diagnosis is considered feasible at various age-thresholds; cut-offs for employing adult work-up differ remarkably, too. Known aetiology, absence of any reversible cause, normotension and mild hypo- to normothermia are prerequisites in all countries. Testing is performed by 2 clinicians or more (paediatrician or neurologist), comprising of absence of pupillary reactivity, ocular motility, corneal-, gag-, cough-reflex and persistent apnoea. Repeated clinical testing is mandatory in small infants with different "observational periods". Ancillary testing is either compulsory, restricted to incomplete clinical testing or certain cerebral diagnoses and may shorten observational time. Testing for brain function or perfusion varies due to cerebral lesion, preferences or is not recommended at all.

Our survey reveals diversity in relevant aspects of BD determination across Europe. Adherence to guidelines has not been validated. Guidelines not only stem from scientific evidence but may also reflect ethical perceptions, particularly at the beginning and the end of life.BD diagnosis is closely (but not exclusively!) linked to organ donation. Although organs from paediatric donors are allocated across national borders (allocation networks and beyond), the determination of death varies. Joint efforts advocating for a unified evidence based protocol are warranted to reinforce public and professional trust.

Clinical Ethics / law / psychosocial / public policy Other

OS378 THE PERSPECTIVES OF YOUNG ADULTS ON THE PSYCHOSOCIAL IMPACT OF RENAL FAILURE: A THEMATIC SYNTHESIS OF QUALITATIVE STUDIES

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[1]University of Bristol, United Kingdom; [2]University of Exeter, United Kingdom; [3]University Hospitals Bristol NHS Foundation Trust, United Kingdom

Background: There is limited research on the impact of renal failure on the non-medical aspects of young adults' lives. This study aimed to describe young adults' experiences of the psychosocial impact of being in receipt of renal replacement therapy (RRT).

Methods: This systematic review synthesizes qualitative studies investigating the perspectives of young adults (aged 16–30 years) on the impact of renal failure on the psychosocial aspects of their lives. Electronic databases were systematically searched to August 2016 for full-text qualitative studies without language restriction. The transparency of reporting of each study was assessed using the Consolidated Criteria for Reporting Qualitative Health Research (COREQ) framework, and inductive thematic synthesis was then undertaken.

Results: 7 studies were included, comprising 123 young adults receiving RRT. The studies were from 5 different countries. Comprehensiveness of reporting was variable, with studies reporting 9 to 22 of the 32 possible items

included in the COREQ checklist. Only one study was accompanied by an interview topic guide.

Three global themes about the psychosocial impact of renal failure on young adults were identified: (1) Uncertainty and liminality; (2) Difference – desiring normality; and (3) Thwarted or moderated dreams and ambitions. These reflected five organising themes: (i) Physical appearance and body image; (ii) Activity and participation; (iii) Educational disruption and underachievement; (iv) Precarious employment; and (v) Social isolation and relationship difficulties.
Conclusions: Young adults report that renal failure impacts on their ambitions and life-goals, and their capacity and opportunities to achieve them. They report an impact on the ability to form and maintain intimate relationships, and to achieve goals regarding parenting and parenthood. Themes were similar across different countries, and different forms of RRT.

Clinical Others Other

OS379 TRANSPLANT PREGNANCY REGISTRY INTERNATIONAL: EXPANDING COLLABORATION WORLDWIDE TO BENEFIT RECIPIENTS CONSIDERING PARENTHOOD

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Gift of Life Institute, Transplant Pregnancy Registry International, United States

After 25 years of data collection, the US National Transplantation Pregnancy Registry is expanding to include participation by transplant recipients and healthcare providers worldwide and has been renamed the Transplant Pregnancy Registry International (TPR). Data are collected via questionnaires, interviews and review of medical records; retrospective and prospective pregnancy reports are accepted. Table shows current TPR female recipient enrollment.

	Recipients	Total outcomes	Estimated conception date range	Pregnancies in progress	Fetal losses*	Live offspring
Kidney	1051	1946	1967–2017	20	411	1435
Kidney-pancreas	62	116	1989–2015	1	31	80
Liver	265	521	1985–2016	12	124	359
Liver-kidney	10	16	1993–2016	0	2	14
Heart	91	161	1987–2016	7	42	102
Lung	31	43	1992–2015	0	16	22
Heart-lung	6	6	1994–2015	0	0	6
Pancreas alone	6	11	2000–2015	0	5	6
Intestine	2	3	2008–2012	0	1	2
Total/ Overall	1524	2823	1967–2017	39	631	2026

*Miscarriages, terminations due to fetal anomalies, stillbirths, neonatal deaths, and child deaths due to congenital issues.

The registry follows participants and their children indefinitely. Over 125 grandchildren now comprise a second generation providing the ability to study theoretical concerns about potential effects of in utero exposure to immunosuppressive medications on subsequent generations. TPR analyses have contributed to clinical recommendations regarding advisability and timing of pregnancy, medications, comorbid conditions and other aspects of posttransplant parenthood. Pregnancy considerations vary depending on the organ transplanted; significant factors for successful outcomes for mother and child are stable prepregnancy graft function, avoidance of exposure to mycophenolic acid products during the 1st trimester, and close follow-up during pregnancy and postpartum. TPR welcomes collaboration with or referrals from transplant centers, and inquiries from any organ transplant recipient who is considering pregnancy, who has become pregnant or who fathered a pregnancy posttransplant. TPR can be contacted at: transplantpregnancyregistry.org.

Conclusions: For many recipients, pregnancy after organ transplantation is possible with the majority of the pregnancies resulting in a healthy live birth. The TPR is a resource for the worldwide transplant community. Healthcare providers who counsel transplant recipients about parenthood and transplant recipients themselves are encouraged to contact the registry.

Clinical Ethics / law / psychosocial / public policy Other

OS380 EXPLORING ATTITUDES AND FACTORS INFLUENCING REPRODUCTIVE CHOICES IN RENAL TRANSPLANT PATIENTS (EXPECT-STUDY)

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Erasmus Medical Center, The Netherlands

Background: The number of women who have the desire to have children after renal transplantation (RTX) is rising, despite possible complications for both mother and child. This qualitative study aims to explore the motives for pregnancy after transplantation and the psychosocial and medical factors considered. We also explored the experience of being pregnant and raising children after RTX.
Methods: Women who became pregnant after RTX in the past 5 years were eligible for inclusion. These women were matched with women who had not been pregnant but were the same age (± 5 years) and transplanted at the same time (± 2 years). Semi-structured interviews were conducted and transcribed ad verbatim. Directed content analysis was carried out to identify general themes.
Results: We invited 37 women, of which 20 were willing to participate in the interviews. Preliminary analysis identified the following themes: physical loss; concerns about being able to take care of a child because of tiredness after RTX, but also loss of a child. Guilt was mentioned for different reasons, towards nephrologists for wanting to risk their transplant for a pregnancy, but also towards their children who will grow up with a sick mother. Calculating risks was important because they want to stay in control. Information about pregnancy and RTX was minimal if women did not initiate a discussion with their nephrologist. One was dissuaded not to get pregnant by their nephrologist and did not dare to talk about it ever again. Two factors were identified as being crucial in the decision whether or not to become pregnant: the guidance/advice they received from the professional and the support from their social network
Conclusion: Young women after RTX with or without a desire to have children find it difficult to talk about this with their nephrologist. Because this threshold can be high for these women we suggest that the nephrologist proactively discusses this issue with every women in the child-bearing age.

Clinical Ethics / law / psychosocial / public policy Donation and donor types

OS381 HOW POTENTIAL LIVING KIDNEY DONORS (LKDS) VIEW ESRD RISK: A MULTI-CENTER STUDY

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Purpose: To determine how kidney donors view ESRD risk at initial donor evaluation.
Methods: We conducted a longitudinal, prospective study of LKDs at three centers and report results of LKDs' risk assessment at initial evaluation. LKDs received a novel visual aid representing the probability of post-donation ESRD and filled in a blank diagram to convey the highest chance of ESRD that they were willing to accept (WTA). Participants completed surveys to assess: demographics, relational closeness with the recipient (RCR), health, and risk tolerance. Multivariable multinomial regression assessed correlations between participant characteristics and WTA ESRD. Open-ended verbal probes explored reasons for WTA ESRD; responses from a random subset of 100 participants were analyzed with inductive qualitative coding.
Results: 307 LKDs participated (response rate 85%); 14% planned to donate via paired exchange.

Mean WTA ESRD was 20% (range 0.01–100%); 9% accepted a 100% risk. In multivariate analysis, being black, older, and female was associated with decreased WTA a moderate chance of ESRD (figure 1). Increased RCR and greater acceptance of recreational risks was correlated with WTA moderate chances of ESRD. However, only RCR was associated with accepting the highest ESRD risks. Direct and exchange donors had similar WTA ESRD.

30% of participants reporting anchoring their maximal WTA ESRD to the data provided about actual risks. Common reasons for high WTA ESRD were: RCR (15%), "acceptability" of the risk level (12%), the benefit to the recipient outweighed the risk to the donor (12%), and donors received UNOS waitlist priority if they developed ESRD (8%).

Variable	ESRD 2nd Tertile vs. 1st Tertile		ESRD Max 3rd Tertile vs. 1st Tertile	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Race				
White	[ref]	[ref]	[ref]	[ref]
Black	0.252 (0.083, 0.763)	**0.0147**	0.205 (0.024, 1.720)	0.1441
Other	1.841 (0.665, 5.096)	0.2401	1.747 (0.336, 8.345)	0.4844
Age	0.976 (0.955, 0.998)	**0.0330**	0.995 (0.959, 1.033)	0.7975
Gender (f vs. m)	0.541 (0.314, 0.930)	**0.0263**	0.523 (0.203, 1.346)	0.1792
Closeness of relationship with the intended recipient *(higher = closer)*	1.206 (1.034, 1.406)	**0.0168**	2.416 (1.529, 3.820)	**0.0002**
Willingness recreations risks *(higher = greater acceptance)*	1.299 (1.067, 1.581)	**0.0092**	1.178 (0.831, 1.670)	0.3586

Conclusions: Our results enhance the transplant community's understandings of LKD risk acceptance and reasons for donation. Our interactive instrument provides an educational tool for LKDs to weigh the risk of donation. It also offers transplant professionals an objective method to determine how L.

Clinical Ethics / law / psychosocial / public policy Other

OS383 ETHICAL CONSIDERATIONS IN FACE TRANSPLANTATION

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Background: There have been 37 partial or total face transplantations performed since 2005. While most centers report overall improved functional, aesthetic and psychiatric outcomes, there remain ethical concerns about the procedure. Among the core ethical issues are its utility as life-saving procedure, identity concerns, uncertain functional and aesthetic outcomes, unknown consequences of graft rejection and failure, possibility of death, media attention, informed consent, limited access, cost, and patient selection.
Discussion: Some authors have argued that the functional and aesthetic restoration which face transplantation affords renders it a life-saving procedure. However, long-term functional and aesthetic outcomes are still unknown. Chronic rejection has recently been reported, and graft failure is ever a possibility. The impact of this procedure on patient identity has not been fully elucidated. Media attention may promote unrealistic expectations, and is a challenge to privacy. Face transplantation may imply that a good quality of life cannot be achieved by the facially disfigured. Patient selection criteria and are not yet fully elaborated and uniformly applied. Last, the procedure may serve relatively few from a large pool who would benefit, and the cost may be prohibitive.
Conclusion: The ethical debate on face transplantation is ongoing. Longterm outcomes are still unknown. Emerging data indicate that the concept of face transplantation as a life-saving procedure may still be debatable.

OS384 RISK FACTORS AND IMPACT ON OUTCOMES OF TRAJECTORIES OF ANXIETY AND DEPRESSION AFTER LIVER TRANSPLANTATION: A PROSPECTIVE COHORT STUDY

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Background: Although the burden of psychological problems among liver transplant recipients (LTR) is recognized, little is known about the course of symptoms of anxiety and depression over time. The aim of this study was to examine whether distinct trajectories of anxious and depressive symptoms are present among adult LTRs from before transplantation up until to two years after transplantation; to identify demographic, clinical, and individual characteristics related with the distinct trajectories; and to examine the influence of distinct trajectories on outcomes.
Methods: Data were retrieved by questionnaire before and at 3, 6, 12, and 24 months after transplantation. Clinical data were retrieved by medical record review. Latent Class Growth Analysis was used to identify distinct trajectories and General Linear Mixed Models analysis was used to identify related variables.
Results: Three distinct trajectories for symptoms of anxiety and depression were identified: "no symptoms," "resolved symptoms," and "persistent symptoms." The trajectory of persistent symptoms of anxiety comprised 23% of the LTRs, the trajectory of persistent depressive symptoms 29% of the LTRs. Several clinical and individual variables were found to be related with the trajectories of persistent symptoms: experiencing more side-effects from the immunosuppressive medication, a lower level of personal control, more use of emotional coping, less use of task-oriented coping, less disclosure about the transplant, and experiencing more stressful life events. Transplant recipients within the trajectories of persistent symptoms, reported significantly worse medication adherence ($p < 0.02$) and lower scores for all domains of health-related quality of life ($p < 0.001$).
Conclusion: A significant subset of liver transplant recipients showed persistent symptoms of anxiety and depression. Our results emphasize the importance of psychological care in the transplant population.

Clinical Pancreas/Islet Donation and donor types

OS385 A 10-YEAR NATIONAL ANALYSIS OF PANCREAS DECLINE RATES IN THE UK

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Introduction: The utilization of pancreases for solid organ transplantation remains inferior to that of other organs. Therefore, we undertook an analysis of decline rates in the UK over the last ten years.
Methods: All pancreases offered for solid organ transplantation were identified from the National Transplant Registry. We analysed the number of organs declined, the reasons and the time point of decline as well as centre specific reasons, consistency in decision and trends over time.
Results: 7367 pancreases were offered for transplantation between January 2005 and December 2015. 4807 (65.3%) were Donors after brain death (DBD) and 2551 (34.6%) were Donors after circulatory death (DCD). Overall there was an increase in DCD utilization over the ten-year period.

3645 (49.5%) organs were declined on the basis of donor history and were not retrieved. The main reasons for decline were age, BMI, history of alcohol abuse and cause of death.

3699 (50.5%) pancreases were retrieved. 2303 pancreases were transplanted whilst 1394 (37.7%) were initially accepted but then not used.

2146 were transplanted as simultaneous pancreas-kidney (SPK) or pancreas alone (PA). 1176 (55%) were transplanted on the first offer whilst the remaining 970 pancreases were transplanted after a median (IQR) of 3 (2–

5) offers. 52% of the DBD pancreases were transplanted on the first offer compared with 69% of the DCD organs.

A subgroup analysis of the first offer to a named patient of a whole organ, which was subsequently transplanted as a SPK or PA, between 1st of December 2010 and 31st of December 2015, showed significant centre variations in decline rates [28–61% for DBD and 3–78% for DCD ($p < 0.0001$, c2).

Conclusions: A significant number of solid pancreases are discarded, with wide centre variation, in the UK. A better graft assessment at procurement may minimize unnecessary travel and decrease cold ischemia. A closer link with the islets programs would allow for a be

OS386 PROSPECTIVE NATIONAL STUDY OF DISCARDED PANCREASES IN THE UK

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Introduction: The utilisation of solid organ pancreases in the UK remains low. Fatty graft appearance, long cold ischaemic time and organ damage are the main reasons for discard. We set to prospectively assess the reasons for discard and investigate if utilisation could be increased by refining acceptance criteria.

Method: All pancreases discarded in the UK over a six-month period (July 2016-January 2017) were assessed in Edinburgh and Oxford. Assessment was undertaken by a consultant surgeon independent of the initial discard decision and involved a video recording before and after preparing the graft for implantation. Evaluation included assessment of fatty infiltration, organ damage, vascular and duodenal integrity, placement of the mesenteric staple and iliac graft integrity. Donor data and the reasons for the initial decline were captured from the National Transplant Database. The concordance between initial assessment and second evaluation was assessed.

Results: 53 pancreases [37 DBD (69.81%) and 16 DCD (30.18%)] were evaluated. The median donor age was 44 years old (range: 9–62 years) with a median BMI of 23.9 (range: 19 –35 years).

51 organs (96%) were discarded after being accepted by the centre at the top of the offering sequence. Two were discarded at procurement. 26 organs (49%) were declined due to fatty appearance and 19 (35.84%) due to various degree of damage including 9 major capsular or vascular injuries.

19 organs (35.84%) were subsequently deemed transplantable by the additional assessment. The variation between decisions was primarily related to the size of capsular injury and the degree of steatosis.

Conclusions: The discard decision appears inconsistent in a third of cases. A better and more timely assessment at the point of retrieval may reduce cold ischaemic time and lead to better utilisation. A video assessment may assist this decision.

Clinical Pancreas/Islet Other

OS387 PANCREATIC ALLOGRAFT THROMBOSIS: SUGGESTION FOR A CT GRADING SYSTEM AND MANAGEMENT ALGORITHM

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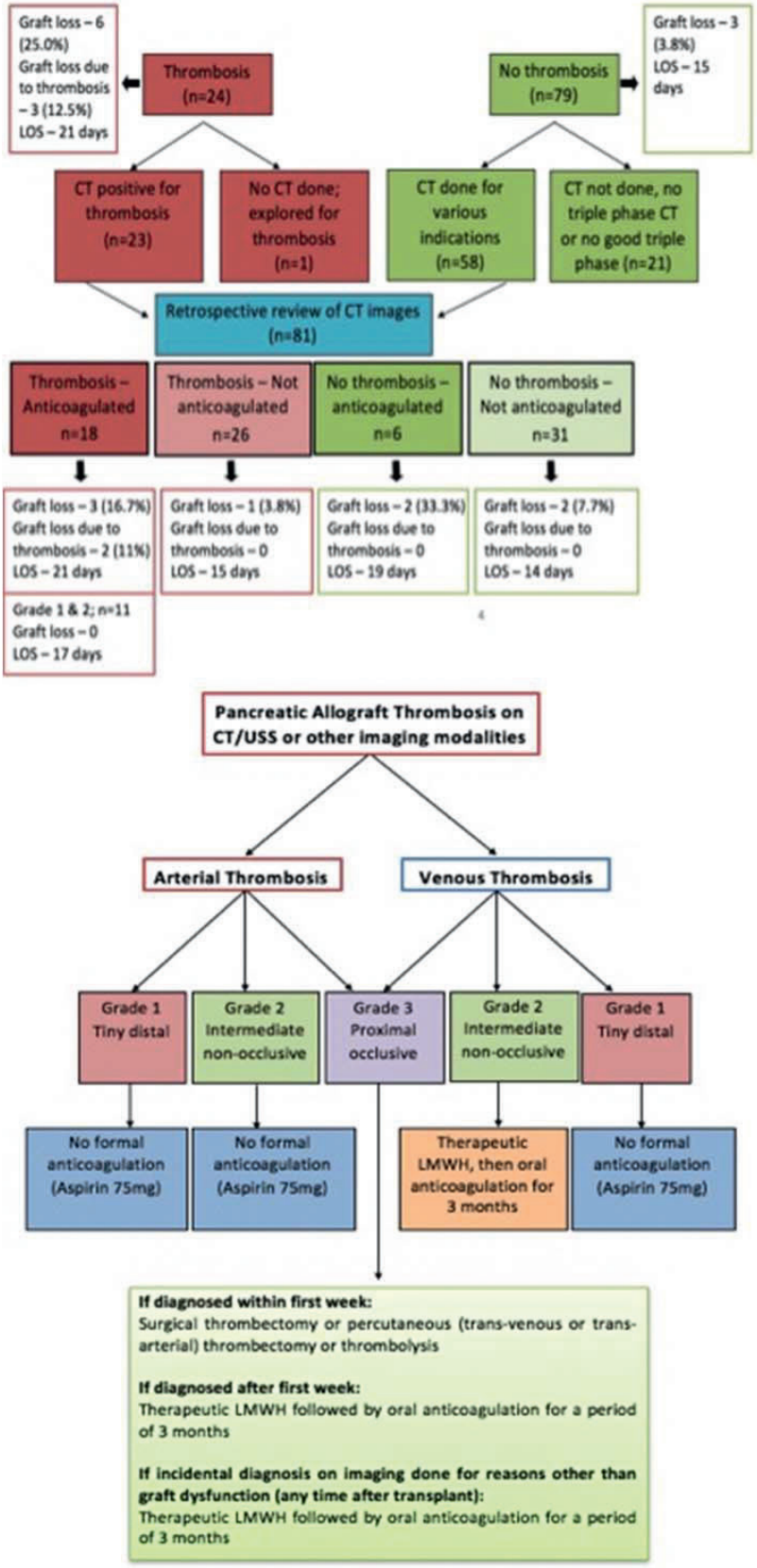
Background: Pancreatic allograft thrombosis (PAT) remains the leading cause of non-immunological graft failure. There is currently no consensus on the reporting and management of partial PAT. Herein we propose a new CT grading system of PAT to identify risk factors for allograft loss and outline a management algorithm.

Methods: Retrospective review of all consecutive pancreatic transplants performed at our centre between 2009 and 2014. Triple phase CT scans were retrospectively graded independently by two radiologists as; Grade 0 – No allograft thrombosis, Grade 1 – Tiny peripheral thrombosis, Grade 2 – Intermediate non-occlusive thrombosis and Grade 3 – Central occlusive thrombosis.

Results: Twenty-four of 103 (23.3%) pancreas transplant recipients were diagnosed with allograft thrombosis during the original admission. There were three grafts lost, all due to portal vein thrombosis [(two grade 3 and one grade 2); 2.9%]. On multivariate analysis, pancreas after SPK/pancreas after kidney transplant, acute rejection and CT finding peri-pancreatic oedema and/or peri-pancreatic inflammatory change were significant risk factors of allograft thrombosis. Retrospective review of CT images revealed more grade 1 and 2 thromboses than were initially reported, enabling comparison of outcomes of patients with grade 1 and 2 thrombosis who were anticoagulated with those who were not. There was no significant difference in graft or patient survival, length of stay or morbidity, suggesting that therapeutic anticoagulation is not necessary for grade 1 and 2 arterial thrombosis and grade 1 venous thrombosis.

Conclusions: The proposed grading system can assist clinicians in decision making, help standardise communication between radiologists and clinicians and provide standardised scoring and reporting to further interrogate the impact of thrombosis on outcome.



Clinical Pancreas/Islet Cardiovascular complications

OS388 TYPE 1 DIABETIC PATIENTS HAVE BETTER ENDOTHELIAL FUNCTION AFTER SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION THAN AFTER KIDNEY TRANSPLANTATION WITH CONTINUED INSULIN THERAPY

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Background: Restored normal blood glucose metabolism in type 1 diabetic (T1D) patients with end stage renal disease (ESRD) after simultaneous pancreas-kidney transplantation (SPK) is anticipated to slow the progression of vascular damage, as compared to patients after kidney transplantation (KTx). The aim of the study was to analyze the influence of SPK or KTx on endothelial function and systemic inflammation in T1D patients with ESRD in follow-up period after transplantation.
Methods/Materials: 39 SPK, 39 T1D KTx, and 52 non-diabetic KTx recipients were enrolled into the study. In all participants flow mediated dilation (FMD) was measured, and glycated haemoglobin (HbA_{1C}), creatinine, nitrites (NO_2^-) and nitrates, asymmetric dimethylarginine, soluble vascular cell adhesion molecule-1 (sVCAM-1), intercellular adhesion molecule-1, E-selectin, high-sensitivity C-reactive protein, tumour necrosis factor-α, interleukins 1β and 6 levels were assessed in blood, serum, or plasma.
Results: During 58 $\pm$ 31 months follow-up period, SPK but not KTx resulted in normalization of HbA_{1C}. FMD and NO_2^- were greater in SPK than in KTx group [10.4 $\pm$ 4.7 vs. 7.7 $\pm$ 4.2%, $p < 0.05$ and 0.94 (0.74–1.34) vs. 0.24 (0.20–0.43) μmol/l, $p < 0.01$, respectively]. In combined group of T1D SPK or KTx recipients, NO_2^- positively correlated with FMD ($r = 0.306$, $p < 0.05$), and inversely – with HbA_{1C} ($r = -0.570$, $p < 0.001$). Multivariate regression analysis revealed that NO_2^- was linked to HbA_{1C} and estimated glomerular filtration rate (eGFR), whereas FMD – to NO_2^-. The levels of all measured inflammatory markers with the exception of sVCAM-1 were similar in both diabetic groups, and the difference in sVCAM-1 was not explained by HbA_{1C} and other inflammatory markers levels, or eGFR.
Conclusion: Normalization of blood glucose metabolism achieved by SPK is associated with better endothelial function as evidenced by FMD and NO_2^- compared to KTx, but does not cause improvement in plasma levels of proinflammatory cytokines.

