29 cases of late extra-hepatic biliary strictures, occurring 6 weeks to 3 years after transplantation, were identified by MRCP, ERCP or PTC in recipients of deceased donor liver transplants between 2002 and 2011 (n=286). Their preoperative sera were retrospectively examined for DSA using Luminex single bead assays. Donor cells were cross-matched using flow cytometry. 20 recipients with no evidence of biliary pathologies served as control. Acute rejection, hepatitis and demographic criteria were considered for matching the control group. Cumulative class II MFI >500 and/or B-cell cross-match positivity was found to be strongly associated with the incidence of late extra-hepatic biliary strictures. Class I DSA did not reveal any association. The study group showed cumulative class II DSA >500 MFI in 24/29 patients (83%) and B-cell crossmatch positivity in 20/29 patients (69%). Using both criteria, 26/29 recipients (90%) could have been identified prior to transplantation for being at risk to develop late biliary strictures. Only 3/20 recipients (15%) of the control group showed B-cell cross-match positivity. None of them had a cumulative class II MFI >200. None of 4/20 controls (20%) with cumulative class II MFI >500 showed a positive B-cell cross-match.

This is the first evidence indicating that pre-transplant class II DSA and B-cell cross-match positivity are strongly associated with the risk of developing late extra-hepatic biliary strictures following liver transplantation. These data are suggestive for an immunological aetiology of non-vascular late biliary strictures.

Abstract# 447
Increased Incidence of Non Anastomotic Biliary Strictures in Case of Donation after Circulatory Death Versus Donation after Brain Death Liver Transplantation but Equivalent Graft and Patient Survival.
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Because of the concerns regarding short & long-term outcomes after Liver Transplantation (LTx) using Donation after Circulatory Death (DCD) compared to Donation after Brain Death (DBD) donors, we reviewed the results of DCD-LTx at our center. Between 2003 and 2010, 30 DCD-LTx and 385 DBD-LTx were performed. Demographics, LTx indications, post-LTx peak aspartate amino transaminase (AST peak), delayed graft function (DGF), preoperative characteristics, biliary non-anastomotic strictures (NAS), early post-LTx kidney dysfunction (RIFLE criteria), re-transplantation rate and patient/graft survival were analyzed. Mean DCD donor warm ischemia (stop ventilation to cold perfusion) was 23±11'. Median cold ischemia was 6h54' for DCD compared to 8h40' for DBD-LTx; p=0.0001. Mean labMELD was similar for DCD and DBD-LTx (15 vs. 16; p=0.59). Median post-LTx AST peak was higher after DCD vs. DBD-LTx (1178 IU/L vs. 651 IU/L; p=0.005). DGF rate was similar between DCD and DBD-LTx (25 vs. 24%; p=0.8). The rate of NAS was higher after DCD vs. DBD-LTx (33% vs. 12%; p=0.001). Incidence of early post-LTx kidney dysfunction was not statistically different after DCD and DBD-LTx (37% vs. 23%; p=0.08). On the other hand, regardless of the donor type, the AST peak - a surrogate of ischemia-reperfusion injury often used as an appropriate criterion for DGF evaluation - was associated with a higher rate of early post-LTx kidney dysfunction if greater than 2000 (28 vs. 10%; p=0.001) but not with NAS (12 vs. 15%; p=0.59). Re-transplantation rate within one year post-LTx was 3% after both DCD and DBD-LTx. The 1, 3, & 5 year patient/graft survival were similar after DCD and DBD-LTx (93, 85, 85% vs. 88, 87 & 72%; p=0.9, and 90, 82, 82% vs. 85, 74 & 68%; p=0.5, respectively). Despite substantial ischemic injury, short-term patient/graft survival after DCD-LTx is comparable to DBD-LTx. Careful donor/recipient selection, rapid donor surgery and short ischemia times are key factors to optimize outcome after DCD-LTx. However, strategies to reduce ischemic injury and biliary complications remain warranted.

Abstract# 448
Late Versus Early Biliary Complications after Liver Transplantation.

Introduction: Biliary complications (BC) cause major morbidity and mortality after liver transplantation (LT). Literature is replete with articles on early BC (less than 1 year post LT); however, little is known about late BC.

Methods: We reviewed retrospectively our prospectively collected data for adult LTx from 1/1/97 to 12/31/07. Multorgan transplants were excluded. Patients with BC more than a year after LT (late BC) were compared to patients with BC in the first year (early BC) and patients who never had BC. Fisher exact tests with post hoc Bonferroni test and Kruskal-Wallis analysis with post-hoc Dunn’s test were used for comparisons. Univariate and multivariate Cox regression analysis was performed.