Clinical Pancreas/Islet Surgical technique

OS389 IS IPSILATERAL GRAFT PLACEMENT FOR SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANTATION A JUSTIFIED OPTION? A COMPARATIVE STUDY WITH 5 YEAR OUTCOMES

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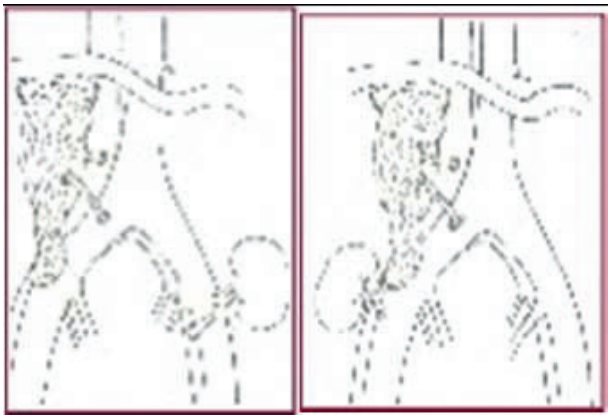
Introduction: During simultaneous pancreas and kidney transplantation the pancreas is usually placed in the right and the kidney in the left iliac fossa. Implantation of both grafts in the same side remains controversial. Potential disadvantage of ipsilateral transplantation could be that the pancreas might jeopardise the usually distally implanted kidney, nonetheless this technique is quicker than the conventional contralateral implantation and preserves the other side for subsequent transplantation.
Methods: From October 2008 to October 2011 67 simultaneous pancreas and kidney transplantations were performed in our unit. In 18 cases both pancreas and kidney were placed in the right iliac fossa (ipsilateral graft placement) and in 49 cases the pancreas in the right and the kidney in the left iliac fossa (contralateral graft placement). Patient and graft survival, surgical and non surgical complications, ITU/HDU stay and hospital stay were compared between the two groups.
Results: There was no difference in donors and recipients demographics, apart from more females and a trend to younger recipient for the ipsilateral group. There was also shorter cold ischaemia time for the ipsilateral group. The frequency of complications was similar. ITU/HDU and overall hospital stay were also comparable.
Summary: Ipsilateral placement of pancreas and kidney transplants is safe and results in similar patient and graft survival as contralateral placement of the grafts. The incidence of surgical and non surgical complications is also comparable. Ipsilateral graft placement is safe, faster and may preserve the contralateral side for future transplants.

*$p < 0.05$	Ipsilateral graft placement	Contralateral graft placement
Male patient	28%*	90%
5 year patient survival	94%	84%
5 year pancreas survival	84%	74%
5 year kidney survival	89%	82%
Patient required reoperation	22%	35%
Theatre time (min)	293*	359



Translational Pancreas/Islet Other

OS390 THE ESTABLISHMENT OF EFFECTIVE DIFFERENTIATION PROTOCOLS FOR INSULIN-PRODUCING CELLS USING 3D CULTURE SYSTEM FROM RAT ADIPOSE-TISSUE DERIVED MESENCHYMAL STEM CELL

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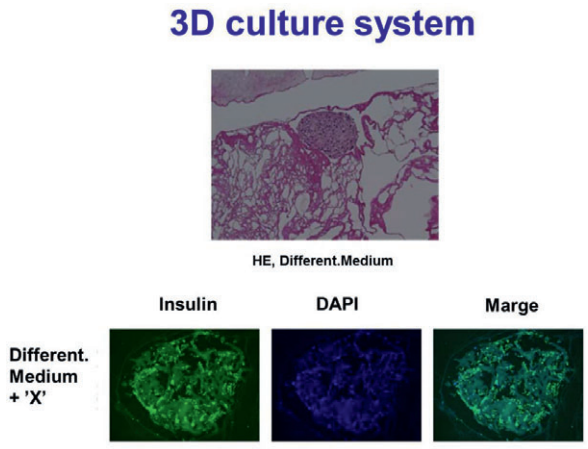
Background: We here show a new strategy for the future islet transplantation with adipose tissue derived stem cells: ADSCs. Considering severe donor shortage in Japan, the new cell source must be investigated. Thus we focus on ADSC's totipotency; differentiation from ADSCs to Insulin-producing cells: IPCs.
Materials and methods: IPCs generated from rat ADSC (purchased from DS pharma, Co., USA) were investigated after the differentiation by the conventional method (Control) or our new-established 2-step protocol with adding 1 mM HDAC inhibitor which concerns pancreatic lineage. We have also investigated the new cell culture system with 3D scaffold named 'compound X'* for ADSCs. Cell quality (cell diameter, cell viability, hormonal expression, etc.) and glucose response were investigated.
Results: Our established 2-step protocol with HDACi addition accelerated differentiation duration (38 days vs. 21 days, $p < 0.05$, compared to control medium; without HDACi), and stimulation index showed good insulin response (3.1). These IPCs derived with 'compound X' formed large cell cluster (diameter of the cells, compared to control; without 'compound X' medium, $p < 0.01$), showed good cell viability (compared to control; without 'compound X' medium, $p < 0.01$), and immunohistochemistry showed strong insulin expression without central necrosis.
Conclusions: The established our new 2-step protocol with 'compound X' can generate functional IPCs *in vitro*. That strategy may be not only the alternative cell source but also a breakthrough for clinical islet transplantation as a 'true' regenerative medicine.
*The name of this compound cannot be disclosed due to the intellectual property right.



Large cell cluster expressed insulin in 'Compound X' group.

Clinical Pancreas/Islet Rejection

OS391

113 CONCURRENT BIOPSIES IN PANCREAS GRAFT RECIPIENTS: DISCORDANT FINDINGS BETWEEN DONOR DUODENUM AND PANCREAS GRAFTS

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Background: Pancreas graft rejection is diagnosed upon morphological findings in a pancreas graft biopsy. The use of percutaneous transabdominal pancreas graft biopsies has been restricted due to potentially severe complications. Endoscopic duodenal cuff biopsies, as surrogates for biopsies of the pancreas graft itself, have been proposed, but its utility is uncertain. During the last few years we have sampled concurrent biopsies of both the duodenal- and pancreas graft to investigate the potential of duodenal biopsies to reveal a simultaneous rejection of the pancreas graft.
Methods: 113 endoscopic biopsies from donor duodenum and pancreas grafts were sampled September 2012- November 2016, from 65 pancreas graft recipients with exocrine drainage to native duodenum. 97 biopsy couples were sampled per protocol, 16 when indicated for diagnosis of rejection. Pancreas graft biopsies were evaluated according to the BANFF criteria and donor duodenum biopsies were rated according to Wu et. al.
Results: Rejection of the pancreas graft was found in 21/113 biopsies. In these cases concurrent histological findings in donor duodenum showed rejection in only 2 cases, giving a sensitivity of about 10% for detection of a pancreas rejection. In the other cases the biopsies were either normal in 12 cases or uncertain in 7 cases. Rejection of the donor duodenum was found in only 6/113 biopsies. In paired pancreas biopsies only 2 also showed pancreas rejection giving a specificity of duodenal biopsies of about 30% for detection of a pancreas rejection. Three pancreas biopsies were normal and one indeterminate.
Conclusion: Duodenal biopsies had a very low sensitivity for revealing a pancreas graft rejection. The rejections of the donor duodenal part were in most cases isolated and thus not associated with pancreas graft rejection.

Clinical Pancreas/Islet Other

OS392

OUTCOMES OF PANCREAS TRANSPLANTATION WITH SINGLE FUNCTIONAL ARTERY

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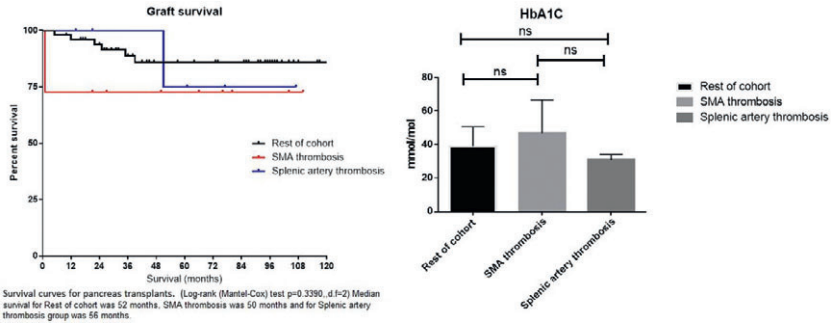
Introduction: Standard arterial re-construction techniques aim to utilise a donor iliac Y graft to re-vascularise whole organ pancreas transplants using splenic (Sp) and superior mesenteric arteries (SMA). In our institution we have routinely assessed patients using protocol and "for cause" CT angiography and observed a number of patients with a solitary functional artery.**Methods:** Retrospective review of graft loss and arterial patency following pancreas transplant in a single centre between January 2007 and May 2016.
Results: 81 pancreas transplants were performed; all were DBD transplants but 1 DCD. Of these, 17 (22%) developed an arterial occlusion in one limb of the Y graft. The occlusions were 11 (65%) in the SMA and 6 (35%) in the Sp artery. The majority, 14, were SPK and the remaining 3 were PAK transplants. Management of the recipients varied; 4 were managed with anticoagulation alone, 7 were managed with angioplasty and/or stenting of the occlusion and 6 (55%) no specific intervention. 5 recipients with functional grafts and solitary vessels subsequently lost their grafts; 1 due to severe pancreatitis, 2 due to progressive arterial thrombosis, 1 of mixed arterial/venous thrombosis, 1 unknown (Figure 1). The mean HbA1c (including graft loss) 1 year post-transplant is 46.8 mmol/mol in SMA group, 30.1 in the Sp group, and 38.7 in remaining cohort ($p = 0.11$).
Conclusion: Pancreas transplants with a single functional artery (>20%) can maintain normal long term graft function. In patients with no signs of dysfunction intervention may not be warranted (>50%).



Survival curves for pancreas transplants. (Log-rank (Mantel-Cox) test p=0.3390, d.f=2) Median survival for Rest of cohort was 52 months. SMA thrombosis was 50 months and for Splenic artery thrombosis group was 66 months.

Clinical Pancreas/Islet Histology

OS393 ULTRASOUND-GUIDED ALLOGRAFT PANCREAS BIOPSY: SAFETY AND DIAGNOSTIC USE

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Background: Post-transplant monitoring of enteric drained pancreas transplants is large limited to serum glucose and amylase, often leading to empirical immunotherapy for presumed rejection. Pancreas allograft biopsy is seldom performed because of concerns about its safety and reliability. Our aim was to analyse our experience of pancreas allograft biopsy.
Methods: All pancreas allograft biopsies performed at a single centre over an 8 year period were analysed retrospectively using electronic databases and MDT outcomes.
Results: 91 transplants were performed during the study period (76 SPK, 14 PAK, 1 PTA). All were implanted extra-peritoneally onto the external iliac vessels. 72 biopsies were performed in 42 patients; 71 were ultrasound-guided. The indication in 62 (86%) was elevated amylase, deranged glucose or both. Using a 16 or 18 gauge needle, 1–2 cores were taken in 54 (75%). 9 (12.5%) were inadequate, 18 (25%) were 'normal', 21 (29%) showed rejection, 20 of which were T-cell mediated, 24 showed sclerosis, fibrosis, inflammation or other. 49 (68%) biopsies, including 4 rejectors, were managed conservatively; all remaining rejectors bar one received pulsed methylprednisolone +/− MMF, IVIg or plasma exchange. 2 patients with normal biopsies received PEx for DSA, 1 patient with a normal biopsy received methylprednisolone pre-biopsy. One patient developed immediate post-biopsy haemorrhage requiring 4 units red cell and 1 unit FFP; 1 patient developed biopsy-induced pancreatitis.
Conclusions: Ultrasound-guided biopsy of extra-peritoneal pancreas allografts is safe (97%), reliable (87.5%) and means unnecessary immunotherapy can be avoided, as was the case in 68% of cases.

Clinical Pancreas/Islet Rejection

OS394 PANCREAS AFTER LIVING DONOR KIDNEY TRANSPLANTATION PRESENTS WORSE GRAFT OUTCOMES: TIME TO RETHINK THIS ALTERNATIVE STRATEGY?

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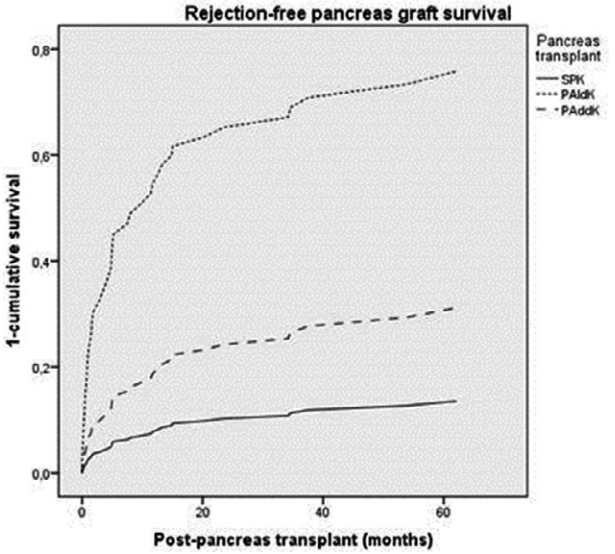
Introduction: Increasing waiting-listed patients for simultaneous kidney-pancreas (SPK) transplantation has led many centers to perform a living donor kidney transplant (LDKT) and afterwards a deceased pancreas donor (PAldK).



Methods: We conducted a retrospective analysis including all pancreas transplants (PTx) performed at our center since the beginning of the PAldK program in 2007, including PAldK, SPK and pancreas after deceased kidney transplant (PAddK; either pancreas retransplant or previous ddKT alone).
Results: A total of 189 pancreas transplants (SPK = 142; PAddK = 29) were performed. Eighteen PTx were performed to 15 recipients of LDKT (2 ABOi, 1 paired kidney exchange program). Two pancreas were lost due to thrombosis and three patients died during follow-up. An average of 13 ± 5 months elapsed between kidney and first pancreas transplant.

Overall patient, kidney, and pancreas graft survivals (death-censured) at 12 months was 98%, 99%, and 86%, respectively, and at 5 years 93%, 96%, and 80%. Pancreas graft survival was inferior for PAldK when compared to PAddK and SPK (log-rank p = 0.004).

Pancreas graft rejection was significantly increased in PAldK (72%; 1.8 ± 1.4 episodes/graft) when compared to PAddK (24%; p = 0.001) (figure 1), with a tendency towards presenting later (5.2 [3.5–20.2] vs. 1.5 [0.3–2.8] months; p = 0.58). HLA compatibilities between kidney and pancreas donors didn't increase pancreas rejection risk, nor did pancreas donor-recipient HLA mismatching, pre-transplant sensitization, induction immunosuppression, dialysis vintage, or graft cold ischemia time (p > .05).
Conclusion: Pancreas graft survival was inferior and rejection higher in PAldK when compared to SPK and PAddK. Centers should individually evaluate their expected waiting time before proposing this alternative to patients.

Clinical Pancreas/Islet Allocation

OS395 WHOLE ORGAN PANCREAS TRANSPLANTATION IS SAFE IN OLDER RECIPIENTS

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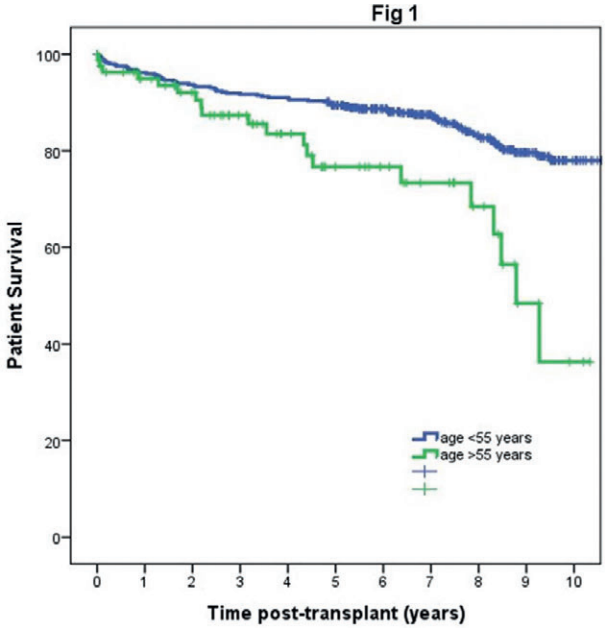
Background: An increased number of older people are being referred as potential recipients for pancreas transplantation. We aimed to investigate the outcomes after pancreas transplantation in our older recipient cohort to establish if offering transplantation to this cohort is justified.
Methods: A prospectively-maintained retrospective database was interrogated. Data relating to donor and recipient variables, post-transplant cardiac events, graft survival and patient survival were recorded. The cohort was divided into those <55 years at transplant and those >55 years at transplant and compared.
Results: 444 transplants were performed in patients aged 23–54 years, and 83 transplants in patients aged 55- 67 years (n = 59 aged 55–59 years, n = 19 aged 60–64 years and n = 5 aged 65–67 years). There was no difference in death-censored pancreas graft survival or kidney graft survival between the groups. Rates of post-transplant cardiac events and interventions were low in

Fig 1



both groups. Patient survival was inferior in the older age group; early patient survival was equivalent with divergence evident only beyond 2 years post-transplant ($p < 0.001$, fig 1). In an adjusted multivariate Cox regression model, risk of mortality was independently associated with recipient age (HR 1.05, $p < 0.001$), post-transplant MI (HR 7.25, $p = 0.006$), pancreas failure (HR 1.91, $p = 0.003$) and kidney failure (HR 3.55, $p < 0.001$) were independently associated with death. Older recipients with good pancreas graft function had higher patient survival compared to those who had suffered graft failure ($p = 0.018$).
Conclusion: Graft survival is comparable to outcomes in younger recipients. Mortality is higher in older patients, with divergence in survival increasing over time and strongly associated with pancreas and kidney graft failure. This study suggests that pancreas transplantation is feasible in older recipients, but careful selection of donor organs to optimise graft survival.

Clinical Pancreas/Islet Donation and donor types

OS396 CAN A VIDEO ASSESSMENT OF THE PANCREAS GRAFTS AT THE TIME OF ORGAN PROCUREMENT INCREASE UTILISATION?

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Background: Assessment of pancreases for solid organ transplantation is highly subjective and as a result, a significant number of grafts are discarded. In the absence of clear criteria, we piloted a video assessment as a tool to assist organ utilisation decisions.
Methods: Four discarded pancreases underwent an independent assessment and a high definition video was recorded prior to and after bench preparation. The video focused on assessment of fatty infiltration, pancreas damage, vascular and duodenal integrity, placement of the mesenteric staple and iliac graft integrity. The videos were sent to five consultant surgeons in different transplant centres. Surgeons completed an assessment proforma and provided feedback on the quality of recording, the information presented and whether the video assisted the decision to use the organ.
Results: The videos provided sufficient information for the surgeons to reach a decision to use the graft. However, the additional video after bench preparation did not provide any supplementary information to change the decision. All surgeons correctly identified major injuries and agreed with the discard decision. There was a discrepancy in the interpretation of capsular injuries reflecting the risk taking attitude of the transplant surgeons.

Although the videos were found useful, all surgeons suggested that a commentary on the consistency of the graft and a guided video reflecting main problem (fatty infiltration or damage) would be more beneficial than a completely blinded assessment.
Conclusion: The use of a video evaluation of the pancreas may increase organ utilisation. Furthermore, availability of the video at the time or organ procurement may reduce unnecessary travel and direct the grafts to the centres with a higher risk threshold to ensure they are transplanted.

Translational Heart Rejection

OS397 GENE EXPRESSION PROFILING FOR THE IDENTIFICATION AND CLASSIFICATION OF ANTIBODY-MEDIATED HEART REJECTION

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The specific effects of anti-HLA antibodies on heart allograft injury have not been addressed at a population level.

We prospectively monitored 617 heart recipients referred from 4 French heart transplant centers (2006–2011) for antibody-mediated rejection (AMR). We compared AMR patients ($n = 50$) to a matched control group of 50 patients without AMR. We characterized all patients using histopathology (ISHLT 2013), immunostaining, gene expression assessments of allografts (microarray) and circulating anti-HLA DSA at the time of biopsy. We studied an external validation cohort of 98 heart recipients transplanted in Edmonton (Canada) including 27 pAMR cases and 71 controls.

240 heart transplant EMB were assessed. AMR showed a distinct pattern of injury characterized by microcirculation inflammation by monocytes/macrophages and NK cells, and very selective changes in endothelial/angiogenesis and NK cell transcripts. The AMR selective gene sets discriminated patients with AMR from those without and included NK (AUC = 0.87), endothelial activation (AUC = 0.80), macrophage (AUC = 0.86) and IFNG transcripts (AUC = 0.84, $p < 0.0001$ for all comparisons). These 4 gene sets showed increased expression with increasing AMR ISHLT grades ($p < 0.001$), association with DSA levels and chronic allograft vasculopathy. The unsupervised PCA analysis demonstrated a high proportion of molecular inactive pAMRI+ compared with a significant molecular overlap between pAMR1H+ and pAMR2-3 reclassifying 25% of AMR cases. The molecular architecture and selective AMR transcripts, and the gene set discrimination capacity for AMR were highly conserved in the external validation cohort.

Antibody-mediated heart rejection is mainly driven by NK burden, endothelial activation, macrophage burden and IFNG effects. Molecular intragraft measurements for these specific pathogenesis-based transcripts classify AMR with great accuracy and correlate with the degree of injury and disease activity.

Clinical Heart Rejection

OS398 A NEW DIAGNOSTIC SCORE OF INTRAVASCULAR ACTIVATED MONONUCLEAR CELLS IN ANTIBODY-MEDIATED REJECTION IN HEART TRANSPLANTATION

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Background: The ISHLT classification defines Intravascular Activated Mononuclear Cells (IAMC) as one of the histopathologic features of Antibody-Mediated Rejection (pAMR) in heart transplantation. However, no accurate grading of IAMC correlating with pAMR diagnosis has been proposed. The aim of this study was to develop a score to grade the extent and the pattern of the IAMC in endomyocardial biopsies (EMB) with AMR.
Methods: This case-control study included heart transplant patients from five French referral centers with biopsy-proven AMR (pAMR1-3) ($n = 64$) and a matched control group of 44 patients without rejection (pAMR0). IAMC on EMBs was graded blind of pAMR grades by two skilled pathologists according to the percentage of the area with IAMC in capillaries and to the maximum number of IAMC in the most affected capillary on a 0 to 3 scale and a positivity defined by a grade ≥ 1. The score was compared to the gene expression profile in EMBs by microarray using the ABMR molecular score and pathogenesis-based transcripts reflecting endothelial activation (ENDAT), DSA (DSAST), macrophage burden (QCMAT), gamma-interferon response (GRIT) and NK-cell burden (NKB) (http://atagc.med.ualberta.ca).
Results: 100% of control EMBs were graded as IAMC score 0. All pAMR1 (I+) EMBs and none of the pAMR1 (H+) and pAMR2-3 were graded as IAMC score 0. The highest IAMC score 3 was mainly distributed in pAMR2-3 (Fischer's exact = 0.000). Increase in the IAMC score was associated with an increase in the proportion of C4d and CD68 (macrophage marker) positive EMBs, and a higher proportion of DSA positive at EMB. It was also associated with an increase in the expression of ENDAT, DSAST, GRIT, NKB and QCMAT transcripts (All Kruskal-Wallis<0.001).
Conclusion: The IAMC score is associated with molecular activation in grafted myocardial tissue. The IAMC score could help pathologists for AMR diagnosis, emphasizing the value of IAMC in AMR detection.

OS399 HEART TRANSPLANTATION WITH PREFORMED DONOR SPECIFIC ANTIBODIES: ANTIBODY-MEDIATED REJECTIONS ARE FREQUENT AND EARLY BUT DO NOT IMPACT MID-TERM PROGNOSIS

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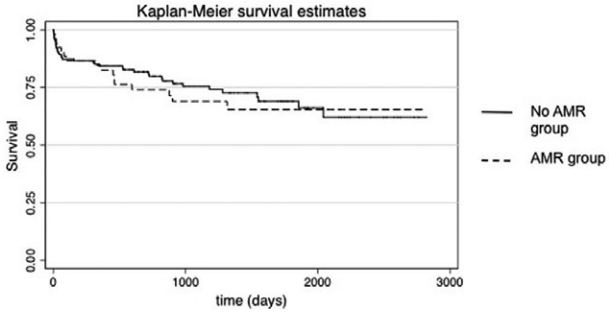
Background: Little is known about antibody-mediated rejection (AMR) due to pre-formed donor specific antibodies (pfDSA) after heart transplantation.

Methods: We performed a prospective, single center, observational study, including all consecutive heart transplant recipients between January, 1st 2009 and December, 31th 2015 with high titer anti HLA pfDSA. A prospective immunosuppressive protocol was applied to these patients including induction therapy, plasmapheresis and intravenous immunoglobulins. Our objectives were to describe clinical characteristics of AMR in this subgroup of patient and to analyze the impact of AMR on mortality, allograft function and cardiac allograft vasculopathy (CAV).
Results: We included 194 heart transplant recipients with high titers pf DSA. Among them, 52 patients were diagnosed with at least one episode of AMR (26.8%). First episode of AMR occurred early after transplantation (median = 24 days, IQR = 15–160 days). Survival of patients with and without AMR was similar (1 year survival after transplantation: respectively 82 and 83%, log rank test: p = 0.69, see figure). Recurrences of AMR were common (42% of patients). Graft function evaluated on left ventricular (LV) ejection fraction and cardiac allograft vasculopathy grade were similar between groups. However, three "recurrent AMR" patients had persistent LV dysfunction and 2 experienced rapidly progressive CAV.



Conclusion: Antibody mediated rejection after heart transplantation with pfDSA was early, frequent and did not impact mid-term prognosis. However, recurrent forms of AMR might be associated with worse outcomes.

Clinical Heart Immunology

OS400 IDENTIFICATION OF THE TOLERANCE INDUCTION PROFILE FOLLOWING HEART TRANSPLANTATION

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Background: Tolerance-inducing cell subsets which support the organ acceptance following heart transplantation (HTx) can be found among dendritic cells (DCs) and regulatory T cells (Tregs). At present, it is unknown which cell subsets change during tolerance induction and maintenance. Therefore, pre-HTx and long-term HTx (LT-HTx; HTx longer than 5 years ago) patients were investigated for their immunological tolerance-inducing profile.
Methods/Materials: Heparinized whole blood samples of $n = 20$ patients with end-stage heart failure (pre-HTx) and $n = 20$ LT-HTx patients without rejection episodes were analyzed for DC cell subsets expressing BDCA1, 2, 3, 4 and for the Treg subsets expressing CD39, CD62L, CD120b and CD147. Percentages and mean fluorescence intensities (MFIs) of the cell subsets were documented. The cytokine profile of IL2, IL4, IL10, IFNg, IL17A, IL34 and IL35 was detected by multiplexing.
Results: Single DC subsets showed changes between pre-HTx and LT-HTx patients: BDCA2 + and 4 + plasmacytoid DCs were increased (%BDCA-2+ p = 0.029; %BDCA4 + p = 0.017) in LT-HTx patients compared to pre-HTx patients. The percentage of total Tregs and the highly suppressive CD62L+ subset was higher in pre-HTx patients compared to LT-HTx patients (%Tregs p = 0.003, %CD62L+ p = 0.013). LT-HTx patients showed a more balanced cytokine level. The tolerance-mediating cytokine IL34 plasma level was higher in LT-HTx patients (36.9 ± 25.8 pg/ml) compared to pre-HTx patients (21.0 ± 21.0 pg/ml).
Conclusion: BDCA-2+ and -4+ plasmacytoid DCs, CD62L+ and CD39 + Tregs and an increased IL34 plasma level seem to be the adjustment screws to obtain transplant tolerance and will serve as targets for the development of new tolerance-inducing strategies.

Clinical Heart Other

OS401 EXTRACORPOREAL MEMBRANE OXYGENATION OUTCOMES IN EARLY GRAFT DYSFUNCTION

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Background: Early graft dysfunction (EGD) remain as the main isolated risk factor for death within the first 30 days after heart transplantation (HT). To date, there is limited literature on the effect of extracorporeal membrane oxygenation (ECMO) support after HT. The aim of this study was to report the early clinical course and outcomes in a cohort of ECMO versus non-ECMO supported patients (p) with EGD.
Methods: Retrospective review. From 2012 to 2016, 119 adults orthotopic heart transplant were performed in our program. Categorical data were shown as frequencies/percentages and continuous variables as means with standard deviations. Comparison of categorical data was carried out with the Fisher's exact test and the continuous variables with Student's t test. Univariate analysis was performed to determine predictors for mortality. The level of statistical significance was set for 2-tailed values at $p < 0.05$.
Results: Overall median recipient age was 49 ± 14 years; 68% were male. Twenty one patients (p) (17%) presented EGD and this was associated with 1-year mortality (OR: 8.3; 95% CI: 2.57–26.59; p = 0.0006). Six p (29%) of this group received ECMO support. There were 3 deaths in the ECMO group (50%) vs. 5 non-ECMO support (33%) (p = ns). There was no statistically significant difference between ECMO and non-ECMO p intensive care unit stay (20 vs. 19 days; p = ns), length of mechanical ventilation (11 vs. 13 days; p = ns) and hospital stay (38 vs. 37; p = ns). ECMO support p had lower creatinine values within the first week vs. non-ECMO p (1.45 vs. 2.08; p = 0.017). Graft function's recovery was 100% in both groups.
Conclusion: Early ECMO support in this recovery period after transplant provides hemodynamic stability and oxygenation, allowing short-term graft dysfunction recovery avoiding others end organs injuries. Despite survival rates were lower in p who present EGD, in our cohort mortality rates did not reach statistically significance between those p who require ECMO vs. non-ECMO support.

Clinical Heart Biomarkers and molecular changes

OS402 ROLE OF PROINFLAMMATORY CYTOKINES AS PREDICTIVE BIOMARKERS FOR PRIMARY GRAFT DYSFUNCTION AFTER HEART TRANSPLANTATION

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Background: Donor brain death, cold preservation, and subsequent ischemia-reperfusion injury all participate in the pathology of primary graft dysfunction (PGD) and trigger immune responses. Our experimental studies suggest that this early immune response may initiate pro-inflammatory and pro-fibrotic processes and develop into chronic rejection, limiting long-term survival of HTx patients. In this clinical study, we investigated the role of proinflammatory cytokines as biomarkers for PGD.
Methods: We analyzed 84 donor-recipient pairs collected in a prospective, blinded single-center trial conducted 2010–2015. We collected donor and recipient plasma samples and measured heart failure and myocardial injury markers proBNP, TnT, and CK-MBm as well as a panel of 47 inflammatory factors with a Multiplex immunoassay before transplantation and 1, 6, and 24 h after reperfusion.
Results: According to ISHLT criteria, 7.1% of patients had mild, 11.9% had moderate, and 9.5% had severe PGD. Clinically, mild and moderate PGD differed little from normal graft function. Mild PGD presented similar cytokine response as patients without PGD. Moderate PGD associated with increased post-op levels of CX3CL1, and IL-6 and -18 ($p < 0.05$).

Severe PGD was linked to increased TnT and lactate release ($p < 0.001$), longer hospital and ICU length of stays ($p < 0.005$), and increased 30-day mortality ($p < 0.001$) compared to patients without PGD. In addition, severe PGD involved increased post-op levels of CCL20, CX3CL1, CXCL1, IL-6, -10, and -18, PlGF, and VEGF-A ($p < 0.05$–0.0001). Interestingly, severity of PGD did not correlate with early rejections. Increased donor plasma levels of IP10, CXCL12, and CX3CL1 were linked to moderate PGD ($p < 0.05$–0.01) with AUC for each 0.76–0.80.
Conclusions: Our results suggest that proinflammatory biomarkers may predict moderate to severe PGD after HTx. We suggest that these biomarkers may be used for risk evaluation and as a platform for therapeutic interventions in PGD.

Clinical Heart Rejection

OS403 DETERMINANTS AND OUTCOMES OF CARDIAC ALLOGRAFT VASCULOPATHY: MAJOR ROLE OF DONOR-SPECIFIC ANTIBODY

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The role of circulating anti-HLA DSA in addition to traditional cardiovascular risk factors in the development of CAV has not been demonstrated.

This observational, prospective cohort study included 723 heart recipients from 2 centers between 2004 and 2011. Participants were screened for traditional cardiovascular risk factors, circulating anti-HLA antibodies (specificity, HLA class, strength). All patients underwent prospective heart allograft biopsies and angiogram with assessment of CAV lesions. We assessed the independent determinants of CAV at 3 years after transplantation.

A total of 145 patients (20.1%) had circulating DSA at transplantation. 170 patients (23.5%) experienced acute rejection in the first 3 years post-transplant with 128 cases (17.7%) of grade 2R ACR and 83 cases (11.5%) of antibody-mediated rejection (ISHLT pAMR+). At 3 years post transplant, 29.7% of patients had CAV (20.8%, 7.4% and 1.5% with CAV scores of 1, 2 and 3 respectively). After adjusting on traditional risk factors (recipient age, primary heart disease, gender, hypertension, tobacco use, dyslipidemia, diabetes mellitus, BMI), donor factors (age, gender, BMI, cause of death), transplant characteristics (cold ischemia time, center, emergency heart transplantation), immunological parameters (circulating DSA at transplantation and acute rejection), and CMV disease occurence, the independent determinants of CAV at 3 years were: donor age (RR = 1.05; 95% CI = 1.03–1.08), recipient dyslipidemia (RR = 2.1; 95% CI = 1.02–4.29), presence of circulating DSA at transplantation (RR = 2.45 95% CI = 1.45–4.12). Occurrence of pAMR2 post-transplant was also a strong and independent factor associated with CAV at 3 years post-transplant (RR = 3.51, IC95% = 1.84–6.69). This group showed decreased patient survival (HR = 1.8 p = 0.01).

Circulating DSA are major determinants of severe arteriosclerosis, independent of traditional cardiovascular risk factors. Antibody-mediated CAV is associated with reduced patient survival.

Clinical Heart Other

OS404 MELD-XI SCORE PREDICTS EARLY AND LONG-TERM PROGNOSIS AFTER HEART TRANSPLANTATION

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Background: The Model for End-Stage Liver Disease excluding INR (MELD-XI) is a possible risk factor for mortality after heart transplant (HT). Its relevance in the context of donor and recipient factors is poorly explored. Herein we investigate how MELD-XI combined with donor (D) and recipient (R) factors may improve risk stratification for early and long-term outcomes after HT.
Methods/Materials: We reviewed pre-HT data of adult patients (pts) transplanted between 1999 and 2015, excluding combined HT and those with a left ventricular assist device. Graft-related and overall mortality were study endpoints, as estimated at 30-days (30 days) and 10 years survival rates.
Results: 427 pts, mean age 53 y, 80% males, 41% ischemic etiology (CAD), were included. 30 days and 10 years graft-related mortality was 3.8 ± 0.9% and 17.2 ± 2.1%, while overall mortality was 6.1 ± 1.1%; and 33.2 ± 2.5%. MELD-XI was linearly associated with graft and overall survival both at 30 days and 10 years ($p < 0.01$ for all). At multivariate analysis, predictors of 10-y graft-related mortality were: high MELD-XI (RR: 6.4), pulmonary vascular resistances (PVR) > 3 (RR: 2.5), CAD (RR: 1.9), BMI > 28 (RR:1.9), donor death for cerebral hemorrhage (ICH) (RR:1.89); $p < 0.05$ for all. Predictors of 10 years overall death were: high MELD-XI (RR:1.7), PVR > 3 (RR:1.7), need for postoperative ECMO (RR:3.3), R age (RR:1.01/year), D age > 40 years (RR:1.6), D death for ICH (RR: 1.6); $p < 0.05$ for all. High MELD-XI and PVR > 3 predicted 30-d cardiac (RR: 6.1; 6.9) and overall death (RR: 3.4; 3.7); $p < 0.05$ for all.
Conclusion: MELD-XI independently influences short and long term graft related and unrelated mortality. These data study support the concept that renal and liver function, as estimated by MELD-XI, represent an important independent marker of overall comorbidity to carefully consider in evaluating transplant benefit in HT candidates.

Clinical Heart Allocation

OS405 TO ACCEPT OR NOT ACCEPT, THAT IS THE QUESTION: DONOR HEART SELECTION PROCESS AND OUTCOME OF DISCARDED ORGANS TRANSPLANTED IN ANOTHER CENTER

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Purpose: The decision making process to accept a donor heart is very complicated, subjective and less associated with evidence based decisions. In this analysis we evaluated donor heart acceptance, reasons for rejection, alternative center acceptance and outcome over a 15 year period in a big center
Methods: All donor heart offers reported to our center from 2001 to 2015 [$N = 2205$] were analysed. Heart acceptance (Ac) rate and transplantation rate were calculated. Reasons for non-acceptance were divided into quality (Qu) and non-quality (nQ) reasons. Rejected Donor hearts, accepted in other centers were analysed for transplant rate and outcome (1-year & 3-year survival and compared with transplant outcomes in our center.
Results: A total of 699 (31.7%) donor hearts were accepted. Of these 124 (17.7%) were rejected at time of procurement. Main causes were CAD (37%), impaired LVEF (21%), hemodynamic instability (16%), other (26%). Of those 1506 hearts not accepted primarily, 869 (39.4%) were rejected due to quality reasons (Qu: age: 20%, hypertrophy 14%, impaired LVEF 12%, hemodynamic instability 14%, virology 11%, other 20%) and 637 (28.9%) due to non-quality reasons (nQ: mismatch: 71%, capacity 14%, other 15%). 231 (26.6%) of Qu and 346 (54.3%) of nQ hearts were accepted in other centers and of these 170 (73.6%) and 303 (87.6%) were transplanted. One and three year survival post transplantation was significant different between Ac, Qu and nQ respectively (1 year: Ac: 83.7% vs. Qu: 73.5% vs. nQ: 81.1%; $p = 0.011$; 3 Year: Ac: 79.1% vs. Qu: 64.9% vs. nQ: 75.8%; $p < 0.0001$).
Conclusions: Donor hearts not accepted in our center that were transplanted in another center were associated with a higher mortality if rejected for quality reasons, whereas heart discarded for non quality reasons had similar outcome. There is a strong need for better understanding on donor heart selection.

Clinical Heart Other

OS406 THE PREVALENCE AND VARIABILITY OF NON-ADHERENCE TO THE NON-PHARMACOLOGICAL TREATMENT REGIMEN AFTER HEART TRANSPLANTATION INTERNATIONALLY: FINDINGS FROM THE BRIGHT STUDY

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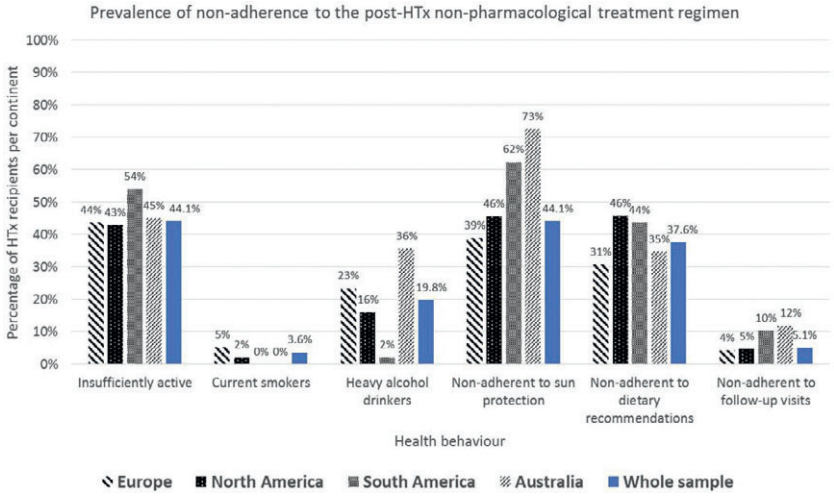
Background: Heart transplant (HTx) recipients need to follow a complex therapeutic regimen consisting of pharmacological and non-pharmacological components (i.e. regular physical activity, not smoking, limiting alcohol intake, applying sun protection, following dietary recommendations, and attending follow-up visits). We assessed the international variability in the prevalence of non-adherence to the non-pharmacological treatment regimen.
Methods: Using data from the BRIGHT study, an international multi-centre cross-sectional study including 1397 adult HTx recipients (72.4% males, mean age 54.3 years (SD 14.5 years), 1–5 years post-transplant) from 36 HTx centres in 11 countries and 4 continents, the prevalence of non-adherence to the post-HTx non-pharmacological treatment regimen was assessed using self-report (see table for details on tools). Findings were summarized by descriptive statistics and using figures.
Results: The overall prevalence in the sample was: 44.1% for insufficient activity, 3.6% for smoking, 19.8% for heavy alcohol drinkers, 44.1% for not applying sun protection, 37.6% for not following recommended diets, and 5.1% for missing ≥1 follow-up appointment. While Australia had the highest percentage of heavy alcohol drinkers, sun protection non-adherents and appointment non-adherents, European countries had the lowest percentage of non-adherents to the latter 2 behaviours as well as dietary recommendations. North America had the highest percentage of non-adherents to dietary recommendations but the lowest to physical activity. The prevalence of self-reported smoking was 0% in Australia and South America. More details are illustrated in the figure.

Variable	Instrument	Recall period	Response options	Scoring
Physical activity	Brief Physical Activity Assessment tool	1 year	No. times/week 20′ of vigorous activity & no. times/week 30′ of moderate activity	Insufficiently active: <3x/week vigorous activity OR <5x/week moderate activity OR <5x/week combination of both
Smoking	One item from the Swiss health survey			Not adherent: currently smoking
Alcohol intake	Investigator developed	1 year		Heavy drinker: >1 drink/day (women), >2 drinks/day (men)
Sun protection	Swiss study on health of people with cancer and Cambridge university hospitals' perception of skin cancer in Tx recipients scale	1 year	5-point Likert scale (from '1 = never' to '5 = always') & SPF	Not adherent: not always applying protection against sun or using sunscreen with SPF ≤ 30 or no sunscreen
Dietary recommendations	Investigator developed	1 year	5-point Likert scale (from '1 = never' to '5 = always')	Not adherent: not frequently or not always following the diet
Follow-up visits	Investigator developed	Last 5 appointments		Not adherent: missed ≥1 appointment



Conclusion: Non-adherence to all aspects of the non-pharmacological treatment regimen is high and shows variability internationally. These findings point towards a need for integrating support for adherence in transplant follow-up care.

OS408 TRANSPLANT PREGNANCY REGISTRY INTERNATIONAL: PREGNANCY OUTCOMES IN THORACIC TRANSPLANT RECIPIENTS

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The purpose of this study is to describe pregnancy outcomes in thoracic transplant recipients. Data were collected from the Transplant Pregnancy Registry International (TPR) via telephone interviews and review of medical records. There are 87 heart recipients (148 pregnancies), 31 lung recipients (41 pregnancies) and 6 heart-lung recipients (6 pregnancies) participating in the TPR. Outcomes are listed in the table.

	Heart	Lung	Heart-Lung	*p Value
Recipients/ pregnancies	87/148	31/41	6/6	
Age at 1st transplant (years)	19.8 + /- 8.7 #	26.9 + /- 6.7	28.3 + /- 2.9	<0.001
Transplant to conception interval (years)	7 + /- 5.4	3.7 + /- 2.9 #	6.7 + /- 3.7	0.001
Unplanned pregnancies	46%	61%	80%	NS
Terminations	4.6%	12%	0	NS
Ectopic pregnancies	1.3%	0	0	NS
Miscarriages	27%	30%	0	NS
Live births	67% (n = 102)	58% (n = 25)	100% (n = 6)	NS
Gestational age (wks)	36.2 ± 3.5	34.0 ± 5.1	35.0 ± 2.3	0.03
Birthweight (g)	2561 ± 693	2181 ± 879	2117 ± 672	0.03
Drug treated hypertension	45%	54%	17%	NS
Preeclampsia	26%	9%	33%	NS
Rejection during pregnancy	10%	17%	0	NS

*by Chi^2 or ANOVA; # p < 0.05 compared to each other group; NS = not significant.

Heart recipients were significantly younger at the time of transplant (likely due to more pediatric heart transplants) while the lung recipients have a significantly shorter transplant to conception interval. Overall, 51% of the pregnancies in thoracic transplant recipients are unplanned. Notably, the average newborn of a lung or heart-lung recipient is preterm and low birthweight. At last TPR follow-up 8 years postpartum, adequate transplant function was reported in 64% of heart recipients (31% deceased), 65% lung recipients (23% deceased) and 50% heart-lung recipients (50% deceased).

Conclusions: Successful pregnancies are reported in thoracic transplant recipients. However, such pregnancies carry considerable risks both during pregnancy and postpartum potentially impacting maternal survival. Additionally, infants born to lung and heart-lung recipients are at risk as they will likely be preterm and low birthweight. The number of unplanned pregnancies in these recipients highlights the importance of counseling regarding contraceptive options and family planning before and after transplant and throughout the child-bearing years.

Clinical Liver Other

OS409 PREVALENCE AND RISK FACTORS OF PORTAL VEIN THROMBOSIS IN PATIENTS WITH LIVER CIRRHOSIS AND ITS IMPACT ON OUTCOMES AFTER LIVER TRANSPLANTATION

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Background: Although portal vein thrombosis (PVT) is prevalent in patients with liver cirrhosis its associated risk factors are not well established. Furthermore, the impact of PVT on liver transplantation outcomes is still controversial. This study aimed to investigate the prevalence and risk factors of PVT in patients with liver cirrhosis and its impact on post liver transplant outcomes.
Methods: In a cross-sectional study, all adult (>18 years) patients with liver cirrhosis undergoing liver transplantation between March 2013 and March 2015 at Shiraz Organ Transplant Center, Shiraz, Iran were included. The presence of PVT in pre-transplant period confirmed by abdominal computed tomography, laboratory data and other characteristics as well as rejection episodes, survival and mortality after transplantation were recorded.
Results: From 1009 patients with liver cirrhosis, 115 patients (11.4%) (35 men and 80 women) had PVT. Diabetes mellitus ($p = 0.005$) and presence of large esophageal varices ($p < 0.001$) were associated with PVT in univariate analysis. Lower platelet count, lower total bilirubin and higher fasting blood sugar were also associated with presence of PVT ($p < 0.05$). In regression analysis, presence of large esophageal varices (grade II and III) was independently associated with PVT (OR: 3.81; 95% CI: 2.05–7.08, $p < 0.001$). No significant association was found between presence of PVT and rejection episodes after liver transplantation (OR: 1.18; 95% CI: 0.70–1.98, $p = 0.301$). In regression analysis, PVT was an independent predictor of early mortality following liver transplantation (OR: 1.88; 95% CI: 1.09–3.2, $p = 0.022$). The mean post-transplant survival was 52.74 ± 5.4 months in patients without PVT and 48.94 ± 19.1 months in patients with PVT ($p = 0.022$).
Conclusions: PVT is prevalent in patients with liver cirrhosis and may predict early mortality in post-transplant period. Proper management in pre-transplant period may be warranted to prevent post-transplant complication.

OS410 PROGNOSIS OF BILIARY ATRESIA: FRENCH NATIONAL STUDY 1986–2015

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Background: This study analyses the prognosis of Biliary Atresia (BA) in France since 1986, when both Kasai operation (KOp) and Liver Transplantation (LT) became widely available.
Methods: The charts of all patients diagnosed with BA born between 1986 and 2015 and living in France were reviewed. Patients were classified into 4 cohorts according to their years of birth: 1986–1996 (477 patients), 1997–2002 (278), 2003–2009 (364) and 2010–2015 (237).
Results: 1356 patients were included; 1276 (94%) underwent KOp. Age at KOp (median 59 days, range 6–199) was stable over time. Survival with Native Liver (SNL) after KOp was 42%, 36%, 27% and 24% at 5, 10, 20 and 30 years, and was stable in the 4 cohorts. Independent prognostic factors for SNL after KOp were: age at KOp (25-year SNL: 38%, 29%, 23%, 18% in patients operated in the 1st, 2nd, 3rd month of life or later, respectively; $p = 0.0001$), polysplenia syndrome (25-year SNL: 28% and 8% in patients without/with polysplenia; $p < 0.0001$), anatomical pattern of the extra-hepatic biliary remnant (25-year SNL: 76%, 37%, 30%, 23% in types 1 to 4 of the French classification; $p < 0.0001$).

16%, 7%, 7%, 7% of patients died without LT in the 4 cohorts, respectively ($p = 0.0001$).

753 patients (55%) underwent LT. Patient survival after LT was 79% at 30 years. 5-year patient survival was 76%, 91%, 88%, and 93% in cohorts 1 to 4, respectively ($p < 0.0001$),

Actual BA patient survival (from diagnosis) was 80%. 5-year BA patient survival was 72%, 88%, 87%, 88% in cohorts 1 to 4, respectively ($p < 0.0001$).
Conclusion: With the sequential treatment of Kasai operation and liver transplantation if needed, 24% of BA patients reach the age of 30 years with their native liver, and 88% of BA patients can live. Continuous improvement of BA prognosis was mainly due to reduced mortality without LT, and better outcomes after LT.

Acknowledgments: to the physicians and surgeons of the 45 centers participating to the French Observatory of BA.