Results: 1621 LTx were included, 92.4% primary and 7.6% re LTx. 29.3% patients had BC with 24.3% early BC (n=384) and 5% late BC (n=82). Late BC included anastomotic (53.6%) and nonanastomotic (21.9%) strictures, papillary stenosis (14.6%), stones (21.9%), biliary (10.9%) and tumors (1.2%). In the late BC group, 18.2% patients had surgical repair; 47.5% patients had resolution of BC, 9.7% had stent LT and 32.9% patients died in follow-up. Main causes of death in late BC group were Hepatitis C (29%) and hepatic artery thrombosis (HAT) (14%). Late BC were associated with simultaneous acute cellular rejection (ACR) (21%), chronic rejection (7%) or recurrent primary biliary cirrhosis (3.5%). On stepwise multivariate Cox regression, use of T-tube (hazard ratio [HR] 2.0, 95% confidence interval [CI] = 1.0-4.0), HAT (HR: 5.3, 95% CI=1.8-15.4), use of Cyclosporine (vs. Tacrolimus) (HR: 3.7, 95% CI=2.1-6.6) or steroids (vs. no use) at 4 weeks post LT (HR: 2.0; 95% CI=0.9-4.8), female donor gender (HR: 1.6; 95% CI=0.94-2.75) and black recipient race (HR: 1.9; 95% CI=0.8, 4.2) were predictors of late BC. Patients with early BC had longer ICU stay, higher rates of ACR, HAT and infections, higher recipient BMI and donor age, longer warm ischemia time and association with re LT.

Between the 3 groups there were no differences in regards to MELD score, cold ischemia time, intraoperative hepatic artery flow, intraoperative blood transfusion, donor BMI, B or T cell positive crossmatch and Sirolimus use at 3 months.

Conclusions: While early BC are related to perioperative events, late BC seem to be related to disease recurrence or an immunological event. Most late BC do not require surgical repair.

Concurrent Session 63: Kidney Issues in Liver Transplant Candidates and Recipients

Abstract# 449
Spectrum of Renal Pathologic and Gene Expression Profiles of Kidney Biopsies in Patients with Cirrhosis Listed for Liver Transplantation.
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Introduction: We previously demonstrated universal glomerular abnormalities in kidney biopsies after orthotopic liver transplantation (OLT). We hypothesize that these changes exist prior to OLT and may play an important role in the development of renal failure after OLT. We investigated the mechanism of kidney disease in patients listed for OLT by immunohistoopathologic and genomic analysis of kidney biopsies (KB). Methods: Analysis of clinical and pathological data of 21 cirrhotic patients (pts) listed for OLT who underwent KB. The Gene expression profile of KB specimens was studied by Affymetric HuGene 1.0 ST expression assay and was compared with pre-implantation living donor KBs. Results: Etiology of liver disease: hepatitis C (71%), alcoholic hepatitis (24%) and autoimmune hepatitis (5%). Mean MELD, serum creatinine, GFR and proteinuria were 17±5, 1.9±0.7 mg/dl, 42±17 ml/min and 0.5±0.8 gm/day, respectively. Twelve pts had low complement levels. Mesangial proliferation was seen in 20 KBs by light microscopy. Five pts had nodular glomerulosclerosis (3 DM), and 1 MPGN. Immunofluorescence staining showed mesangial, capillary wall or tubular basement-membrane deposition of IgG (16), IgM (18), IgA (10), CIQ (11) and C3 (12). Electron microscope in 16 pts showed effacement of podocytes (15) and duplication and widening of glomerular basement membranes (10). Gene expression profiles by Gene Ontology revealed significant up-regulation of genes implicated in immune response, including IL18, CYLD, IL10 and platelet activation and differentiation. Pathogenesis-based transcripts revealed significantly increased expression of quantitative cytotoxic T-cell, quantitative macrophage, B-cell, natural killer cell, and endothelial cell associated transcripts, indicating an ongoing inflammatory immune response.

Conclusion: This study demonstrates the universal presence of glomerular abnormalities in KBs of cirrhotic patients. The majority had increases in mesangial matrix, podocyte effacement and widening and duplication of glomerular basement membrane, as is also seen in patient’s post-OLT. The increased gene expression profiles related to immune activity could indicate immune-mediated mechanisms in development of kidney disease in cirrhotic patients.

Abstract# 450
Superior Renal Function Sustained for 24 Months through Early Everolimus-Facilitated Reduction of Tacrolimus Versus Standard Tacrolimus in De Novo Liver Transplant Recipients: Results of a Randomized Trial. P. De Simone, 1 O. Detry, 1 G. Kintmalm, 1 J. Goss, 2 M. Pecorimm, 1 M. Rossi, 1 A. Moya, 1 P. Lopez, 2 G. Junge, 2 D. Joseph, 1 C. Duvoux, 1 1From the H2304 Study Group, Pisa, Italy; 1Novartis Pharma AG, Basel, Switzerland; 1Novartis Pharmaceuticals Corporation, New Jersey.