OS411 RISK FACTORS FOR AND LONG-TERM PROGNOSIS OF BILIARY COMPLICATIONS FOLLOWING PEDIATRIC LIVING DONOR LIVER TRANSPLANTATION

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Background: Post-transplant biliary complications (BCs) are classified as anastomotic stricture (AS) or non-anastomotic stricture (NAS). Herein, we investigated our institution's experience with the risk factors for and long-term prognosis of post-transplant BCs.
Methods: Between May 2001 and September 2016, a total of 279 living donor liver transplantations (LDLTs) were performed, including transplantations in 271 pediatric recipients. The median age at LDLT were 1.4 years old (0.1–16.5). The observation period ranged from 0.3–15.6 years. All the biliary reconstructions at LDLT were hepaticojejunostomy without a stent, or with an internal, or external stent. Post-transplant BCs were diagnosed when radiological, endoscopic, or surgical intervention was performed because of liver dysfunction or cholangitis.
Results: Post-transplant BCs were presented in 51 cases (18.3%), including AS in 35 cases, AS+NAS in 8 cases, NAS in 6 cases, and others in 2 cases. The median time to diagnosis of the post-transplant BCs was 161 post-operative days (3–2269). Re-laparotomy after LDLT was a risk factor of post-transplant BCs ($p = 0.019$), and the occurrence rate of post-transplant BCs in the case of hepaticojejunostomy using an external stent was less than in the other cases ($p = 0.004$). The first treatment for post-transplant BCs was percutaneous transhepatic biliary drainage (PTBD) in 29 cases, double-balloon enteroscopy (DBE) in 18 cases, and surgical revision in 4 cases. The graft survival rates in patients with and without post-transplant BCs were 94.1% and 91.7%, respectively ($p = 0.519$), but in 2 patients who underwent re-LDLT, the cause was intractable cholangitis due to NAS.
Conclusion: Post-transplant BCs can be prevented by hepaticojejunostomy using an external stent, and the long-term prognosis is good with early treatment with DBE or PTBD. However, the long-term prognosis of multiple NASs is poor because of continuous liver dysfunction and intractable cholangitis.

OS412 IMMUNOLOGICAL RISK FACTORS RELATIVE TO NON-ANASTOMOTIC BILIARY STRICTURES AFTER LIVER TRANSPLANTATION

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Background: The purpose of this study was to investigate immunological risk factors associated with NAS (Non-anastomotic Biliary Strictures) after LT (Liver Transplantation).
Methods/Material: the study included 303 patients, in 309 adult liver transplantation performed from August 2005 and April 2016, with a radiological or surgically proven biliary stricture. About 36 potential risk factors for biliary strictures were studied.
Results: A biliary stricture was diagnosed in 26.7% of transplants, the anastomotic type (AS) and the NAS complicated the transplantation in 18.15% and 4.62% of cases respectively. Patients with both of forms were 3.96%. Univariate analysis using logistic regression showed that the cholestatic diseases ($p < 0.001$), the donor age >46 years old ($p = 0.007$), the positive crossmatch ($p = 0.048$), occurrence of rejection ($p = 0.040$) and ABO mismatch ($p = 0.034$) were all significantly associated with the development of NAS. At the multivariate analysis, the cholestatic diseases ($p < 0.001$), the recipient age >54 years ($p = 0.001$), the crossmatch positivity ($p = 0.008$), the acute cellular rejection ($p = 0.008$) and ABO mismatch ($p = 0.034$) appeared to be the only variables independently associated with the development of NAS (table 1).
Conclusion:

	p	OR	IC 95.0%
Recipient Age >54 years	0.001	5.259	1.997–13.846
Cholestatic Disease	<0.001	10.090	3.153–32.292
Positive Crossmatch	0.008	8.037	1.707–37.843
Acute cellular rejection	0.008	3.154	1.346–7.391
ABO mismatch	0.042	3.762	1.051–13.462

Immunological risk factors (cholestatic diseases, crossmatch positivity, ABO mismatch, acute cellular rejection) emerged as being the most important variables associated to the development of NAS after LT.

OS413 THE LONG-TERM OUTCOME OF ADULT ABO-INCOMPATIBLE LIVING DONOR LIVER TRANSPLANTATION

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Background: We started adult ABO-incompatible living donor liver transplantation (ABOI-LDLT) in 1998. We investigated the long-term outcome of recipients who underwent ABOI-LDLT in our center.
Patients and Methods: We retrospectively assessed medical records of recipients who underwent ABOI and non ABOI-LDLT since 1997 and survived longer than 1 year after transplantation. We analyzed survival rate, incidence of de novo malignancy occurrence (solid cancer and PTLD), incidence of rejection, rate of biliary tube possession, and the levels of total bilirubin, creatinine, eGFR, and HgbA1C at the time of 1, 3, 5, and 10 years after transplantation.
Results: There were 26 cases of ABOI-LDLT (ABOI group) and 88 cases of non ABOI-LDLT (compatible or identical) (non ABOI group). There were no significant differences of patient background between the groups except calcineurin inhibitor usage (tacrolimus and cyclosporine, 81% and 19% in ABOI, 51% and 49% in non ABOI, $p < 0.05$). Five-year survival rates were 90.0% and 92.7% in ABOI group and non ABOI group, respectively. Incidences of solid cancer were 11.5% and 6.8% and those of PTLD were 3.8% and 4.5% in ABOI group and non ABOI group, respectively. There were no significant differences of survival rate and the incidences between the groups. There was no statistical difference of the rate of acute cellular rejection occurrence and biliary tube possession. There were also no differences of values of total bilirubin, HgbA1c, and creatinine. As for eGFR, a significant difference was detected at 3 years after transplantation (72 ± 25 in ABOI, 58 ± 20 in non ABOI, $p < 0.05$).
Conclusion: Our data suggest that the long-term outcome of recipients who underwent ABOI-LDLT is comparable to that of non ABO-LDLT.

OS414 BRIDGING TO LIVER TRANSPLANTATION: SAVE YOUR ARTERY

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Background: Hepatic artery (HA) complications are feared complications in the postoperative course after liver transplantation (LT), which may compromise the biliary tract (BT), graft and patient survival. The objective of this systematic review and meta-analysis was to compare risk of HA and BT complications after LT in patients who underwent neo-adjuvant trans-arterial chemoembolization (TACE) vs. no TACE.
Methods: Comprehensive searches were performed in Embase, MEDLINE OvidSP, Web of Science, Google Scholar and Cochrane databases to identify studies concerning hepatocellular cancer patients (HCC) undergoing pre-LT TACE. Quality assessment of studies was done by the validated checklist of Downs and Black. Meta-analyses were performed to evaluate the incidence of HA complications, HA thrombosis and BT complications, using binary random-effect models.
Results: Fourteen retrospective studies, representing 1122 TACE patients, met the inclusion criteria. After LT the following HA complications were reported: stenosis, thrombosis and (pseudo)aneurysm. Pre-LT TACE carried a significantly increased risk for HA complications after LT (OR: 1.57, 95% CI 1.09–2.26, $p = 0.02$). No evidence was found for an increased risk for HA thrombosis or BT complications after LT. In three studies comprising 183 TACE and 388 non-TACE patients, cumulative numbers of re-interventions related to HA complications were 10 (5.5%) in TACE vs. 4 re-interventions (1%) in non-TACE patients. There were 4 reported deaths due to HA complications in the TACE group (2.2%) and none in no-TACE group.
Conclusion: Increased risk of HA complications after LT should be carefully balanced against the benefits of TACE prior to LT.

OS415 LIVER REGENERATION RATE ANALYSIS IN LIVING DONOR LIVER TRANSPLANTATION

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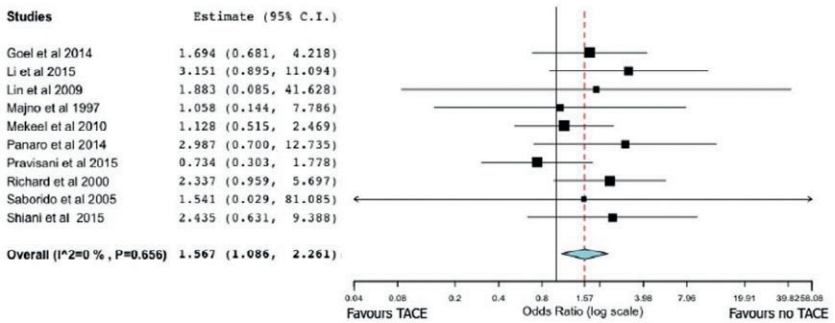
Background: Liver surgery has had an exponential development making possible the use of partial liver grafts for living donor liver transplantation (LDLT). Nonetheless, LDLT indication still depends on the graft size used for the recipient, due to the development of "small for size syndrome" (SFSS) which can be better understood through the study of hepatocellular regeneration.
Materials and methods: A retrospective study was performed of the LDLT in Hospital Clinic of Barcelona analyzing the liver regeneration through radiologic imaging made at different moments in the follow-up with which we calculated a liver regeneration rate (LRR). We used SPSS v20 for statistical analysis.
Results: From January 2005 to December 2015 a total of 50 LDLT have been performed. Meaning a total of 100 patients were included. Forty-six of these transplants (92 percent) a right liver graft was transplanted, and in only four (8%) we used the left liver as graft. We analyzed different clinical factors that could alter LRR.

We found that the LRR was greater in the recipient than in the donor, and in both the rate diminishes at the second month of surgery approximately, having almost no chances beyond the third month. There was no difference between left and right graft recipient LRR, with the limitation of having very few left liver living donor transplantation.

By analyzing factors associated with regeneration rate we found significant difference in de percentage of initial graft weight. Also recipients with VHC infection regeneration rate was lower during the first 3 months.
Conclusions: These findings give a better understanding of the differences in recipients and donors of the liver regeneration rate in time. Also, the knowledge of clinical factors that could be associated or alter LRR, could allow physicians and surgeons to detect individual characteristics of donors and recipients that could be modified or for better surveillance for the prevention of SFSS in LDLT and liver surgery.



Clinical Kidney Cancer

OS417 POST-TRANSPLANT CANCERS NEGATIVELY AFFECT SURVIVAL OF KIDNEY TRANSPLANT RECIPIENTS: RESULTS FROM THE ITALIAN MULTICENTRIC COHORT STUDY

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Background: It is well known that kidney transplant recipients (KTR) have a 2-fold higher risk of cancer than sex- and age-matched people in the general population, but few data are available on the impact of post-transplant cancers (PTC) on survival of such people. The aim of the study was to quantify the role of PTC on the survival of KTR.
Materials and methods: Observational, multicentric cohort study on 10870 KTR enrolled over all of Italy in 19 transplant centers between 1990 and 2010 (median age at transplant: 50.3 years, 64% men). At baseline (i.e., at transplant) information were collected on socio-demographic indicators and clinical data; vital status and the eventual diagnosis of cancer were updated at follow up visits. Survival was computed from date of transplant to death, cancer diagnosis o date of last follow-up. Statistical differences in survival were computed according to the Kaplan Meyer method.
Results: 1367 KTR were diagnosed with 1 or more cancers during follow-up, including: 680 solid tumors, 619 skin cancers non melanoma, 124 post-transplant lymphoproliferative disorders (PTLD, most of all, NHL) PTLD, 101 Kaposi sarcoma (KS). Overall, the post-transplant survival ranged from 97.8% at 1-year to 94.0% at 5-years and 86.7% at 10 years. It decreased with aging (it was 66.6% at 10 years in KTR $\geq$ 60 years) and in KTR with a cancer diagnosis. As compared to 88.9% of KTR without cancer who was alive 10 years after transplant, 67.5% of KTR with any type of cancer was alive -in particular, 65.3% with PTLD ($p < 0.05$).
Conclusions: The reduced survival (up to 20% at 10 years after transplant) shows the need of implementing specific programs of primary and secondary cancer prevention to improve the survival in KTR in Italy.
*On behalf of the Italian Immunosuppression & Cancer Study Group

OS418 USE OF MTOR INHIBITOR SIROLIMUS IN RENAL TRANSPLANTED PATIENTS WITH MALIGNANCIES IN GERMANY

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Renal transplant recipients have an increased cancer risk. The mTOR inhibitor sirolimus has immunosuppressive and antitumor activities. Current knowledge regarding renal transplant recipients converted to sirolimus because of a malignancy is still limited. In this retrospective study from 10 German transplant centers, we present data on patient and graft survival of 726 renal transplant patients treated with sirolimus comparing patients with a history of cancer prior to conversion and those without.

In 230 patients (31.7%) a malignancy prior to conversion was reported. The most common class of cancer was skin cancers ($N = 137$) and solid cancers ($N = 102$). In 16 patients the cancer type was unreported. In some patients more than one malignancy was reported. The distribution of entities and patients is shown in table 1 and demographics in table 2.

Patients with a malignancy prior to conversion were older at the time of transplantation, had longer cold ischemia time and fewer previous renal or non-renal transplantations. They were more frequently treated with azathioprine and less frequently treated with tacrolimus or mycophenolic acid. At conversion they were older, had a longer time since transplantation, had a higher eGFR, less proteinuria and developed fewer biopsy-proven acute rejection episodes after conversion. They were more frequently on dual immunosuppression, had lower loading dose of sirolimus, lower trough levels and dosing after 3 months following conversion.

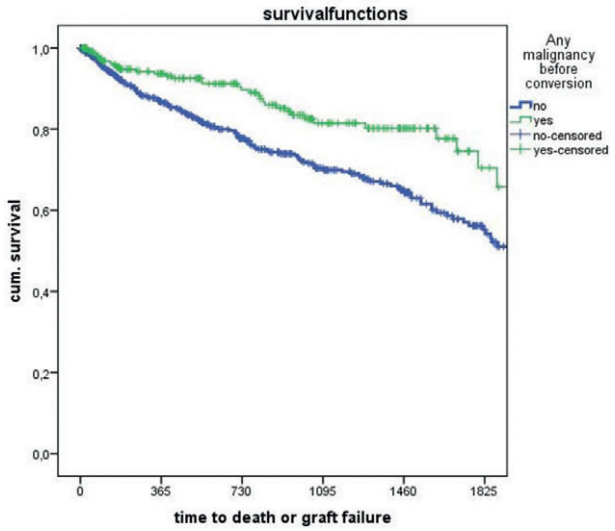
The transplant and patient survival after 5 years was better in patients with previous malignancies than in patients without previous malignancies.

Patient survival did not differ significantly after 5 years.

Conversion of renal transplant recipients to sirolimus because of a malignancy is safe. Renal outcome parameters indicate fewer rejection episodes and a better GFR in patients converted to sirolimus after 1 year in patients with a history of malignancies.

	N	%
Skin	101	13.9
Solid	63	8.7
Skin and solid	32	4.4
Lymphoma	8	1.1
Solid and lymphoma	4	0.6
Lymphoma and skin	2	0.3
Hematological	1	0.1
Solid and hematological	1	0.1
Lymphoma, solid and skin	1	0.1
Skin, solid and hematological	1	0.1
Unknown	16	2.2
No tumor	496	68.3

	Whole population (*N* = 726)	No malignancy before conversion (*N* = 496)	Malignancy before conversion (*N* = 230)	p
Recipient age at transplantation (years)	43.3 ± 13.6	41.5 ± 13.4	47.0 ± 13.2	<0.001
Recipient gender (% males)	63.6	63.1	64.8	0.662
Caucasian ethnicity (%)	99.0	98.8	99.6	0.542
Cause of ESRD (%)				
Diabetic nephropathy	12.4	16.1	4.4	0.002
Hypertensive nephropathy	3.6	3.7	3.5	
Polycystic kidney disease	11.4	11.4	11.4	
Glomerulonephritis	43.4	40.9	48.7	
Tubulointerstitial disease	14.3	14.5	14.0	
Other inherited diseases	3.6	2.9	5.3	
Other diseases/unknown	11.3	10.5	12.6	
Living donor transplantation (%)	16.4	18.1	13.0	0.094
Kidney/pancreas transplantation (%)	9.1	12.1	2.6	<0.001
Donor age (years)	44.3 ± 15.9	44.5 ± 15.2	43.8 ± 17.1	0.716
HLA matches on loci A,B,DR (*n*)	2.4 ± 1.6	2.5 ± 1.6	2.2 ± 1.6	0.267
Cold ischemia time (hours)	14.2 ± 8.0	13.5 ± 7.8	15.8 ± 8.3	0.001
Delayed graft function (%)	25.0	25.3	24.3	0.807
Initial Immunosuppression (%)				
Cytotoxic antibodies	15.6	16.5	13.7	0.335
IL-2-receptor antibodies	20.3	18.6	23.9	0.100
Cyclosporine	62.0	60.0	66.4	0.103
Tacrolimus	26.8	31.4	16.8	<0.001
Azathioprine	31.7	25.7	44.7	<0.001
Mycophenolate	53.5	59.0	41.6	<0.001
Corticosteroids	96.6	96.7	96.5	0.850
Others	5.7	6.1	4.9	0.615
Acute rejection treatments before SRL initiation (%)	38.1	39.3	35.9	0.615
BPAR after conversion (%)	9.0	11.1	4.3	0.003
Age at conversion (years)	49.8 ± 13.4	46.8 ± 13.0	56.4 ± 11.5	<0.001
period between transplantation and conversion (years)	6.1 ± 6.1	4.8 ± 4.9	8.8 ± 7.7	<0.001
Diabetes (%)	23.6	24.4	21.7	0.432
Hypertension (%)	84.7	83.2	87.9	0.105
Body weight (kg)	73.8 ± 15.5	73.8 ± 16.0	73.6 ± 14.4	0.922
BMI (kg/m^2)	24.9 ± 4.2	24.9 ± 4.4	25.1 ± 3.9	0.276
eGFR at conversion (ml/min)	39 ± 19	35 ± 18	49 ± 22	<0.001
eGFR at 1 year after conversion (ml/min)	41 ± 20	37 ± 18	49 ± 22	<0.001
proteinuria at conversion (mg/l)	431 ± 726	497 ± 819	297 ± 466	0.038
Immunosuppressive regimen before conversion (%)				
triple	39.4	46.4	24.5	<0.001
dual	51.9	46.1	64.2	
mono	8.7	7.5	11.3	
SRL loading dose (mg)	6.4 ± 4.8	7.4 ± 5.1	4.5 ± 3.5	<0.001
SRL maintenance dose at conversion (mg/day)	2.9 ± 1.6	3.1 ± 1.8	2.6 ± 1.2	0.003
SRL maintenance dose at 3 months after c onversion (mg/days)	2.7 ± 1.8	2.9 ± 1.9	2.2 ± 1.4	<0.001
SRL trough level at 3 months (ng/ml)	8.1 ± 3.8	8.4 ± 4.0	7.6 ± 3.4	0.149



OS419 COLORECTAL CARCINOMA AFTER RENAL TRANSPLANTATION: SCREENING LOOKS LIKE A VALUABLE OPTION

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Background: The risk of developing colorectal carcinoma (CRC) is increased after transplantation. We investigated the incidence and characteristics of CRC in Dutch renal transplant recipients (RTRs) and evaluated whether screening is required after transplantation.
Methods: After linking the Dutch Organ Transplant Registry (NOTR) with the Dutch Cancer Registration (IKNL), we registered all RTRs who developed CRC. We calculated the incidence rate of CRC in the RTRs using the general Dutch population as reference. Further statistical analysis calculated survival, age at diagnosis and absolute risks.
Results: Between 1968 and 2014, 21016 renal transplantations were performed in 17771 RTRs in the Netherlands. 198 RTRs developed 208 CRC after transplantation. The incidence of CRC in our RTRs was increased by a ratio of 2.34 (2.04–2.86). When divided per age group at diagnosis we found; 35–39 years: 5.26 (1.97–14.03), 45–49 years: 2.48 (1.41–4.36) and 50–54 years: 2.38 (1.61–3.53). The incidence ratio gradually increased along the years of immunosuppression. An exposure of 5 years resulted in a relative risk of 1.4 (1.08–1.82), till 4.8 (2.59–8.13) after 31–35 years of immunosuppression. RTRs developed CRC at a mean age of 60–64, compared to 70–74 years in the general population. The absolute risk of CRC in RTRs was comparable to that of a 10-year older person in the general population. Median survival time after diagnosis of CRC is 2 (range 0–19) years. A cox regression showed that the age at transplantation significantly influences the risk of developing CRC (1.08 (1.06–1.09, p = <0.001) per year).
Conclusion: Age at transplantation and years of immunosuppressive treatment significantly increased the incidence of CRC in Dutch RTRs compared with the general population. The absolute risk of CRC in RTRs at the age of 45 years is similar to that of the general population at 55 years, which makes it prudent to start screening 10 years earlier.

OS420 POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE IN KIDNEY TRANSPLANT RECIPIENTS: A SINGLE CENTER EXPERIENCE

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Background: Post-transplant lymphoproliferative disorder (PTLD) is the second most common malignancy encountered after kidney transplantation. The aim of this study was to determine the prevalence, presentation, characteristics and outcome of PTLD in our cohort of kidney transplant recipients (KTR).
Methods/Materials: Retrospective study including adult patients transplanted with a kidney between 1974 and 2012 who developed PTLD. Patients with combined transplantation were excluded.
Results: 2949 adults were transplanted with a kidney. 24 KTR developed PTLD (92% Caucasian; 50% male), a period prevalence of 0.81%. Age at first transplantation was 33 years (min 20-max 75). Two thirds of patients were treated with induction therapy at transplantation; 38% had a past history of treated acute rejection. Age at PTLD diagnosis was 51 years (min 33-max 75). Time from first transplantation to PTLD diagnosis was 13 years (min 0.6-max 30). Median duration of follow-up was 17 years (min 1.6-max 42). PTLD presented mainly with gastrointestinal (38%) and constitutional non-specific symptoms (21%); 79% with diffuse disease at time of diagnosis (Ann Arbor IV 75%). Tumors were B-cell related in 92%. Histological subgroup included mainly monomorphic PTLD (n = 22) with a majority of Large Diffuse B-Cell Lymphoma (n = 18). In 21 KTR with available information, only 7 tumors were Epstein-Barr Virus positive. Immunosuppression reduction was applied in all but 3 patients. 23 patients were treated: 16 achieved total remission; 3 relapsed; 4 failed to respond. 7 patients died from PTLD (29%). At last follow-up, 58% of KTR had died.
Conclusions: PTLD prevalence in our cohort of KTR is 0.81%. Tumors were mainly late-onset, monomorphic, high-grade invasive B lymphomas, not EBV-driven. Mortality from PTLD was 29%.

Clinical Liver Cancer

OS421 ALPHA-FETOPROTEIN PROGRESSION SLOPE AS A DISCRIMINANT FACTOR OF RECURRENCE AFTER LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA IN CIRRHOTIC PATIENTS WITHIN MILAN CRITERIA

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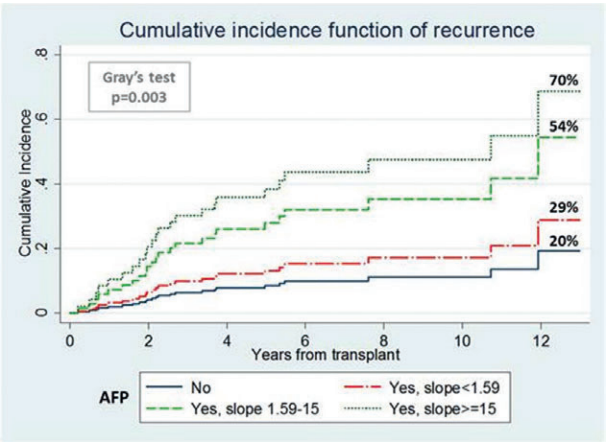
Background: The identification of patients at low risk of developing hepatocellular carcinoma (HCC) recurrence after liver transplant (LT) is a great challenge. We aim to analyze the role of Alpha-fetoprotein (AFP) in prediction



of recurrence based on secretion tumor pattern in patients satisfying Milan criteria.
Methods: From January 2001 to June 2013, 114 patients were reviewed and stratified in four groups according to AFP behavior. Receiver operating characteristics (ROC) analysis for recurrence based on slope of progression of AFP (SOP) showed 1.59 ng/ml/month (Sensibility: 57%; Specificity: 83%) as the best cutoff. We also considered SOP cutoff of 15 ng/ml/month previously proposed in literature (64.7% within Milan criteria). Group A included 37 patients (32.5%) with preoperative AFP < 10 ng/ml at all times irrespectively of pre-LT treatment (non-producing HCC). Group B, C and D included respectively 43 patients (37.7%) [SOP < 1.59]; 21 patients (18.4%) [SOP > 1.59 but < 15]; and 13 patients (11.4%) [SOP > 15].
Results: 24 patients experienced HCC recurrence (median follow-up: 798 days [IC 95%: 583–1360]). Recurrence was significantly lower in patients with non-producing HCC (Group A: 20% vs. Group B 29% vs. Group C 54% vs. Group D 70%; p = 0.003; [Image].). Total Tumor Volume (>22.3 cm), micro vascular invasion and AFP stratification (Group A,B,C,D) were identified as factors associated with recurrence at multivariate analysis (Hazard Ratio and related 95% CI for AFP stratification: group A = 1.00 [Ref.]; group B = 1.96 [0.65–5.87]; group C = 3.15 [0.96–10.34] and group D = 4.78 [1.45–15.76]).
Conclusion: AFP progression reflects the biologic behavior of HCC and represents an excellent predictor of HCC recurrence, with different levels of risk according to the slope, even in patients satisfying Milan criteria.

Clinical Intestine Cancer

OS422 CYTOREDUCTION AND MODIFIED MULTIVISCERAL TRANSPLANTATION FOR PATIENTS WITH END-STAGE PSEUDOMYXOMA PERITONEI

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Background: Pseudomyxoma peritonei (PMP) can be cured by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. In those with small bowel involvement or recurrence, major tumour debulking can still prolong survival with good quality of life. However, the inevitable disease progression results in nutritional failure from small bowel obstruction and abdominal wall failure with fistulating disease. This leads to poor quality of life and is eventually fatal. Radical cytoreduction and modified multi-visceral small bowel transplantation could offer a life prolonging opportunity in selected patients.
Methods: Between 2013–2016, 6 PMP patients underwent transplantation. All patients had previous surgery for PMP and further cytoreduction was deemed not feasible due to extensive bowel involvement. Three patients underwent radical debulking and 3 complete cytoreduction followed by modified multi-visceral transplantation.
Results: Median operating time was 14 h with a median of 14 packed cell transfusion. Post-op ITU stay was 12 days (range 2–45). Time on PN postoperatively: median 31 (range 19–51) Follow up: 4 patients were alive at the time of review (24, 20, 6 and 4 months following surgery); 2 died (Day 26 and day 64). The first one from anastomotic leak and GVHD with associated fungal and bacterial chest sepsis. The other one had an anastomotic leak and died because of a GI bleed. No episodes of acute rejection of the intestinal graft were seen but a single episode of grade 1 skin rejection of abdominal wall graft at day 68 treated with methylprednisolone. QOL data using EQ5D: 3 pre-tx patients gave a VAS average 30 (range 10–50). One month post Tx VAS single data point was 60. All 4 surviving patients are independent of TPN and well at home.
Conclusion: Cytoreductive surgery followed by modified multi-visceral transplantation is a technically feasible operation for end stage PMP. The long-term outcomes will determine the effectiveness of this procedure.

Clinical Heart Cancer

OS423 HEART TRANSPLANTATION FOLLOWING MALIGNANCY

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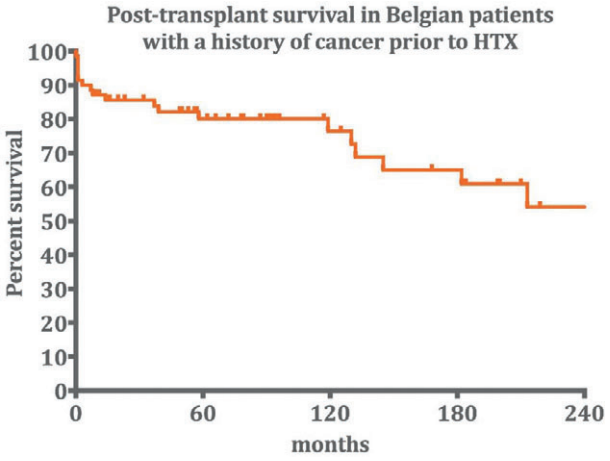
Background: Cancer treatment is frequently complicated by cardiac dysfunction. Some of these patients may become heart transplant candidates. On the oher hand, malignancy is a well-known complication of solid organ transplantation. Since there are very few data in the literature reporting evolution of heart transplant recipients with a history of cancer, we aimed to describe baseline characteristics and outcome of heart transplant recipients with a history of cancer prior to heart transplantation (HTX).
Method: We performed a multicentric retrospective study including all HTX recipients with prior malignancy transplanted in Belgium over the last 30 years (1987–2016).
Results: We identified 70 recipients with prior cancer (51% male; 49% female). Median age at HTX was 46 ± 15 years. Median time from cancer to HTX was 12 ± 10 years. The types of cancer were haematologic (26%), breast (14%), genitourinary (18%) and soft tissues (10%). The types of cardiomyopathy leading to HTX were toxic (53%), ischemic (17%) and idiopathic (11%). Survival at 5, 10, 15 and 20 years of study population compared to overall belgian HTX population was respectively 80% vs. 72%, 76% vs. 56%, 60% vs., 39% and 54% vs. 22% (p < 0.05).



Twenty-seven% developed post-transplant malignancy during follow-up (78 ± 87 months). Patients transplanted <5 years following cancer were more likely to have cancer recurrence (4/16; 25%), while patients transplanted >5 years following cancer had more new cancers (11/56; 20%) (p < 0.05). Cancer recurrence and new cancers were the cause of respectively 2% and 3% of mortality.
Conclusion: In our series, baseline characteristics of study population vary from general HTX recipients (more female, more toxic cardiomyopathies). A history of cancer prior to HTX is not associated with an increased incidence of cancer or with an increase in post-transplant mortality. (cfr. Lund et al. J Heart Lung Transplant. 2016).

Basic Kidney Biomarkers and molecular changes

OS424 IDENTIFICATION OF KIDNEY TRANSPLANT PATIENTS AT RISK FOR SKIN CANCER BY DIFFERENTIALLY METHYLATED REGIONS IN T CELLS

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Erasmus Mc, The Netherlands

Background: Skin cancer, specifically cutaneous squamous cell carcinoma (cSCC), is the most often occurring malignancy in patients after organ transplantation with an incidence of 100–200 times more than in the general population. Biomarkers to predict post-transplant cSCC are unavailable. We hypothesized that individuals at increased risk for post-transplant cSCC could be identified by epigenetic alterations in T cells, which are crucial in tumour immune surveillance. Therefore, we studied genome-wide DNA methylation in T cells at time of transplantation and prior to the clinical onset of cSCC in kidney transplant (KTx) patients.
Methods: Pure T cells were isolated by FACS sorting from PMBCs of KTx patients with (n = 46) and without cSCC after transplantation (n = 46). Patients with post-transplant cSCC were matched to patients without cSCC. Genome-wide DNA methylation was measured using Illumina's Infinium 450K array. To find differentially methylated regions (DMRs), we applied linear mixed modelling to adjust for confounders followed by comb-p to find the regions.
Results: The results showed 16 DMRs at time of transplantation between patients with post-transplant cSCC and those without post-transplant cSCC. The majority (11/16) of these DMRs were hypomethylated in patients with post-transplant cSCC and 13 of these 16 DMRs were located within the promoter region of a gene. After transplantation but prior to the clinical onset of cSCC, 7 DMRs were found. These results include an intragenic region of SERPINB9, an

actively transcribed gene in T cells, and a known tumour suppressor microRNA. No overlap was found so far between the two groups.
Conclusion: These findings support the hypothesis that differentially methylated regions can potentially serve as a predictive tool for the development of post-transplant cSCC, both at time of transplantation and prior to the clinical onset of cSCC.

Clinical Kidney Immunosuppressive agents

OS425 VALIDATION OF TOOLS FOR ANNUAL ADHERENCE EVALUATION OF KIDNEY TRANSPLANT RECIPIENTS

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Background: Adherence to immunosuppressive therapy is important for patient and graft survival. For capture of adherence data it is recommended to combine different subjective and objective tools. An optimal adherence tool should easily be applicable in routine clinical setting. We aimed to validate the questionnaire "Basal Assessment of Adherence to Immunosuppressive Medication Scale" (BAASIS®) for annual capture of adherence data in kidney transplant recipients (KTxR).
Method: A total of 300 KTxR using Tac as part of their immunosuppressive therapy were included in a single center open randomized prospective trial. Two thirds of the recipients were included within four weeks after transplantation and followed for one year, the other third was investigated cross-sectional at their 1-year post KTx control. All recipients completed the BAASIS® at inclusion and an additional 2–8 times. Comparative validation-tools were clinician's collateral reports scoring patient adherence and variation in tacrolimus (Tac) trough concentration. The recipients were grouped as adherent (Ad-group)/non-adherent (NoAd-group) according to the BAASIS® answers. Results from the 2 groups were then compared to the response from the 2 comparative tools mentioned above and 1-year renal outcome.
Results: Mean age at inclusion was 55 (22–80) years, 72% males and 31% received living donor kidneys. The results show an increasing number of NoAd recipients with increasing time after transplantation: 9% 8-weeks post-transplant and 30% 1 year after transplantation according to BAASIS®. The tools show some degree of overlap, but capture different NoAd populations. Tac variation contributed with little additional information over the two other tools in the early post-transplant phase.
Conclusion: NoAd seems to increase with time after transplantation. The combination of BAASIS® and clinician's score can identify a relevant proportion of risk patients, and these scores are possible to collect on an annual basis.

Clinical Others Immunosuppressive agents

OS427 TRANSPLANT PREGNANCY REGISTRY INTERNATIONAL: FATHERED PREGNANCY OUTCOMES WITH EXPOSURE TO MYCOPHENOLIC ACID PRODUCTS

Michael Moritz, Lisa Coscia, Dawn Armenti, Serban Constantinescu
Gift of Life Institute, Transplant Pregnancy Registry International, United States

The purpose of this study was to compare pregnancy outcomes fathered by male solid organ transplant recipients maintained on mycophenolic acid products (MPA) and those not maintained on MPA. Data regarding 917 male abdominal and thoracic transplant recipients were collected by the Transplant Pregnancy Registry International (TPR) via questionnaires, followed by telephone interviews and review of medical records. As background, females are advised to avoid MPA during pregnancy due to fetotoxicity (miscarriage rate 53%) and the increased incidence (15%) and pattern of birth defects in surviving infants. In the US general population, the miscarriage rate is approximately 10–20%, major birth defect rate 3%, preterm birth rate 7% and low birthweight (LBW) rate 8%. The table shows the comparison of pregnancy outcomes of male fathered pregnancies with and without exposure to MPA. There was no significant difference in outcomes between these two groups. The fetal risks known to exist when the mother takes MPA during pregnancy do not exist for pregnancies fathered by male transplant recipients who take MPA at the estimated time of conception.

	Male MPA Exposed	Male No MPA	p value*
Pregnancy outcomes	295	1092	
Miscarriages	9.2%	6.2%	NS
Stillbirths	0.7%	0.7%	NS
Ectopic pregnancies	0	0.6%	NS
Terminations	0	0.6%	NS
Live births	90.2%	91.9%	NS
Neonatal deaths	0.4%	0.6%	NS
Gestational age (weeks)	39 ± 2.5	39 ± 2.3	NS
Preterm (<37 weeks)	12.8%	12.8%	NS
Birth weight (g)	3323 ± 635	3362 ± 592	NS
LBW (<2500 g)	8.5%	6.6%	NS
Birth defects	3.5%	3.1%	NS

*Chi^2 or *t*-test.
Conclusions: The outcomes of pregnancies fathered by male transplant recipients maintained on MPA are indistinguishable from those not maintained on MPA and are comparable to the general population. The results of this study do not support the avoidance of MPA for male transplant recipients considering parenthood

OS428 TRANSPLANT PREGNANCY REGISTRY INTERNATIONAL: PREGNANCY OUTCOMES WITH EXPOSURE TO MTOR INHIBITORS

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Gift of Life Institute, Transplant Pregnancy Registry International, United States

The purpose of this study was to describe pregnancy outcomes with exposure to mTOR inhibitors (sirolimus or everolimus). Data were collected by the Transplant Pregnancy Registry International (TPR) via telephone interviews and review of medical records. Of the 1524 female recipients (2823 pregnancy outcomes) reported to the TPR, there were 37 recipients (20 kidney, 6 liver, 7 heart, 2 lung, 1 heart-kidney and 1 kidney-pancreas) maintained on sirolimus (SRL) during pregnancy and 4 recipients (2 kidney and 2 heart) maintained on everolimus (EVL) during pregnancy.

	Sirolimus	Everolimus
Recipients	37	4
Pregnancies	48	5
Outcomes	50	6
Concomitant MPA exposure	19	0
Miscarriages	15 (30%)	1 (17%)
Live births	33 (66%)	5 (83%)
Birth defects without concomitant MPA	2/33 (6%)	1/5 (20%)
Birth defects with concomitant MPA	2/33 (6%)	0

Five infants exhibited birth defects: (1) cystic hygroma (EVL), (2) Tetralogy of Fallot (SRL), (3) vermian hypoplasia of the cerebellum (SRL), (4) facial malformations (SRL) and (5) multiple malformations (cleft lip and palate, microtia, and heart issues) (SRL). The latter two defects were reported in infants with concomitant *in utero* mycophenolic acid product (MPA) exposure.
Conclusions: Successful pregnancy outcomes with exposure to sirolimus or everolimus have been reported in various solid organ transplant recipients. To date, sirolimus exposure during pregnancy does not appear to be associated with a pattern of birth defects. Data are limited regarding everolimus exposure during pregnancy. All transplant centers are encouraged to report posttransplant pregnancies to the Transplant Pregnancy Registry International.

OS429 EXPOSURE TO MYCOPHENOLATE AND FATHERHOOD – IS THERE A RISK?

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Background: Mycophenolic acid (MPA) is the active immunosuppressive substance in both mycophenolate mofetil and mycophenolate sodium and it is widely used after organ transplantation. MPA is known to be teratogenic and females are recommended to stop prior to pregnancy. MPA withdrawal increases the risk of rejection. There is a lack of knowledge regarding possible influence of MPA on spermatogenesis and outcome of pregnancies fathered by males exposed to MPA.
Method: We compared outcomes in pregnancies fathered by renal transplant males according to whether they had been exposed to MPA or not at time of conception. All were on prednisolon and a calsinurin inhibior (Cyclosporine A or tacrolimus). A nation-wide population-based retrospective cohort study was

performed. Data from the Norwegian Renal Registry with all renal transplanted men alive between Jan. 1st 1995 and Dec. 31st 2015 were included and relevant outcome data were extracted from the Medical Birth Registry of Norway.
Results: During the given time period 230 immunosuppressed renal transplanted males fathered 350 children (155 on MPA/195 not on MPA). There were no increased risk of malformation (3.9% vs. 2.6%, p = 0.49) in MPA exposed vs. unexposed cohorts of children. The average (±SD) dose of mycophenolate was 1.42 ± 0.3 g/day and the individual median MPA trough concentration in the time period of anticipated conception and pregnancy was 2.8 ± 1.6 mg/L. There was no clinical differences between the age of the fathers on MPA vs. not on MPA (36.1 ± 5.6 vs. 35.7 ± 6.0 years, p = 0.59) or age of mothers (31.9 ± 4.7 vs. 31.0 ± 4.8, p = 0.12). Birth weight was similar in exposed and unexposed cohorts of children; 3381 ± 681 vs. 3429 ± 714 g (p = 0.53).
Conclusion: Paternal exposure to MPA did not increase the risk of adverse birth outcomes in children fathered by male kidney transplanted patients. These results are reassuring and support the continuation of paternal MPA treatment in males wanting to become fathers.

Clinical Kidney Immunosuppressive agents

OS430 COMPARISON OF LOW DOSE AND VERY LOW DOSE EXTENDED-RELEASE TACROLIMUS/MMF IN DE NOVO KIDNEY TRANSPLANT RECIPIENTS

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Introduction: Randomized clinical trial regarding to low dose (LD) and very low dose (VLD) Once-daily tacrolimus extended-release formulation (TACER)/ MMF protocol in de novo kidney transplant recipients were performed.
Patients and methods: Fifty Living-donor kidney transplant recipients were prospectively randomized into two group, (1) LD group (n = 26); targeting TAC-AUC 0–24 250 ng•hr/ml during the first 1 months and reduced to 200 ng•hr/ml after 3 months. (2) VLD group (n = 24); targeting TAC-AUC0-24 200 ng•hr/ml during the first 1 months and reduced to 150 ng•hr/ml after 3 months. All administered MMF, corticosteroid and basiliximab induction. MMF was started with 1250 mg BID and reduced to 750 mg BID at 2 weeks after transplant, and adjusted to achieve MPA-AUC0-12 between 30–60 μg·h/l. Protocol biopsy were evaluated after 1 and 12 months, and anti-HLA antibody/ DSA were evaluated annually.
Results: With a mean observation of 31 months (16–47), patients and graft survival are 100% in both groups. Mean tacrolimus C0 at 1 month and 2 year after transplant was 5.5 ± 1.8 and 4.9 ± 1.0 ng/ml in LD, and 4.7 ± 1.1 and 3.7 ± 0.9 ng/ml in VLD. Subclinical or clinical T cell mediated rejection were observed in 0% in LD and 8.3% in VLD, while incidence of CMV infection was reduced in VLD (16.7%) compared to LD (30.7%) respectively. CNI toxicity were observed in 7.7% in LD and 12.5% in VLD in 1 month protocol biopsies, but those findings were alleviated in 1 year protocol biopsy (7.7% in LD and 8.3% in VLD). Mean eGFR were equivalent between the two groups; 54.2 ± 12.8 ml/min/1.73 m^2 in LD and 51.8 ± 12.4 ml/min/1.73 m^2 in VLD at 2 year after transplant. Flow PRA and Luminex solid phase assay revealed incidence of DSA production was 0% at 2 years in LD and 8.3% in VLD.
Conclusions: Tacrolimus exposure with TACER / MMF can be safely reduced to very low level with reduced CMV infection rate and without increased rejection rate and DSA production.

OS431 EVEROLIMUS SUPPRESSES IGA DEPOSITION AND RECURRENCE OF IGA NEPHROPATHY AFTER KIDNEY TRANSPLANTATION

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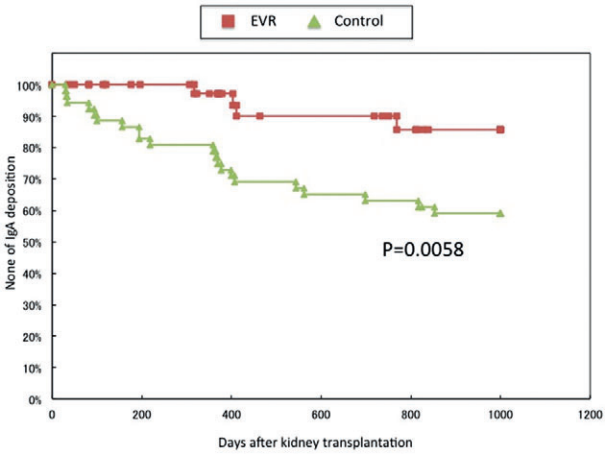
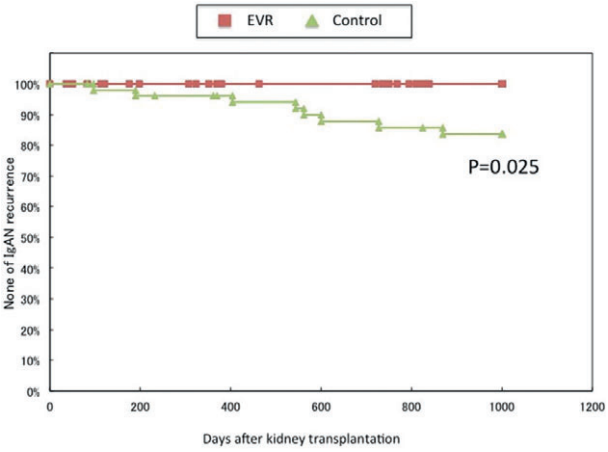
Background: Immunoglobulin A nephropathy (IgAN) is one of the most common primary glomerulonephritis and leads to end-stage renal disease in about 20 to 40% of the patients. Moreover, IgAN is very likely to recur in the renal graft after kidney transplantation (KT). Various immunosuppressants are now available in clinical practice, but the recurrence of IgAN after KT remains to be solved.
Methods: Out of 142 kidney recipients in our hospital who had originally IgAN, 97 consecutive patients since 2004 were surveyed. According to the immunosuppressive protocols, the patients were divided into two groups. One is Control Group (n = 52) consisting tacrolimus/mycophenolate mofetil/corticosteroid. The other is everolimus (EVR) Group (n = 45) in which EVR was added to the three agents from the initiation. EVR was started with a 1.5 mg/day for the loading dose and adjusted a dose according to the trough level aiming at the range 3 to 8 ng/ml. In the cases of ABO blood type incompatible and/or anti-donor specific antibody positive KT, we used rituximab and some sessions of plasmapheresis just before KT. We compared histological IgA deposition (IgAD) and IgAN recurrence by 1000 days after KT between the two groups. The pathological diagnosis was done with non-episodic protocol or episodic graft biopsy specimens.
Results: The patients' characteristics were almost comparable though preoperative tonsillectomy tended to be done much more in EVR group (p = 0.05). Interestingly, IgAD were fewer seen in EVR Group than in Control Group (p = 0.0058, Fig. 1).
Moreover, there was no IgAN recurrence in EVR group (p = 0.025, Fig. 2).





In EVR group, all kidney grafts are well functioning and patients are alive without any severe events.
Conclusion: EVR has great potential as a new preventive treatment option for IgAD and IgAN recurrence of kidney grafts. However, that would be a synergistic effect of preoperative tonsillectomy, so designed prospective randomized studies are required.

Clinical Others Immunosuppressive agents

OS432 SUCCESSFUL LIVE DONOR UTERUS TRANSPLANTATION: IMMUNOSUPPRESSIVE TREATMENT, REJECTIONS AND OUTCOME

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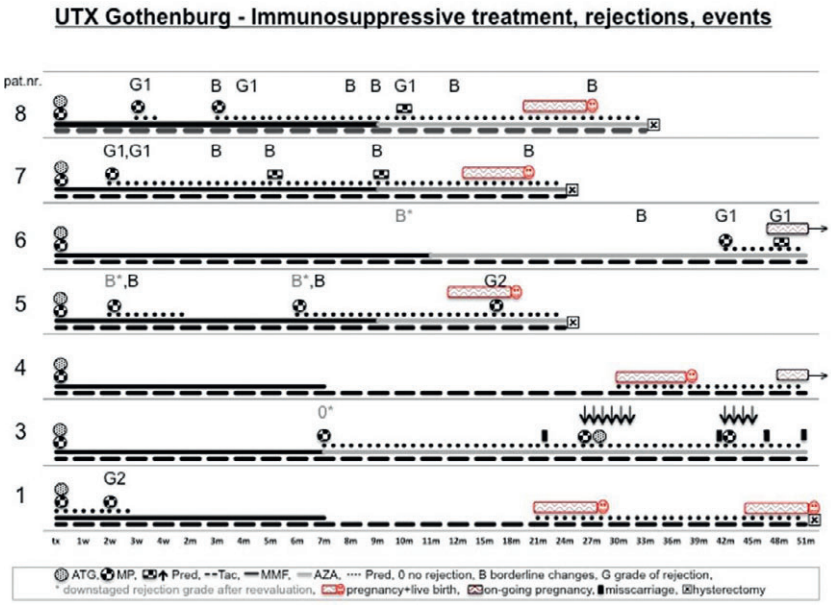
[1]Transplant Institute, Sahlgrenska Academy, University of Gothenburg, Sweden; [2]Department of Obstetrics and Gynecology, Sahlgrenska Academy, University of Gothenburg, Sweden; [3]Department of Pathology and Genetics. Sahlgrenska Academy, University of Gothenburg, Sweden

Uterus transplantation is the only possibility for women with absolute uterine factor infertility to give birth. Nine women underwent live donation uterus



transplantation in Gothenburg University Hospital. Seven transplantations were successful resulting in the birth of six healthy babies.

Two transplants were lost early (<3 months). Seven patients with successful grafts have been followed up to 5 years after transplantation. A multidisciplinary team conducted follow-up. The designed immunosuppressive treatment consisted of induction with anti thymocyte globulin (ATG) and Methylprednisolone (MP) and maintenance therapy based on tacrolimus (Tac) and, during the first 6 months, mycophenolate mofetil (MMF). Tac-monotherapy thereafter until in-vitro fertilizing was planned.

Early rejection (within one month) was diagnosed in three patients, all treated with a short course of steroids, in two cases steroids could be ceased when histology had normalized, one patient with only partial response was kept on prednisolon (Pred). Four patients experienced late rejection (>3 months), all treated with steroids; one patient was given ATG due to prolonged steroid-resistant rejection. Two late rejections occurred during pregnancy, both treated without any complications to the foetus. Only two patients were treated according to the predefined immunosuppressive protocol and, in their early pregnancy, a low dose Pred was added to Tac in order to minimize risk for rejection due to possible Tac trough level fluctuation. Remaining five patients received triple treatment (Tac + ASA + Pred).

Uterus transplantation is today a reality and 6 healthy babies have been born up to date. All rejections were treated successfully, however the total immunosuppression had to be increased in relation to the original protocol. In future we intend to use combination of Tac and Aza.

Clinical Lung Donation and donor types

OS433

CONTROLLED DONATION AFTER CIRCULATORY DEATH (DCD) LUNG DONORS: A PROVEN SOURCE THAT SIGNIFICANTLY INCREASES LUNG TRANSPLANT NUMBERS WITH QUALITY 10 YEAR OUTCOMES

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Background: In May 2006 our institution commenced using controlled (Cat III) DCD lungs for Lung transplantation (LTx). Detailed DCD lung donor referral processes, acceptance criteria and surgical techniques have been developed and refined over the 10 years. This paper reports on the 10 year outcomes of 150 DCD LTx from a single institution.

Methods: A retrospective analysis of all Bilateral LTx (BLTx) and Single LTx (SLTx) done between May 2006-Feb 2017 ($n = 696$) was undertaken to compare DCD and Donation after Brain Death (DBD) LTx cohorts. Recipient and donor demographics, short and long-term outcomes, including survival and causes of death were analysed. Of note, Ex-Vivo Lung Perfusion (EVLP) is not used at our institution.

Results: Of the 696 LTx done between May '06 and Feb 17, 150 were DCD LTx and 546 DBD LTx. Results comparing DCD vs. DBD are shown in the Table 1. DCD recipients had a significantly reduced median waiting times (101 vs. 120 dys, p = 0.03), longer cold GIT (323 vs. 283 mins, p < 0.01) and more received BLTx (97% vs. 90%, p < 0.01). Mean DCD LTx donor age was older (47 vs. 42 years, p < 0.01) DCD donors were more frequently male than DBD (64% vs. 51%, p < 0.01), distant donors (>300 km) were more common in the DBD cohort (35% vs. 20%, p < 0.01). Overall 1, 5 and 10 yr survival rates did not differ (DCD 96%, 69% & 53% vs. DBD 92%, 64% & 51%, p = ns) and causes of death were similar between both cohorts, with chronic rejection (CLAD) contributing 34% of DCD deaths vs. 45% DBD deaths (p = 0.26)

	VARIABLE	DCD ($n = 150$)	DBD ($n = 546$)	p Value
Recipient factors	Waiting time (med days)	101	120	0.03
	Age (mean years)	51.2	49.8	0.30
	Male gender (%)	57	51	0.23
	DIAGNOSIS (%)			p = 0.50
	COPD	46	41	
	CF/Bronchiectasis	21	25	
	ILD/ IPF	19	23	
	PAH	9	5	
	Re-LTx	4	6	
	LTx TYPE (%)			<0.01
	BLTx	97	90	
	SLTX	3	10	
	cold GIT (mean mins)	323	283	<0.01
	ICU Stay (med days, range)	5 (2–124)	4 (2–51)	0.22
	Hospital stay (med days, range)	21 (8–127)	20 (2–163)	0.10
Donor factors	Age (mean years)	45.6	41.6	0.01
	Male gender (%)	64	51	<0.01
	Distant donor retrieval (>300 km) (%)	20	35	0.01

Conclusions: Controlled DCD now contributes an additional 25–30% LTx annually and has significantly and safely increased LTx numbers, reduced waiting list time and mortality, whilst providing excellent long term LTx outcomes. These results prove that EVLP is not required to undertake successful controlled DCD LTx.

OS434 INFLUENCE OF LUNG DONOR MANAGEMENT ON LUNG PROCUREMENT: A NATIONWIDE COHORT STUDY

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Background: Lung management of organ donors after brain death (DBD) was shown to impact lung procurement and transplantation outcomes. This observational prospective study aimed to depict the current lung donor management in France and to evaluate its impact upon lung recovery.
Methods: All DBD aged 18–70 years. without lung donation contraindication with at least one organ recovered between 01/01/2016 and 30/12/2016 were included. Lung donor management was surveyed through a systematic questionnaire collecting information throughout intensive care, aside from the national database CRISTAL. Association between factors and organ recovery was tested using Chi-square or Student T-tests and multivariable logistic regression.
Results: At one year, 797 donors were included, 541 (68%) had one or both lungs proposed among whom 329 (61%) had one or both lungs recovered. Donor mean age was 51 years, 40% were female, 52% smokers, 55% died of stroke, and 17% had a history of lung disease. 98% of donors had a thoracic CT scan, 26% underwent bronchoscopy before brain death, in 82% the ventilator was disconnected during the apnea test, recruitment maneuvers were performed in 23% and physiotherapy in 6% of the cases. In 44% a closed circuit was used for tracheal suction. Overall 44% of included donors were under protective ventilation (positive end-expiratory pressure >5 cmH_2O and tidal volume<8 ml/kg of predicted body weight) at the time of qualification. After adjustment for donor age, sex, smoking status, blood group, protein blood level and scanner abnormalities, PaO2/FiO2 at qualification, recruitment maneuvers, respiratory rate and duration of mechanical ventilation were associated with lung procurement.
Conclusion: This ongoing study depicts a rather low adherence to the current good clinical practice for lung donor management. Further inclusions and analyses should indicate whether ventilatory pattern influences lung procurement.

Translational Lung Immunology

OS435 NORMOTHERMIC DONOR LUNG PRESERVATION WITH PORTABLE EVLP SIGNIFICANTLY REDUCES ISCHEMIA/REPERFUSION INJURY IN LUNG RECIPIENTS BY PROMOTING CYTOKINE ANTAGONISTS

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Objectives: The INSPIRE trial revealed significant reduction of PGD grade 3 using the Organ Care System (OCS) compared to the standard of care (SOC) for lung preservation. To investigate immunological mechanisms initiated by cold vs. normothermic preservation, blood and perfusate samples were assessed for proteins involved in immune and tissue responses. We hypothesized that OCS preservation supports an anti-inflammatory milieu.
Methods: Blood plasma and perfusion solutions from 33 patients with OCS and 26 patients with SOC-preserved lungs were analysed for 95 plasma proteins by multiplex assays. Donor, recipient demographics, cold ischemic times (CIT), PGD scores at T0, T24 were assessed and correlated with protein levels.
Results: Clinical evaluation (OCS/SOC) revealed mean recipient age of 50/49 years, diagnoses: idiopathic fibrosis (n = 17/10), cystic fibrosis (n = 7/8), idiopathic pulmonary hypertension (n = 3/3), emphysema (n = 6/5), mean total cold ischemic times (549 ± 22 / 258 ± 6 min $p < 0.0001$). In the OCS group, no cumulative PGD score >2 was observed compared to 19% PGD3 in SOC ($p = 0.035$). IL-6, CXCL8-10, CCL2, sICAM-1 plasma levels at T0 were significantly reduced in OCS patients ($p < 0.01$). Significantly higher levels of these factors were observed in OCS vs. SOC perfusates (all $p < 0.001$). IL-6 plasma levels at T0 in SOC recipients showed strongest correlation to CIT ($p = 0.031$), PaO2/FiO2 ratio ($p = 0.092$) and PGD score >2 at T0 ($p < 0.05$), T24 ($p < 0.05$). We show a new mechanism of IRI modulation during EVLP by induction of cytokine antagonists. IL-1RA was significantly higher in OCS vs. SOC perfusates. The Th2 cytokine IL-31 was highly correlated with IFN-g ($p = 0.001$) in OCS, but absent in SOC perfusates.
Conclusion: Recipients of OCS-preserved lungs show significantly reduced IRI by reduced levels of pro-inflammatory cytokines. The correlation of IL-6 with PGD score, PF and CIT in SOC but not OCS patients argues for a direct impact on inflammation by induction of natural antagonists.

Clinical Lung Surgical technique

OS436 COMPARISON OF OUTCOMES OF LUNG TRANSPLANTATION (LTX) WITH ELECTIVE CARDIO-PULMONARY BYPASS (CPB) VERSUS OFF PUMP TECHNIQUE

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Background: The opinion of surgical community about the benefits and adverse effects of cardiopulmonary bypass (CPB) in lung transplantation (LTx) is divided. This study compares outcomes after LTx utilizing different CPB strategies- elective CPB vs. off-pump vs. off-pump procedures with unplanned conversion to CPB.
Methods: Total 302 LTx performed over 7 years were divided into three groups: 'off-pump' group (n = 86), 'elective on-pump' group (n = 162) and 'conversion' group (n = 54). 1:1 propensity score matching was used to create a group of patients who were operated using elective CPB with risk profile similar to that of patients who were operated off-pump as well as emergently converted from off-pump to CPB intraoperatively.
Results: The 'conversion' group had significantly more number of patients with primary pulmonary hypertension, pulmonary fibrosis, preoperative mechanical ventilation and preoperative extracorporeal life support (ECLS). Postoperatively, patients from the 'conversion' group had significantly poorer PaO2/FiO2 ratios postoperatively, longer ventilation duration, ICU stay and higher requirement for ECLS compared to 'off-pump' and 'elective on-pump' groups. Overall cumulative survival at 1, 2 and 3 years was also significantly worse in patients from the 'conversion' group compared to 'off-pump' and 'elective on-pump' groups. The 'off-pump' group had significantly better PaO2/FiO2 ratio as well as significantly shorter ventilation duration, ICU and hospital length of stay compared to the propensity matched 'elective on-pump' group.
Conclusions: After segregation of unplanned CPB conversion cases from elective on-pump cases, better early post-operative outcomes and trend towards better early survival was observed with 'off-pump' strategy. There is a substantial proportion of high-risk patients requiring intraoperative conversion from off-pump to CPB and bears poor postoperative outcomes.

Clinical Lung Donation and donor types

OS437 TRANSPLANT OUTCOMES IN RECIPIENTS OF ORGANS FROM DONORS THAT DIED FROM PRIMARY HYPOXIA: THE UK EXPERIENCE

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Introduction: There is concern that use of organs from donors that die from hypoxia secondary to hanging, drowning, or carbon monoxide (CO) inhalation may be associated with inferior transplant outcomes, but there is a lack of good evidence to support or refute this view.
Methods: The UK Transplant Registry was used to identify organ donors who died from hypoxia as a result of hanging, drowning, or CO inhalation over a 13 year period up to 31/12/2015, and the transplant outcome of recipients of organs from such donors compared with those from all other types of deceased donor.
Results: Of 17 262 consented deceased donors over the study period, 546 (3.2%) died from hypoxia secondary to hanging, drowning or CO inhalation, of which 469 (85.9%) proceeded to organ donation. Compared to all other deceased donors, such donors were significantly younger (median age 33 years IQR (22–45) vs. median age 51 IQR (38–61), $p < 0.001$), and more likely to be male (64.6% vs. 53.3%, $p < 0.001$). They provided organs for 1296 transplants and unadjusted patient and graft survival (at 5–10 years) was significantly better for those who received a kidney or liver from a donor dying from hypoxia compared to those receiving organs from all other deceased donors ($p < 0.001$). Adjustment for donor age obviated this survival advantage for kidney transplant recipients (Hazard Ratio (HR) 0.915 (95% Confidence Interval (CI) 0.682–1.228, $p = 0.555$). One year unadjusted patient survival after lung transplantation was significantly worse for recipients of lungs from hypoxic donors, even after adjustment for donor age, recipient age, and smoking status (HR 1.784 (95% CI 1.134–2.805, $p = 0.0122$)
Conclusion: Donors who die following hanging, drowning or CO inhalation are a valuable source of organs for transplantation and give good transplant outcomes following kidney and liver transplantation, although they are associated with inferior outcomes following lung transplantation.

Clinical Heart Allocation

OS438

IMPACT OF CANDIDATE AND CENTER-SPECIFIC FACTORS ON GEOGRAPHIC INEQUITIES IN ACCESS TO HEART TRANSPLANTATION: A NATIONWIDE STUDY

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Context: Registration on the waiting list for heart transplantation represents the ultimate chance for patients with terminal heart failure. This study aimed to investigate the influence of candidate and center-specific factors on geographic inequities in access to heart transplantation.
Materials and methods: All adults ($n = 2437$) registered on the French waiting list between January 1, 2010 and December 31, 2014 were included. The association of candidate and transplant center ($n = 23$) characteristics with transplant rate 1-year after listing was assessed with survival mixed models.
Results: Within 1-year of listing, 1525 of 2437 candidates (65%) underwent transplantation.

Blood type O and A and sensitized candidates, together with patients with body mass index ≥30 kg/m² had significant lower access to transplantation, while females and candidates with severe heart failure (NYHA class IV symptoms, hospitalization at listing, need for inotropic infusion or temporary mechanical circulatory support, arrhythmias, high plasma natriuretic peptides levels) and high serum bilirubin levels had significant greater access to transplantation.

Center-specific factors associated with transplantation were heart procurement rate in the center geographic zone, proportion of high-urgency candidates in center and center graft discard rate.

Crude center effect was detected for 11 centers. After adjustment for candidates and center-specific factors, between-center variability decreased but remained significant with 3 centers with lower and 2 with higher access to transplantation.
Conclusion: Aside from candidate profile, the main center-specific factors associated to heart transplantation were heart local procurement rate and team medical policy (priority and refusal rates). Within a context of setting up the future French allocation system, further analysis of geographic disparities in access to heart transplantation in outlier centers should be carried to reduce these inequities.

Basic Lung Immunosuppressive agents

OS439

THE BENEFICIAL EFFECT OF PREDNISOLONE TREATMENT OF LUNGS FROM BRAIN-DEAD DONOR RATS ON AN EX VIVO LUNG PERFUSION (EVLP) PLATFORM

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Ex vivo lung perfusion (EVLP) is a clinically important tool to treat marginal donor lungs suffering from edema. Prednisolone is applied in donor management and thus routinely added to the perfusate during EVLP. Experimentally, prednisolone enables prolonged ex vivo perfusion of pre-injured lungs, but mechanism of action has not been described. This study investigates the effect of prednisolone in a newly established rat EVLP model.

Heart-lung blocks were procured from Lewis rats 3 h after acute brain death (BD) induction and cold preserved for 1 hour in Perfadex. Thereafter, normothermic EVLP was performed for 6 h. Tidal volume was set on 7 ml/kg body weight, PEEP on 5 cmH_2O, frequency 60/minute and FiO2 was set on 21%. The lungs were perfused with STEEN solution and cefuroxime on a maximal pulmonary arterial pressure of 12 mmHg. In the treatment group, 40 mg prednisolone was added to the perfusate. Ventilation parameters, lung oxygenation capacity and flow were recorded and perfusate was sampled over time. The lungs were macroscopically scored and analyzed for Wet/Dry ratio, qPCR and patho-histological changes.

Flow and lung oxygenation capacity were comparable between both groups. Positive Inspiratory Pressure (PIP) was significantly worse in untreated BD lungs (25.6 vs. 18.0 cmH_2O, at 6 h of reperfusion), possibly because of reduced pulmonary edema formation in the treated group (W/D ratio 6.2 vs. 5.5). Dynamic compliance of the treated BD donor lungs was significantly better (0.1 vs. 0.2 ml/cmH_2O, at 6 h of reperfusion).

Prednisolone reduced gene expression of cytokine IL-6. Levels of cytokines IL-1β (2.7 vs. 1.2) and MCP-1 (2.8 vs. 0.2) were decreased as well, suggesting that the effect of prednisolone is mainly focused on macrophages.

Prednisolone treatment of BD donor lungs on EVLP attenuates inflammation and stabilizes PIP by limiting pulmonary edema formation. Therefore, adding prednisolone to the perfusion solution in EVLP is clinically advisable.

Basic Heart Donation and donor types

OS440

EFFECTS OF HYPERTONIC SALINE SOLUTION ON CARDIAC AND PULMONARY CHANGES AFTER BRAIN DEATH: AN EXPERIMENTAL STUDY

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Background: Brain death (BD) induces hemodynamic instability with microcirculation hypoperfusion leading to increased heart and lung tissue inflammation and dysfunction. This study aimed to investigate the effects of 7.5% hypertonic saline (HS) on cardiac and pulmonary changes after BD.
Methods: BD was induced in male Wistar rats by rapid inflation of intracranial balloon catheter. Rats were divided in: NS, treated with normal saline (0.9% NaCl, 4 ml/Kg) immediately after BD; HS, treated with HS (7.5% NaCl, 4 ml/Kg) immediately or 60 min after BD (HS60). Left ventricle (LV) function (conductance microcatheter) and lung function were evaluated for 6 h. Thereafter, heart and lung were collected for histological analysis, and to investigate heart expression of vascular cell adhesion molecule (VCAM)-1, the anti-apoptotic (BCL-2) and pro-apoptotic (caspase3) proteins by immunohistochemistry.
Results: Relative to baseline values, preload recruitable stroke work and dp/dt (max) were reduced in NS rats, and preserved in HS and HS60 treated rats. LV ejection fraction was reduced in NS rats (41 ± 6%) compared to HS60 (72 ± 6%, $p < 0.001$). Lung expirated CO_2 decreased in NS rats (1.5 ± 0.2%) compared to HS (2.0 ± 0.2%, $p = 0.0221$). Migrated leukocytes into the lungs increased in NS rats (12.0 ± 0.7 cells/100 μm^2) compared to HS (8.0 ± 0.7 cells/100 μm^2, $p < 0.0001$) and HS60 (10.0 ± 0.7 cells/100 μm^2, $p = 0.0270$), without differences in heart tissue, as well edema and hemorrhage in the heart and lung. Heart VCAM-1 expression increased in NS rats compared to HS ($p = 0.0244$) and to HS60 ($p = 0.0078$), and expression of anti-apoptotic protein BCL-2 decreased in NS rats compared to HS ($p = 0.0083$) and HS60 ($p = 0.0042$).
Conclusions: Treatment of BD rats with hypertonic saline improves LV function, reduces VCAM-1, protects against apoptosis, and reduces lung damage.

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Clinical Pediatric transplantation Rejection

OS441

MEDICATION NON-ADHERENCE IS A LEADING CAUSE FOR RENAL GRAFT LOSS IN CHILDHOOD – A LARGE CENTRE STUDY

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Background: Despite continued advances in transplantation, it has been observed that the rate of renal graft failure is disproportionately high amongst the adolescent population. This study looked into why grafts fail in children.
Methods: Retrospective observational study in a single paediatric transplant centre between 2003 and 2016. All patients transplanted during study period and those transplanted previously and followed up during the study period were included.
Results: During the study period, 171 paediatric kidney transplants were performed. Median follow up was 8 years (IQR 10 years). Fifteen grafts failed before adulthood. Graft loss was caused by recurrent acute rejections following medication non-adherence in four patients (27%) and chronic antibody mediated rejection (CAMR) in five patients (33%). The mean age at time of transplant was 6.4 years and average age at the time of graft loss 15.7 years (range 2–17.9). Living and deceased donors were evenly distributed and well matched. HLA antibodies were detected in 70%. There was no statistically significant difference in graft longevity between the CAMR group and the medication non-adherence group ($p = 0.07$)

The medication non-adherence group were 12–17 years old at the time of graft failure. All were well matched (MM 110/111) with graft lifespan 21–120 months. All had DSA, multiple episodes of rejection (Banff 2b and 4a), with an average of five biopsy proven episodes each and low/undetectable CNI levels.

Conclusion: Medication non-adherence was a significant contributor to poor transplant outcomes in the adolescent population. We propose a multidisciplinary staged adherence pathway to improve graft outcomes for paediatric recipients. This encompasses early identification of vulnerable patients, enrolment into a hospital passport program overseen by play specialists, MDT meetings, adherence workshops and early psychology and psychiatry referral pathways for vulnerable patients.

Clinical Pediatric transplantation Other

OS442 10 YEAR EXPERIENCE OF 420 PAEDIATRIC KIDNEY TRANSPLANTS ACCORDING TO DONOR TYPE AND HLA MISMATCH

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Background: The aim of this study was to determine patient & renal allograft survival over the last decade in two large UK centres according to donor type & HLA mismatch (MM).
Methods: Data was retrieved from a prospectively collected database, electronic records and hospital notes. eGFR was calculated using the Schwartz formula. Graft survival was assessed according to donor type using Kaplan-Meier analysis.
Results: 420 children transplant between 2005–2015 were reviewed. 256 (107F, 158M) were from live donors (LD) and 155 (65F, 90M) were from deceased donors (DD). Median donor age was 41 (IQR 35–46) & 38 (IQR 25–45) years in the LD & DD respectively ($p < 0.001$). Median recipient age was 11 (IQR 4–14) & 12 (IQR 7–15) years in the LD & DD respectively ($p = 0.013$). Graft survival was 95.5% for LD & 83.2% for DD at median follow up of 2 (IQR 1–5) & 3 years (IQR 1–5) respectively ($p < 0.001$). The median eGFR from LD was 57 ml/min/1.73 m^2 (IQR 44–69.5) & from DD 49 ml/min/1.73 m^2 (IQR 39–64) [$p = 0.002$]. The odds ratio for graft failure or death for DD transplantation was 4.2 when compared to LD (95% CI 2.0764 to 8.6963, $p < 0.001$). One patient died from the LD group & two from the DD group at maximum follow up of 9 years. On comparing graft failure or death according to number of mismatches (0–6), there was a difference in the LD ($p = 0.015$) group but not in the DD group ($p = 0.845$). On comparing the same outcome according to HLA-A, B & DR mismatches (0–2) in LD vs. DD, results were significantly different for HLA-A and DR in the LD group only (Log Rank $p = 0.011$ & $p = 0.003$ respectively).
Conclusions: Outcomes following LD paediatric kidney transplantation are excellent whereas outcomes following DD are inferior in this cohort by a factor of four. MM did not seem to contribute to outcomes in DD. Patients with 2 MM at HLA-A & DR performed worse in LD. As the number of cases of full MM were small, larger studies.

Clinical Pediatric transplantation Allocation

OS443 DONOR/RECIPIENT WEIGHT RATE IN PEDIATRIC KIDNEY TRANSPLANTATION: BIGGER IS BETTER?

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Background: Recipient weight has been reported as an alloimmune-independent factor determining chronic allograft nephropathy. Hyperfiltration-mediated damage would explain the long-term graft impairment in case of small nephron mass in a large size recipient, but in pediatric kidney transplantation (KT) (and in particular in the living-donor (LD) transplantation) the opposite situation can occur. The aim of this study was to evaluate the influence of the Donor/Recipient Weight Rate (DRWR) on the short-term outcome of KT.
Methods: We retrospectively reviewed deceased and living-donor pediatric KT performed in our center during the period 2011–2016. We divided patients into four sub-groups, based on Recipient Weight (<20 kg or >20 kg) and on DRWR (<3 or >3); short-term complications were considered and compared in a log-rank test.
Results: 78 KT (19/78 LD) were performed: 33 patients <20 kg (8/33 LD; Gr. A) and 45 > 20 kg (11/45 LD; Gr. B). DRWR was >3 in 21/33 (63.6%; Gr.A1) and in 5/45 (11.1%; Gr.B1) patients respectively ($p = 0.008$). Early vascular complications occurred in 9 patients: 7 in Gr. A (6/7 required surgery; 4/6 Gr.A1) and 2 in Gr. B ($p = 0.02$). Continuous i.v. heparin infusion was used during the early post-op in 14 patients: 10 in Gr.A1. Three patients underwent early nephrectomy of the graft. One patient underwent delayed nephrectomy at 3 months due to recurrence of disease; three patients presented a progressive functional impairment at 1 year.
Conclusion: In our experience, DRWR has determined a higher risk of early complications: this is more evident in the group of "smaller" children (<20 kg). Moreover, difficulties in the closure of the abdominal wall and ipsilateral inferior limb swelling in the post-op have been reported more frequently in these patients. The use of continuous i.v. heparin infusion in the post-op period can reduce the vascular complications in selected cases.

Clinical Pediatric transplantation Surgical technique

OS444 CLINICAL USE OF 3 D PRINTING IN COMPLEX PEDIATRIC RENAL TRANSPLANTATION – A PHASE 2A STUDY OF THE IDEAL FRAMEWORK

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Introduction: Anatomical complexities can render implantation infeasible in small paediatric renal recipients. Surgical decision-making currently relies on 3D medical imaging by presentation on 2D screens. As a solution, we assessed the use of 3D printing based on the IDEAL stages of surgical innovation development. We assessed utility by questionnaire (1 = not useful to 5 = very useful).
Methods: We describe 4 patients requiring kidney transplantation:

6 years F (18 kg) with blocked IVC and replaced aorta with jump PTFE graft for aneurysmal disease
2 years M (12 kg) IMA aneurysm.
2 years F (10 kg) with previous laparotomies (bowel ischaemia).
14 kg F, high aortic bifurcation & twisting of CIA's.

All live donors and recipient anatomy was segmented from MR/CT imaging using Mimic Medical v.18 software and printed by an Objet500 Connex1 polyjet printer. The first case served as proof of concept for the subsequent cases. This included a geometrical validation of the printer performance. All cases underwent successful transplants.
Results: Case 1: 5 surgeons independently scored 5 for value in using models for planning.
Case 2: surgeon pre-operatively confirmed the model provided reassurance (score 5). Intraoperative geometric anatomical correlation of the hilar vessels between the model and the patient scored 5.
Case 3: surgeon score = 5 for planning & intraoperative correlation of vessel anatomy/ placement of kidney = 4. The family = 5 for improving procedural understanding with models.
Case 4: surgeon = 5 for usefulness and helped convert surgical feasibility of implantation from 50% to 100% at our multidisciplinary meeting after the 3D models were inspected.
Bland-Altman analysis found the printed model underestimated the original imaging data diameter only by −0.1 mm (95% CI: −0.7 to 0.5 mm).
Conclusion: Our experience using 3D printing (world first) in paediatric transplantation is promising – with progression from proof of concept to safe clinical translation with haptic interaction.

Clinical Kidney Donation and donor types

OS445

PRE-EMPTIVE RENAL TRANSPLANTATION VERSUS TRANSPLANTATION AFTER A PERIOD ON DIALYSIS IN PAEDIATRICS: A META-ANALYSIS OF OUTCOMES

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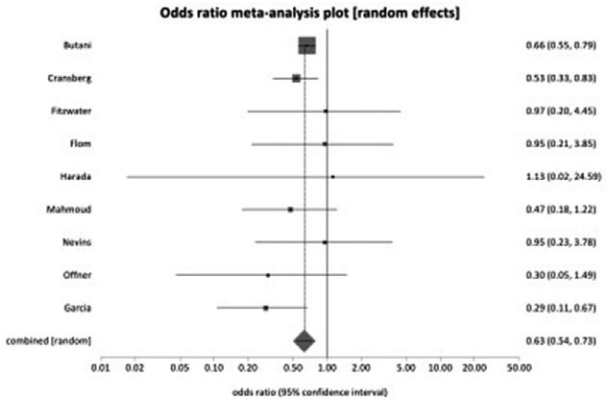
Background: The benefits of pre-emptive renal transplantation (PKT) as compared with transplantation after a period of dialysis (non-PKT) are well reported in adults but less clear in children.
Methods: A comprehensive search was performed of 6 databases including Embase, Medline, Web-of-science, Cochrane, Pubmed publisher and Google Scholar. All studies including the terms pre-emptive renal transplantation were screened. The methodology was in accordance with the Cochrane Handbook of Systematic Reviews of Intervention and written based on the PRISMA statement.
Results: The initial search yielded 3528 results; 222 were selected for examination of the full text; 17 studies were identified as paediatric and data extraction attempted; 11 yielded outcomes that were used for the meta-analysis. In total the analysis included 7278 patients of which 1851 (25%) received PKT. On comparing PKT with non-PKT using a random effects model, there was no difference in patient survival (OR 1.011; 95% CI 0.603–1.695; $p = 0.9665$) at a median follow-up of 5 years (range 1–10 years). There was significantly less graft loss at 5 years (range 3–10 years) (OR 0.63; 95% CI 0.54–0.73; $p < 0.0001$), and acute rejection (OR 0.7; 95% CI 0.6–0.81; $p < 0.0001$) in PKT as compared with non-PKT.



Conclusions: PKT appears superior to non-PKT in terms of renal allograft survival and acute rejection, but not patient survival. Whilst we accept that there is a higher proportion of live donors in the PKT group and that the review included low level evidence with heterogeneity between studies, steps should be taken to prevent the need for dialysis before transplantation in children with ESRD. This means earlier referral for transplantation to allow more time for identification and screening of live donors and transplantation earlier in the course of disease.

Clinical Liver Surgical technique

OS446

LIVING DONOR LIVER TRANSPLANTATION DURING THE FIRST THREE MONTHS OF LIFE: CARVING THE LIVER FOR SMALL BABIES

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Background:
Living donor liver transplantation is now an established technique for treating children with end-stage liver disease. Few data exist about liver transplantation for exclusively young infants, especially infants of <3 months of age. We report our single-center experience with 12 cases in which living donor liver transplantation (LT) was performed during the first 3 months of life and compare the results with those of older infants who underwent LT. All of the patients were treated at the National Center of Child Health and Development, Tokyo, Japan.
Patients and methods: Between November 2005 to November 2016, 436 children underwent LT. Twelve of these patients underwent LT in the first 3 months of life (median age, 41 days; median weight, 4.0 kg). The indications for transplantation were fulminant hepatic failure ($n = 11$) and metabolic liver disease ($n = 1$). We compared the results with those of infants who were 4–6 months of age ($n = 67$) and 7–12 months of age ($n = 110$) who were treated in the same study period.
Results: There were significant differences in the PELD score and the conversion rate of tacrolimus to cyclosporine in younger infants. Furthermore, the incidence of biliary complications, blood stream infection, and CMV infection tended to be higher, while the incidence of acute cellular rejection tended to be lower in younger infants. The overall cumulative 10-year patient and graft survival rates in recipients of <3 months of age were both 90.9%.
Conclusion: Living donor liver transplantation during the first three months of life appears to be a feasible option with excellent patient and graft survival.

Clinical Pediatric transplantation Surgical technique

OS447

WHOLE DECEASED DONOR LIVER TRANSPLANTATION IN PEDIATRIC RECIPIENTS LESS THAN 10 KG: RETROSPECTIVE ANALYSIS OF OUTCOME AND SURGICAL COMPLICATIONS

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Background: Whole deceased donor liver transplantation (DDLT) in small pediatric recipients (defined as children < 10 Kg) is mostly limited by unavailability of suitable graft, technical challenges and questionable function of a young graft. Actually less than 35% of patients younger than 1 year of age receive a whole-DDLT. 2-years patient and graft survival are reported about 90% and 80% respectively. Overall morbidity is approximately 45%. Vascular and biliary complication have been observed in up to 25% and 7.5% respectively. A donor-to-recipient weight ratio (DRWR) < 1.5 is considered as risk for complications. Aim of the study is to determine the outcomes after whole-DDLT in small pediatric recipients.
Methods: We retrospectively analysed all pediatric whole-DDLT between 2005 and 2016 at our centre and evaluated the patient and graft survival and the surgical complications in small children with a weight less than 10 kg.
Results: From 2005 to 2016, 111 LT in 109 children between 0 and 18 years of age were performed at the University Hospital Tübingen. 35 children received a whole-DDLT. 12 of them (35%) weighed less than 10 kg (median weight 6.1 kg (3.5–8.3) at a median age of 10 months (10 days-24 months)). The donors' median weight was 6.75 kg (4–16 kg) and median age 6 months (1–36 months). The median DRWR was 1.2 (0.6–4). The indications of LT were cholestatic disorders in 9 patients, three infants were diagnosed with metabolic liver diseases. No one needed a delayed closure or a patch. Primary function rate was 100%. 3 patients (25%) experienced biliary complications (two late strictures and one early leak) and one patient kinking of the hepatic artery. All of them were reoperated. After a median FUP of 4 years (7–84 months) graft survival is 100%. Overall patient survivals were 100% and 92% at 2 and 5 years, as one patient died at POM 34 because of HSV sepsis.
Conclusion: Excellent results can be achieved in whole-DDLT in small recipients despite a DRWR < 1.5.

Clinical Pediatric transplantation Other

OS448

ANALYSIS OF PROGNOSTIC FACTORS OF PEDIATRIC LIVING DONOR LIVER TRANSPLANTATION: A SINGLE CENTER EXPERIENCE OF MORTALITY ZERO TRANSPLANTATION FOR CHOLESTATIC DISEASE

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Background: Living donor liver transplantation (LDLT) has been recognized as the final therapeutic arm of acute or chronic pediatric liver diseases. The aim of the study is clarification of factors affecting on the survival of the recipient in order to find measure to further improvement of survival.
Methods: From August 1997 to December 2015, Consecutive 60 pediatric cases who underwent LDLT and had over a year of observation period were

evaluated retrospectively. Various data during perioperative phase of liver transplantation were analyzed.
Results: In univariate analysis, non-cholestatic (NCS) disease, graft/recipient body weight ratio (<0.005), cold /warm ischemic time ($p < 0.005/0.02$) and intraoperative blood loss ($p < 0.03$) were found as significant deteriorating factors of survival. But in multivariate analysis, NCS disease was left as the only individual significant worsening factor of survival ($p = 0.0021$). One-, 3- and 5-year survival of the cholestatic ($n = 43$, CS) and NCS ($n = 17$) group were 100 vs. 70.6, 97.4 vs. 58.8 and 97.4 vs. 58.8%, respectively ($p = 0.004$, Log rank). Two groups study between CS and NCS revealed that CS significantly affected on longer op time ($p < 0.04$) and cold ischemia ($p < 0.05$), hepatomegaly of the native liver ($p < 0.05$) and portal plasty ($p < 0.02$). These data suggested that cirrhotic swollen and artery-dominant liver reduced size-originating survival risks such as large for size or anastomosis of small hepatic arteries despite surgical complexity by preceding repeated operations. Poorer survival of NCS group including acute failure supposed to be originated from recurrence of the primary disease and pretending liver manifestation of systemic disease untreatable with LT.
Conclusion: Pediatric CS disease is very suitable for LDLT therapy with excellent prognosis. Improvement of survival of pediatric recipients requires intensive prolapse prevention of primary disease and rapider diagnosis for exclusion of hidden systemic disease.

LOS001 THE TRANSFORM STUDY: 12-MONTH EFFICACY AND SAFETY OF EVEROLIMUS WITH REDUCED CALCINEURIN INHIBITOR IN DE NOVO KIDNEY TRANSPLANT RECIPIENTS

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Background: mTOR inhibitors have potential to improve long-term outcomes in kidney transplant recipients (KTxR) by reducing malignancy and calcineurin inhibitor (CNI)-nephrotoxicity. TRANSFORM (NCT01950819) prospectively compared everolimus+reduced CNI (EVR+rCNI; tacrolimus [TAC]/cyclosporine [CsA]) to mycophenolic acid (MPA)+standard(s) CNI in *de novo* KTxR using a composite endpoint of anti-rejection efficacy and renal function.
Methods: TRANSFORM is a 24-month (M), randomised, multicentre, open-label, non-inferiority study; 2037 KTxR received either EVR+rCNI ($n = 1022$; TAC C0: 4–7, 2–5, 2–4 ng/ml and CsA C0: 100–150, 50–100, 25–50 ng/ml) or MPA+sCNI ($N = 1015$; TAC C0: 8–12, 6–10, 5–8 ng/ml and CsA C0: 200–300, 150–200, 100–200 ng/ml, from Day1-M2, M3-M6, and M7-M24, respectively), with basiliximab/ATG induction+steroids. The primary and key secondary objectives were composite of treated biopsy-proven acute rejection (tBPAR) or estimated glomerular filtration rate (eGFR) <50 ml/min/1.73 m^2 and composite efficacy failure of tBPAR, graft loss (GL), or death at M12, respectively. Safety was also evaluated.
Results: Overall, 76.5% KTxR (EVR+rCNI, 72.1%; MPA+sCNI, 81.0%) completed the study treatment up to M12. EVR+rCNI was non-inferior (10% margin) to MPA+sCNI for the primary endpoint (difference [95% CI]: 3.2 [−1.3, 7.6]). tBPAR and GL were comparable between arms (Table). Mean eGFR over M12 was similar in both arms. Safety was comparable. Mortality was numerically lower for EVR+rCNI vs. MPA+sCNI. Study drug discontinuation due to adverse events was higher for EVR+rCNI (23.0%) vs. MPA+sCNI (11.9%). Viral infections were lower in EVR+rCNI (17.2%) vs. MPA+sCNI (29.2%).
Conclusion: TRANSFORM shows that *de novo* EVR+rCNI provides comparable anti-rejection efficacy and renal function to MPA+sCNI at M12. Graft survival and graft function, a surrogate for long-term outcomes, would be examined during the follow-up.

LOS002 THE TRANSFORM STUDY: LOWER VIRAL INFECTIONS WITH EVEROLIMUS AND REDUCED CALCINEURIN INHIBITOR VERSUS MYCOPHENOLATE AND STANDARD CALCINEURIN INHIBITOR IN DE NOVO KIDNEY TRANSPLANT PATIENTS AT MONTH 12

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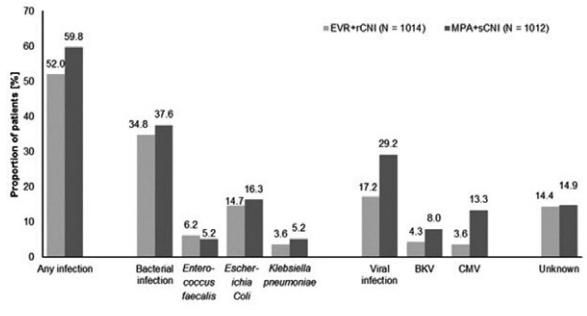
Background: Infections, especially those caused by cytomegalovirus (CMV) and BK virus (BKV), remain a common cause of morbidity and mortality post kidney transplantation (KTx). Everolimus (EVR)-based regimens have shown a significant reduction of viraemia and incidence of CMV infections in *de novo* kidney recipients (KTxRs). Here, we present the incidence of infectious complications in *de novo* KTxRs receiving EVR plus reduced calcineurin inhibitor (rCNI) versus mycophenolic acid (MPA) plus standard CNI (sCNI) at 12 months.
Methods: TRANSFORM (NCT01950819) is a 24-month, multicentre, open-label, two-arm study, randomising *de novo* KTxRs 1:1 to receive EVR+rCNI ($N = 1022$) or MPA+sCNI ($N = 1015$), with induction and steroids within 24 h

Figure: Infections with incidence ≥5% - safety analysis set 12 month analysis



Patient with multiple AEs/infections within an infection type/preferred term is counted only once BKV, BK virus; CMV, cytomegalovirus; EVR, everolimus; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor

Table. Primary and secondary efficacy endpoints at M12 (full analysis set)

	EVR+rCNI (N=1022)	MPA+sCNI (N=1015)	Difference (95% CI)
Primary efficacy endpoint, n (%)			
eGFR <50 mL/min/1.73 m^2 or tBPAR	493 (48.2)	457 (45.1)	3.2 (−1.3, 7.6)
Key secondary efficacy endpoint, n (KM %)			
tBPAR, graft loss, or death	137 (15.1)	122 (12.6)	2.5 (−1.8, 6.7)
Other secondary efficacy endpoints, n (KM %)			
tBPAR	100 (11.6)	83 (8.9)	2.8 (−1.3, 6.9)
Graft loss	32 (3.2)	25 (2.6)	0.6 (−0.9, 2.1)
Death*	16 (1.6)	27 (2.8)	−1.2 (−2.5, 0.1)

*In safety set, deaths were reported as EVR+rCNI, n=16 and MPA+sCNI, n=26
CI, confidence interval; eGFR, estimated glomerular filtration rate; EVR, everolimus; KM, Kaplan-Meier; M, month; MPA, mycophenolic acid; rCNI, reduced calcineurin inhibitor; sCNI, standard calcineurin inhibitor; tBPAR, treated biopsy-proven acute rejection

post-Tx. Pre-emptive CMV therapy and/or prophylaxis therapy for at least 6 months post-Tx was recommended for all donor-positive/recipient-negative and for all CMV-positive recipients. Incidence of CMV and BKV infections reported as adverse event (AE) were summarised by treatment.
Results: Overall, 72.1% of patients in the EVR+rCNI and 81.0% of patients in the MPA+sCNI arms completed the study medication. Incidence of AEs/infections (97.9% vs. 97.2%) and serious AEs/infection (54.9% vs. 56.1%) were comparable between EVR+rCNI and MPA+sCNI arms. Incidence of overall infections (52.0% vs. 59.8%), viral infections (17.2% vs. 29.2%), CMV (3.6% vs. 13.3%) and BKV (4.3% vs. 8.0%) infection were lower with EVR+rCNI versus MPA+sCNI, respectively (Figure).
Conclusions: TRANSFORM, the largest study in *de novo* KTxRs, showed lower incidence of all types of viral infections, including CMV and BKV infection in EVR+rCNI versus MPA+sCNI, confirming the antiviral benefits of EVR when introduced early. Further analyses of the level of viraemia and severity of CMV disease may provide additional evidence on the protective effect of the EVR+rCNI regimen.

LOS003 EVEROLIMUS-BASED VS. TACROLIMUS-MPA REGIMEN IN DE NOVO KIDNEY TRANSPLANT RECIPIENTS: 12 MONTHS SAFETY AND EFFICACY DATA FROM ATHENA STUDY

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Background: The ATHENA study was set up to compare everolimus [EVR] combined with tacrolimus [TAC] or cyclosporine A [CyA] vs. mycophenolic acid [MPA] combined with TAC in de novo kidney transplant [KTx] recipients.
Methods: In this 12 months [M] prospective, open-label, multi-center study 612 patients [pts] were randomized 1:1:1 at time of Tx to either EVR (3–8 ng/ml M1-M12) + TAC (4–8 ng/ml M1-M3; 3–5 ng/ml M3-M12), or EVR (3–8 ng/ml M1-M12) + CyA (75–125 ng/ml M1-M3; 50–100 ng/ml M3-M12) or TAC (4–8 ng/ml M1-M3; 3–5 ng/ml M3-M12) + MPA, all with steroids. Here we report M12 efficacy and safety (208 EVR+TAC, 199 EVR+CyA, 205 TAC+MPA pts).
Results: M12 Kaplan Meier estimates for treated BPAR were 6.7% in EVR+TAC, 17.6% in EVR+CyA and 3.9% in TAC+MPA group, with most events graded BANFF IA (1.9%; 9%; 1.5%) and only few (1.5%, 2% vs. 0.5%) BANFF IIB/III. 5 pts in EVR+TAC, 5 in EVR+CyA and 6 in TAC+MPA died. Few graft losses occured: 10 pts (4.8%) in EVR+TAC, 13 (6.5%) in EVR+CyA, 6 (2.9%) in TAC+MPA arm, including 5 primary non-functioning grafts in each EVR-group and 1 in TAC+MPA arm. Safety profiles were comparable, incidences of AEs/infections leading to study drug discontinuation or dose adjustment/interruption were 56.7% in EVR+TAC, 55.5% in EVR+CyA vs. 61.3% in TAC+MPA arm. Main reasons for changes were infections (7.1%EVR+TAC, 4.5%EVR+CyA, 23.5%TAC control) and lympho-/leucopenia (3.3%, 3.5%, 13.2%). No differences in AEs on wound complications were seen (sum-incidences: 41.9% EVR+TAC, 38.9% EVR+CyA, 43.2% TAC+MPA).
Conclusion: ATHENA as largest European KTx study confirmed good efficacy and event rates within international standards for all 3 groups with no unexpected safety events for this patient population. There were no differences in reported AEs on wound healing and less leucopenia with EVR-based regimens.

LOS004 EVEROLIMUS ALLOWS A SIGNIFICANT AND SAFE REDUCTION OF TACROLIMUS EXPOSURE IN THE DE NOVO LIVER TRANSPLANTATION RECIPIENTS AND IMPROVES KIDNEY FUNCTION: 52 WEEKS DATA FROM REDUCE STUDY

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Background: A key objective to optimize long-term results in liver transplantation (LT), is the development of non-nephrotoxic immunosuppressive strategies preventing acute rejection (AR) and reducing CNI doses.
Methods: This multicenter, open-label, controlled, exploratory 52 Weeks study, enrolled 291 adult patients receiving a first LT who were treated with TAC and MMF for 4 weeks and then randomized to a combination of TAC (≤5 ng/ml) and EVR (EG) or to continue with MMF and TAC (6–10 ng/ml, control group, CG). Kidney function was evaluated by eGFR and by clinical benefit defined as a post-LT improvement in 1 or 2 ranges of eGFR at Week 52 in patients with eGFR values of 30–44 or 45–59 ml/min/1.73 m^2, or stabilization in patients with eGFR values >60 ml/min/1.73 m^2 at randomization. Clinical and epidemiological data, AR, patient survival, and incidence of adverse events (AE) were assessed.
Results: The ITT population comprised 211 patients (105 and 106 in the EG and CG) Although mean eGFR was lower in the EG at randomization (82.2 ± 28.5 EVR vs. 88.4 ± 34.3 ml/min/1.73 m^2), it increased to 86.1 ± 27.9 in the EG and decreased to 83.2 ml/min/1.73 m^2 in the CG at Week 52, with significant mean eGFR changes along the study. The percentage of patients achieving clinical benefit was similar between both groups (81.9 EVR vs. 83.9%, p = 0.6912). The EG presented a 30% and 41% reduction in TAC exposure at weeks 6 and 52, respectively, compared to the CG. Incidence of clinically suspected AR (17.1% EVR vs. 15.1%), and patient survival (94% vs. 97%) were similar in both groups. Similar percentage of patients experienced AEs. Proteinuria and dyslipidemia were more common in EG.
Conclusions: Combination of EVR with low TAC levels allows a significant and safe CNI reduction in comparison with the combination MMF and TAC in the *de novo* LT patients during the first year. This reduction is associated with a significant, though clinically moderate, improvement in the mean eGFR change.

LOS005 LIVER TRANSPLANTATION THROUGH THE PRISM OF DECISION TREE ANALYSIS: UNBIASED DEFINITION OF PATIENTS AT RISK OF SHORT-TERM MORTALITY RISK

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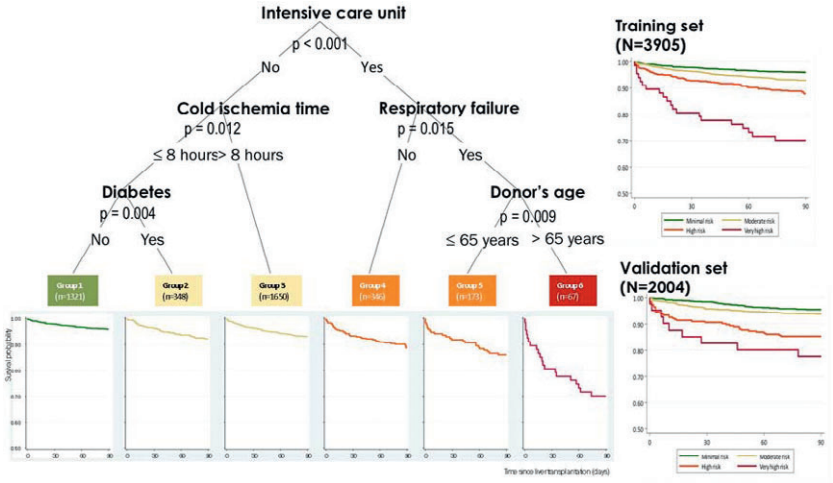
The results of liver transplantation (LT) are steady since years. The combination of candidate's and donor's variables should permit to define subgroups of recipients with poor or good prognosis after LT. In the setting of organ shortage, this should improve the results of LT. In a nationwide LT cohort, we applied decision tree-based approaches in order to reveal subgroups of patients with poor short-term outcome after LT.
Patients and methods: All adult patients with a chronic liver disease, transplanted between 2009–2015 in France and receiving a first non-combined liver graft were included. Study population was split into a training set (2009–2013; $N = 3905$) for model fitting and a test set (2014–2015; $N = 2004$) for temporal validation. Based on around 100 recipients' and 50 donors' features, prognostic models were built using Cox proportional hazards modeling and decision tree-based models (single trees or random forests). The 90 days survival was the end-point.
Results: The multivariate Cox model identified five independent predictors: recipient hospitalized in intensive care unit (ICU), acute renal failure, respiratory failure at the time of LT, donation after stroke and cold ischemia time. In contrast, decision tree analysis revealed more complex associations (Figure), with a 90-day mortality >20% in recipients with respiratory assistance whose donor's age >65 years, and a 90-day mortality >10% in recipients with respiratory assistance whose donor's age <65 years and recipients in ICU without respiratory assistance. The best survival was found in hospitalized in ICU at the time of LT, with a cold ischemia time less than 8 h and without diabetes. These findings were confirmed by random forests approaches and in the test population (C-index: 63.4%)
Conclusion: While conventional Cox model identified variables which had an average effect in the whole population, decision-tree analysis allowed detecting more specific unfavorable subgroups of recipients.



LOS006 RESCUE ALLOCATION IN THE FRENCH NATIONWIDE LIVER GRAFT COHORT: NO REASON TO REJECT UNWANTED LIVER GRAFTS

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Background: The shortage of Liver donor which has progressively led to the use of graft from donors with extended criteria. In France, each graft is proposed to a candidate with the maximal score. When the graft is refused by up to 5 teams, the graft is attributed to a transplant team which in turn chooses among their candidates the most suitable. This rescue allocation (RA) raises a practical issue : should we use liver graft repeatedly unwanted by our colleagues?
Patients and methods: 5025 adults who received a liver graft from 2009 to 2013 in France were included. Among them, 282 received a RA liver. Recipients and donors covariates were compared. An exploratory analysis was performed. We matched 1 :1 RA with « regular allocated » recipients on age, sex, indication and MELD. We performed 200 matching and the corresponding Cox models adjusted on donor and recipient covariates.
Results: Among the 5025 recipients, 282 (5.6%) received a RA graft. Of note, 3 teams performed more than 20 RA, 3 did not performed any RA, 5 teams performed between 10–20 RA and 15 teams transplanted less than 10 RA. Donor of RA liver graft were older ($p < 0.01$) and had an higher BMI ($p < 0.01$). Recipients of RA graft were older ($p < 0.01$), transplanted more frequently for HCC ($p < 0.01$) and had more frequently compensated cirrhosis ($p < 0.01$). Cox models after adjustment with donor covariates (age, gender, BMI, cause of death, ICU stay, cold ischemic time, liver type) and
recipient variables (BMI, decompensated cirrhosis, non-cirrhotic indication, status at LT
Conclusion: This is the largest study on RA. Liver grafts unwanted by at least 5 teams gave results comparable to regular allocated graft. Most RA are used by only few centers RA and were allocated to recipients in good conditions. The macroscopic aspect of the liver graft should have been correct to be given and this may be determinant to explain the overall good results of results of RA grafts.

LOS007 CAN ROTEM PARAMETERS BE USED IN THE EARLY PREDICTION OF INITIAL GRAFT POOR FUNCTION AFTER LIVER TRANSPLANTATION?

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Introduction: Initial graft poor function (IGPF) represents one of the most common early graft complications after liver transplantation. The aim of our study was to investigate if standard and derived ROTEM parameters can be used in the early identification of patients that will develop IGPF after liver transplantation (LT).
Methods: One hundred and seventy six consecutive patients that underwent LT were included. Demographic data, intraoperative blood loss and transfusion were recorded. The patients were divided into two groups: IGPF group ($n = 59$) and non-IGPF group ($n = 117$). IGPF was diagnosed using the criteria published by Nanashima et al. Liver functional tests and standard coagulation tests were recorded daily for the first 4 postoperative days. ROTEM assay (ExTEM, InTEM, ApTEM, FibTEM) was performed 24 h after LT. ROTEM parameters included: standard parameters (clotting time-CT, clot formation time-CFT, maximum clot firmness-MCF) and derived (thrombin potential index-TPI, maximum velocity of clot formation-MaxV, time to MaxV-MaxVt, area under the curve-AUC and maximum clot elasticity-MCE).
Results: The mean age was 50.2 ± 12.5 years. The mean MELD score was. 19.25 ± 6.37. There was no difference in blood loss between groups ($p = 0.63$), but patients in the IGPF group had a larger transfusion of packed red blood cells (6.7 ± 1.0 units vs. 4.5 ± 1.2units, $p = 0.00$) and fresh frozen plasma (12.1 ± 10.8 units vs. 7.9 ± 5.4 units). Patients who developed IGPF had an increased CT ($p = 0.01$) and CFT ($p = 0.00$) in EXTEM and an increased CT ($p = 0.03$) and CFT ($p = 0.02$) in InTEM. Also, patients in the IGPF group had an increased MaxVt ($p = 0.024$) and decreased AUC ($p = 0.04$).
Conclusion: Patients who eventually developed IGPF had a decrease in clot formation time and a decrease in clot formation kinetics. Our results may help in early identification of patients that will develop IGPF.

LOS008 CLINICAL PANCREAS TRANSPLANTATION FROM DECEASED DONOR IN JAPAN – REPORT FROM JAPANESE PANCREAS TRANSPLANTATION REGISTRY

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Objective: Pancreas transplantation (PTX) has been performed from 2000 in Japan. In this paper, we analyzed the national data of PTX from deceased donor and examined the factors which influenced pancreas graft survival.
Method: 311 PTX [281 DBD, 3 DCD, 27 LD] were performed from 2000 to 2016 in Japan. 166 donors (58%) were over 40 years old. The Cause of death was cerebrovascular diseases in 147 donors (52%). 214 donors (75%) were marginal donors. Categories of PTX were SPK; 232 (82%), PAK; 37 (13%) and PTA; 15 (5%). The mean duration of insulin therapy and hemodialysis of the recipients were 28.0 and 7.1 years. Mean waiting period was 1305 days. Almost all the patients underwent the induction therapy using @IL–2R or ATG and the maintenance immunosuppressive therapy using tacrolimus combined with MMF and steroid.
Results: 5-year recipient survival was 95.2%. Pancreas graft survivals were 86.5% at 1-year, 81.1% at 3-year and 75.3% at 5-year. While, kidney graft survivals were 94.2% at 1- and 3-year and 90.8% at 5-year, respectively. According to the multivariate analysis, diabetic history of the recipient (>40 years, RR: 3.41, $p = 0.007$), category of PTx (PAK/PTA, RR: 3.51, $p < 0.0001$) and episode of perioperative rejection (RR: 2.56, $p = 0.003$) were significant risks which influenced pancreas graft survival. 5-year pancreas graft survivals of SPK, PAK and PTA were 82.8%, 48.8% and 29.6%, respectively. Graft survivals of PAK/PTA were significantly lower than that of SPK ($p < 0.0001$). The frequency of venous thrombosis which caused early graft failure was equal between SPK (5%) and PAK/PTA recipients (6%). In 14 of 52 PAK and PTA recipients (27%), rejection was the cause of graft failure. In contrast, only six of 232 SPK recipients (3%) developed rejection which resulted ing raft failure.
Conclusions: Although majority of the deceased donors were marginal in Japan, clinical outcome demonstrated that pancreas transplantation was a promising treatment for severe type 1 diabetic patients.

LOS009 SIGNIFICANTLY LESS CMV- AND BKV-EVENTS WITH EVEROLIMUS-BASED VS. TACROLIMUS-MPA REGIMEN IN DE NOVO RENAL TRANSPLANT RECIPIENTS: 12 MONTHS DATA ON INFECTIONS FROM ATHENA STUDY

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Background: The ATHENA trial was designed to compare everolimus [EVR] in combination with tacrolimus [TAC] or cyclosporine A [CyA] vs. a standard of mycophenolic acid [MPA] and TAC in de novo kidney transplant [KTx] recipients.
Methods: In this 12 months [M], prospective, open-label, randomized study with 15 German and 12 French sites, 612 patients [pts] were randomized 1:1:1 at time of Tx to either EVR (C0 target: 3–8 ng/ml M1-M12) +TAC (C0 target levels: 4–8 ng/ml M1-M3; 3–5 ng/ml M3-M12), or EVR (3–8 ng/ml M1-M12) + CyA (C0 target: 75–125 ng/ml M1-M3; 50–100 ng/ml M3-M12) or to control TAC regimen (4–8 ng/ml M1-M3; 3–5 ng/ml M3-M12) with MPA. All pts continued on steroids. Herein we report M12 outcomes on infections and CMV-/ BKV-events from ITT with 208 EVR+TAC pts, 199 EVR+CyA pts and 205 TAC+MPA pts.
Results: From randomization to M12 total incidences of infections were 73% in EVR+TAC and 72% in EVR+CyA treated pts vs. 82% in TAC+MPA pts. Whilst incidences of bacterial infections were similar between the three treatment groups (44% EVR+TAC, 43% EVR+CyA, 42% TAC+MPA) major differences were seen for viral infections with incidences of 41% in TAC+MPA vs. only 26% in EVR+TAC and 12% in EVR+CyA groups. Incidence of BKV events was 23% in TAC+MPA vs. 17% in EVR+TAC vs. 9% in EVR+CyA pts ($p < 0.01$). CMV events occurred two thirds less in EVR treated pts compared to TAC+MPA control group with an incidence of 21% in TAC+MPA vs. 6% for EVR+TAC and 3% for EVR+CyA treatment pts ($p < 0.001$).
Conclusion: ATHENA as largest European KTx study confirmed comparable efficacy and safety together with less viral infections for EVR-based treatment groups compared to TAC+MPA group. A significant, protective effect of EVR-based regimens vs. CMV-/BKV-events was robustly confirmed.

LOS010 THE TRANSFORM STUDY: EFFECT OF EVEROLIMUS WITH REDUCED-EXPOSURE CALCINEURIN INHIBITOR ON 12-MONTH RENAL FUNCTION OUTCOMES IN DE NOVO KIDNEY TRANSPLANT RECIPIENTS

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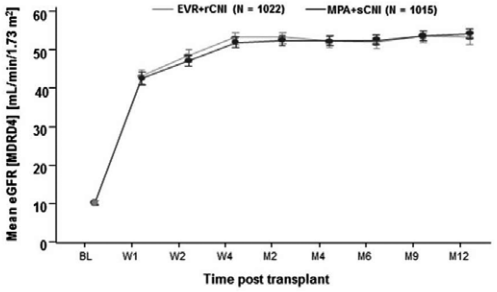
Background: Everolimus (EVR)-facilitated calcineurin inhibitor (CNI) reduction has shown to preserve renal function without affecting the efficacy in kidney transplant recipients (KTxRs). TRANSFORM is the largest study to date evaluating the benefit of EVR with reduced-exposure (r) CNI vs. mycophenolate (MPA) with standard-exposure (s) CNI in *de novo* KTxRs.
Method: TRANSFORM (NCT01950819) is a 24-month (M), phase IV, multicentre, randomised, open-label study in 2037 adult KTxRs, to receive either EVR+rCNI ($N = 1022$; tacrolimus [TAC] trough level [C0]: 4–7, 2–5 and 2–4 ng/ml and cyclosporine [CsA]: 100–150, 50–100 and 25–50 ng/ml for Day 1 (D1)-M2, M3-M6 and M7-M24, respectively) or MPA+sCNI ($N = 1015$; TAC C0: 8–12, 6–10, 5–8 ng/ml and CsA: 200–300, 150–200, 100–200 ng/ml for D1-M2, M3-M6 and M7-M24, respectively), with induction and steroids. The primary objective was to evaluate efficacy using a novel composite endpoint of estimated glomerular filtration rate (eGFR) <50 ml/min/1.73 m^2 or treated biopsy-proven acute rejection (tBPAR) at M12. Other objective included evolution of renal function over time by eGFR (MDRD4).
Results: The baseline characteristics were balanced between both arms. Up to 40% patients (TAC) and 60% patients (CsA) were above the target CNI C0 range in the EVR+rCNI arm. At M12, non-inferiority was achieved in the primary endpoint with EVR+rCNI vs. MPA+sCNI arm (48.2% vs. 45.1%; difference [95% CI]: 3.2 [−1.3, 7.6]; non-inferiority test $P = 0.001$). Mean eGFR was similar between both arms at all time points from RND to M12 (Figure). Incidence of eGFR <50 ml/min/1.73 m^2 was comparable between both arms (EVR+rCNI: 45.4% vs. MPA+sCNI: 42.2%; difference [95% CI]: 3.2 [−1.3, 7.6]).

Figure: Evolution of eGFR by MDRD4 (mean and 95% CI) over 12 months – Full analysis set



BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; MDRD4, Modification of Diet in Renal Disease; M, month; W, weeks

Conclusion: Although majority of patients in the EVR+rCNI arm had CNI C0 above the target range, the renal function outcome was good and comparable vs. MPA+sCNI arm. Further 24M results will help to better define the long-term renal effects of the EVR+rCNI regimen in *de novo* KTxRs.

LOS011 TRANSFORM STUDY: IMPACT OF DONOR TYPE ON 12-MONTH OUTCOMES OF EVEROLIMUS AND REDUCED CALCINEURIN INHIBITOR VERSUS MYCOPHENOLATE AND STANDARD CALCINEURIN INHIBITOR IN DE NOVO KIDNEY TRANSPLANT PATIENTS

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Background: Allograft source (living or deceased donor) impacts long-term patient and graft survival, and renal function post kidney transplant (KTx). TRANSFORM (NCT01950819) is the largest prospective study evaluating the efficacy and safety of everolimus (EVR) and reduced calcineurin inhibitor (rCNI) vs. mycophenolate (MPA) and standard CNI (sCNI) in *de novo* KTx recipients (KTxRs). Here, we present the 12-month (M) results by donor type.
Methods: In this 24M, multicentre, open-label, two-arm, randomised (1:1) study, *de novo* KTxRs received EVR+rCNI ($N = 1022$) or MPA+sCNI ($N = 1015$), with induction and steroids within 24 h post-Tx. Patients were stratified at randomisation by donor type (living, deceased standard criteria, or deceased expanded criteria) and CNI usage (cyclosporine or tacrolimus). Primary objective was to evaluate rates of the composite of treated biopsy-proven acute rejection (tBPAR) or estimated glomerular filtration rate (eGFR) <50 ml/min/1.73 m^2. The study compared EVR+rCNI vs. MPA+sCNI at M12 using a 10% non-inferiority margin.
Results: The study met its primary objective of the composite of tBPAR and eGFR (EVR+rCNI vs. MPA+sCNI: 48.2% vs. 45.1%; difference [95% CI]: 3.2% [−1.3%, 7.6%]). Of 2037 KTxRs (Table 1a), 1017 received grafts from living donors (LD) and 1014 from deceased donors (DD). At baseline, mean body mass index, end-stage disease leading to Tx (except for immunoglobulin A nephropathy), and mean panel reactive antibodies, were balanced between groups. (Table 1b). Analysis of adherence to CNI C0, efficacy and safety outcomes in donor subgroups is currently underway.
Conclusions: In this largest study to date in *de novo* KTxRs, demographics and baseline characteristics were comparable between LD and DD subgroups. Additional data will provide insights on how EVR+rCNI performed vs. MPA+sCNI in different donor types.

Table 1a: Patient disposition

Parameters	EVR+rCNI (N = 1022)	MPA+sCNI (N = 1015)
Donor category, n (%)		
Living related	302 (29.5)	315 (31.0)
Living unrelated	209 (20.5)	192 (18.9)
Deceased heart beating	506 (49.5)	505 (49.8)
Deceased non-heart beating	5 (0.5)	3 (0.3)
Donor characteristics, n (%)[†]		
Standard criteria deceased donor	354 (70.0)	345 (68.3)
Expanded criteria deceased donor	152 (30.0)	160 (31.7)

[†]Percentage is the relative number of deceased heart beating donors
EVR, everolimus; MPA, mycophenolic acid; rCNI, reduced calcineurin inhibitor; sCNI, standard calcineurin inhibitor

Table 1b: Patient demographics and baseline characteristics stratified by living donor vs deceased donor

Recipient characteristics	Living donor (N = 1016)	Deceased donor (N = 1014)
Age, years, mean ± SD	44.8 ± 14.1	52.8 ± 13.3
Male, n (%)	717 (70.6)	695 (68.5)
Race, n (%)		
Caucasian	686 (67.5)	803 (79.2)
Asian	247 (24.3)	45 (4.4)
Others[a]	83 (8.2)	166 (16.4)
BMI, kg/m², mean ± SD	25.0 ± 4.3	26.0 ± 4.1
End-stage disease leading to Tx, n (%)		
Glomerular disease	164 (16.1)	169 (16.7)
Polycystic disease	126 (12.4)	166 (16.4)
Hypertension/nephrosclerosis	110 (10.8)	140 (13.8)
IgA nephropathy	131 (12.9)	59 (5.8)
Diabetes mellitus	133 (13.1)	123(12.1)
Unknown	154 (15.2)	124 (12.2)
Others[b]	198 (19.5)	233 (23.0)
PRA (most recent evaluation), %, mean ± SD	2.1 ± 7.4	2.3 ± 9.2

[a]Includes Native American, Black, Pacific Islander, unknown, and others; [b]Includes drug-induced toxicity, interstitial nephritis, obstructive disorder/reflux, pyelonephritis, renal hypoplasia/dysplasia, vasculitis, other, and missing data.
BMI, body mass index; DR, antigen D related; IgA, immunoglobulin A; PRA, panel-reactive antibody; SD, standard deviation; Tx, transplantation

LOS012 CLINICAL SIGNIFICANCE OF ALLOANTIBODIES IN HAND TRANSPLANTATION – A MULTICENTER STUDY

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Background: Although alloantibodies, and donor-specific antibodies (DSA) in particular, are well-known to negatively impact graft survival in human solid organ transplantation, little is known about their relevance in vascularized composite allotransplantation (VCA). In this multicentre study we analyzed the prevalence of alloantibodies in hand transplantation, and their correlation with rejection and functional outcome.
Methods: All hand transplant centers known in the public domain, as of July 12 2016, were invited to participate. A total of 15 centers joined, comprising 44 patients with available antibody data. Inclusion criteria were met by 43 patients which were assessed for demographics and antibody type (DSA, non-DSA, non-HLA). Functional scoring was available for 35 patients (Hand Transplant Scoring System (HTSS) and Disability of Arm Shoulder and Hand (DASH)). Rejections and antibody status were analyzed with Kaplan Meier comparisons. Functional outcome was analysed before and after the occurrence of antibodies.
Results: The majority of recipients developed de novo DSA, while only a minority was pre-sensitized. There was an association between antibody development and HLA-DR mismatch. Alloantibody positive patients had the highest incidence of grade 1 and 2 acute rejections (Figure 1 A-C). DSA class II was most prevalent, but not a determinant DSA subtype. No major negative effect was seen on functional outcome, although more extensive follow-up is needed.
Conclusions: This is the first multicenter study describing a high occurrence of alloantibodies in hand transplant recipients, and their possible association with acute rejection and functional outcome. This highlights the need for a structured follow-up of VCA patients developing DSA, establishment of strategies for the treatment of antibody mediated rejection (AMR), and implementation of AMR criteria in the current cell-mediated based VCA Banff classification system.

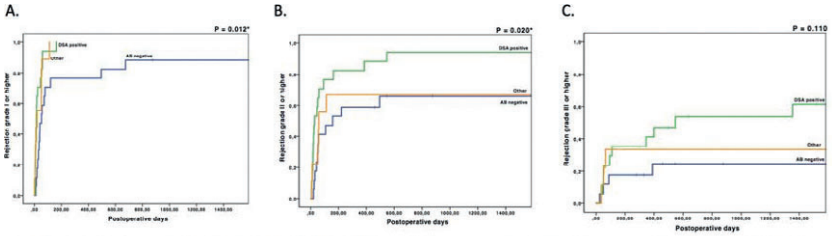

Figure 1. Cumulative incidence of acute rejection grade I, II and III. Kaplan Meier comparisons between DSA positive patients (n=17), non-HLA and non-DSA positive patients (n=9, collectively referred to as "Other"), and antibody negative patients (n=17). (A) 17/17, 9/9, 15/17, of DSA positive, "Other", and AB negative patients, developed grade I rejection or higher, respectively. (B) 17/17, 7/9, 11/17, of DSA positive, "Other", and AB negative patients, developed grade II rejection or higher, respectively. (C) 11/17, 3/9, 5/17, of DSA positive, "Other", and AB negative patients, developed grade III rejection or higher, respectively. Statistics: significant, p-value < 0.05* (log rank test). Abbreviations: antibody (AB), donor specific antibody (DSA).

LOS013 VASCULARIZED HUMAN FINGER DECELLULARIZATION: A SUBUNIT APPROACH TO HAND TISSUE ENGINEERING

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Background: Hand allotransplantation breakthrough is still highly limited by the need for immunosuppression. From our previous results in the porcine ear and human face tissue engineering, we hypothesized an application to human finger and hand scaffold production.
Methods: Nine long-digit grafts were procured postmortem from four fresh human donors, and decellularized by sequential arterial perfusions of detergent/polar solvent solutions. Cellular clearance was assessed by DNA quantification and H&E staining. Extracellular matrix preservation was assessed by Masson's Trichrome (MT) for soft tissues and bone mineral density (BMD) for phalangeal bones. Acellular samples were cultured with fibroblastic cell lines, and examined with vital staining. To challenge *in vivo* the vasculature, a short reperfusion study was performed in a pig recipient. Finally, decellularization was applied to a whole human hand, and vascular tree assessed by angio-CT scan.
Results: Digital grafts were successfully decellularized, with a quick epidermolysis, nail loss and complete bleaching. Cell clearance was demonstrated on H&E sections, associated to 95.3% DNA reduction, compared to native tissues ($p < 0.0001$). MT staining showed microscopic structural preservation. Decellularized phalanx mean BMD was 510 mg hydroxyapatite/cm3, similar to control. Seeded cells were viable and homogeneously distributed on all scaffolds. *In vivo*, blood quickly reperfused the whole scaffold; after 3 h, the vascular tree was still patent, as demonstrated by fluoroscopy, fingertip pulse and 93% oxygen saturation. The extension to a whole-hand graft decellularization was achieved successfully, with an excellent preservation of the superficial and deep vascular tree.
Conclusion: We could produce finger and hand extracellular matrix scaffolds from human cadaveric source, with a preserved and perfusable vascular tree. These results could represent a true alternative to upper extremity allotransplantation.

LOS014 COMBINATION OF IL2/ANTI-IL2 COMPLEXES AND ANTI-INFLAMMATORY THERAPY FOR TOLERANCE INDUCTION

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Introduction: Interleukin-2 (IL2) complexed with a specific antibody against IL2 (IL2cplx) rapidly expands and activates Tregs *in vivo*. Treatment with IL2cplx has shown potency in inducing tolerance towards islet (but not skin) allografts. Here we investigated the potency of IL2cplx based therapy to prolong skin allograft survival and the mechanisms of tolerance.
Methods: Mice received fully or MHC mismatched skingrafts, tolerogenic therapy with IL2cplx and mTOR inhibition (0.5 mg IL-2/2.5 mg JES6-1; 1 mg/kg rapamycin; i.p.,3x/week 4 weeks) and short-term treatment with anti-IL6. Mechanisms of tolerance were investigated by analysis of donor-specific antibodies, flow-cytometric analysis and MLRs. Groups of mice were challenged with a second skingraft to test for infectious tolerance and for memory responses.
Results: We could show that combination of IL2cplx, rapamycin and anti-IL6 significantly prolongs survival of fully mismatched skingrafts (MST = 76 days, $p < 0.0001$) and leads to prevention of acute rejection, even after complete stop of treatment at d29. Importantly, the absence of minor antigens led to graft survival >100 days. Analysis of sera revealed complete absence of donor-specific antibodies ($p < 0.01$) and kinetics of rejection of a second graft suggested additional absence of Tmem response. Flow cytometric analysis of the graft indicates increased frequencies of intragraft Tregs and active regulatory mechanisms. Graft survival was demonstrated to be critically dependent on CD4 + CD25 + Tregs.
Discussion: We could show that Treg expansion via IL2cplx synergizes with rapamycin and anti-IL6, leading to significantly prolonged skin allograft survival and prevention of acute rejection even in the absence of ongoing treatment. Further experiments to uncover the underlying mechanisms are under way. We think these results will have significant impact on the development of new protocols for tolerance induction.

LOS015 DONOR SPECIFIC AND NON-DONOR SPECIFIC HLA ANTIBODIES AND LONG-TERM OUTCOME POST LUNG TRANSPLANTATION

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Donor specific antibodies (DSA) against HLA are associated with chronic lung allograft dysfunction (CLAD) and mortality post lung transplantation, but data concerning prevalence, time of onset, persistence and effects on long-term outcome remain scarce.

We assessed the association between HLA antibodies and CLAD-free and graft survival in a cohort of 362 patients undergoing lung transplantation between 2010 and 2015. We stratified our analysis according to DSA status, persistence of antibodies and timing of antibodies (pre-transplant, early or late post-transplant).

Within our cohort, 61 (17%) patients ever developed DSA (mostly against HLA-DQ), which was associated with worse CLAD-free survival ($p < 0.0001$) and a trend for worse graft survival ($p = 0.059$). Persistent ($p < 0.0001$ HR 3.386 CI 1.928–5.948) as well as transient ($p = 0.0045$; HR 2.998 CI 1.406–6.393) DSA were associated with shorter CLAD-free survival compared to patients without DSA. Persistent DSAs ($p = 0.0005$; HR 3.071 CI 1.632–5.778), but not transient DSA were negatively associated with graft survival compared to patients without DSA, likely due to the higher incidence of restrictive CLAD in the persistent DSA group. Non-DSA HLA antibodies and pre-transplant HLA antibodies had no effect on post-transplant outcome.

We demonstrated an important difference in prognosis between persistent and transient DSA. Moreover, the observed association between DSA

LOS016 HYBRID PSEUDOISLETS GENERATED FROM ISLET CELLS AND AMNIOTIC EPITHELIAL CELLS REVERSE DIABETES AFTER MARGINAL MASS TRANSPLANTATION IN A MURINE MODEL

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Aims: Inflammatory phenomena and delayed revascularization remain a significant obstacle to the success of clinical islet transplantation. Human amniotic epithelial cells (hAECs) exhibit anti-inflammatory, immunomodulatory and regenerative properties, and are widely available. In this study we have engineered functional hybrid pseudo-islets (HPI) composed of dissociated islet cells and hAECs and explored whether they can protect islet cells from ischemic and inflammatory damage and improve their function and engraftment
Methods: Rat pancreatic islets were dispersed into single cells for the generation of pseudo-islets (PI), consisting in 500 islet cells. HPIs were generated from 500 islet cells mixed with 500 hAECs on microwell platforms. PIs and HPIs were assessed for viability and function *in vitro*. *In vivo* function was assessed by transplantation into STZ-diabetic scid mice
Results: Significant enhancement of insulin/glucagon expression and of glucose-stimulated insulin secretion were observed from HPIs as compared to PIs. Transplantation of marginal mass HPIs, corresponding in size to 150 IEQs, under the kidney capsule of diabetic mice normalized blood glucose levels within 3–7 days. In contrast, transplantation of the same mass of PIs or native islets was unable to reverse diabetes. Removal of the islet graft-bearing kidney led to recurrence of hyperglycemia. HPIs were morphologically intact and expressed insulin and glucagon up to 4 months post-transplant. A two-fold increase in graft revascularization, assessed by CD34 staining, was seen in HPIs, compared to PIs and native islets. IPGTT at 1.5 and 3 months post-transplant were identical to non-diabetic controls
Conclusion: This data indicates that hAECs have a significant cytoprotective effect that enhances islet engraftment. hAEC-enriched pseudoislets may represent a novel approach to increase the success rate of islet transplantation and a first step towards the development of a bioartificial pancreas.