mTOR inhibitors have the potential to reduce calcineurin inhibitor nephrotoxicity by minimizing or eliminating the need for their use. The 12 month (M) results of
KIDNEY ISSUES IN LIVER TRANSPLANT CANDIDATES AND RECIPIENTS

H2304 (NCT00622869) study demonstrated superior renal function with everolimus (EVR) plus reduced tacrolimus (rTAC) vs. standard TAC (CNI) in de novo liver transplant recipients (LtxR). Presented here are 24M renal function results. For this 24M, multicenter, open-label study, 719 de novo LtxR were randomized (1:1:1) to receive either EVR (2.5-5 mg) or rTAC (1:3-5 mg) (run-in period with TAC (1:5 mg) at 30-day or 60-day post-LtxR). Of note, patients were included in composite efficacy failure rate in EVR+rTAC was higher with EVR+rTAC vs. TAC-C (Mean±SD: 194±280 vs. 159±284, p=0.006). Early introduction of EVR at 1M post-LtxR with rTAC showed superior renal function for EVR+rTAC vs. TAC-C with an adjusted mean difference in eGFR of 6.6 mL/min/1.73m² (p=0.0018; ITT population). Significantly higher EVR+rTAC was achieved at M2 post-LtxR and was maintained until M24. On-treatment data showed a decrease in mean eGFR from RND to M24 of 6.6 mL/min/1.73m² with rTAC vs. 13 mL/min/1.73m² with TAC-C and 2.5 mL/min/1.73m² gain with TAC-WD. Urinary protein:creatinine ratio (mg/g) at M24 was higher with EVR+rTAC vs. TAC-C (Mean±SD: 194±280 vs. 159±284, p=0.006). Early introduction of EVR at 1M post-LtxR with rTAC showed superior renal function sustained for 24M compared to TAC-C, without compromising efficacy in de novo LtxR.


Abstract# 451

The Influence of Baseline Immunosuppression on Renal Function and Clinical Outcomes in Liver Transplantation. A. Mardis,1 D. Taber,2 H. Meadows, N. Pilch, J. Fleming, C. Jordan,1 K. Morbitzer, C. Makowski,1 J. McGillicuddy,3 C. Bratton,4 K. Chavvin,5 P. Baliga,3 Pharmacy, MUSC, Charleston, SC; Surgery, MUSC, Charleston, SC. Background: Preserving renal function in liver transplantation has become paramount. We sought to determine the influence of baseline immunosuppression on renal function, acute rejection, and clinical outcomes. Methods: This was a large-scale longitudinal cohort study of all liver transplants from Jan 2000 - June 2011. Patients were excluded if they were <18 years old, multi-organ transplants, or experienced graft loss or death within the first 3 months. Patients were divided into 4 groups based on baseline IS (CNI, IL2-RA+MMF+CNI, IL2-RA+CNI, CNI+MMF). Renal function was estimated using the MDRD equation; change in renal function from baseline was assessed by calculating the slope of MDRD. All patients received steroids in conjunction with IS regimens. Results: 635 transplants occurred during this period; 532 were included in this analysis (mean follow-up 4.8 yrs). Baseline demographics and outcome data are shown in Table 1; the only differences at baseline were age, race, MDRD and MELD. Clinical outcomes demonstrated that the combination of IL2-RA+CNI+MMF was the only regimen that statistically significantly improved renal function with lower rates of acute rejection (Table 1). This was achieved through CNI minimization (see FK levels in Table 1). HCV recurrence was not influenced by baseline IS regimens. Death and graft loss were lowest in quadruple IS regimen. However, Cox Proportional Hazard Regression analysis demonstrated that only slope of MDRD influenced graft loss (HR 0.945, p=0.001 [95% CI 0.92-0.96]) in an independent fashion. Conclusions: The results of this study suggest that quadruple IS regimens can safely and effectively preserve renal function and reduce acute rejection rates in liver transplant recipients without influencing HCV recurrence or graft survival.

Abstract# 452

Liver Transplantation (LT) in Patients Receiving Renal Replacement Therapy (RRT): Predicting Renal Recovery and Post-Transplant Futility. V. Agopian,1 J. Baber,1 A. Dhillon,2 H. Petrowsky, A. Zarrinpars, F. Kaldas, H. Yerusiz,1 D. Farmer,1 J. Hiatt, R. Busuttil,2 Surgery, UCLA, LA, CA; Anesthesiology, UCLA, LA, CA. Background: The Model for End-Stage Liver Disease (MELD) system prioritizes liver allocation to patients in renal failure, increasing the number of simultaneous liver-kidney transplants (SLK). Identifying predictors of post-transplant futility (90-day or in-hospital mortality) and renal recovery could maximize utilization of these scarce resources. Methods: Analysis of adult LT recipients on pre-transplant RRT from July 2004 to September 2012 at a single-institution using 33 recipient, donor, and operative variables. Multivariable logistic regression was used to identify predictors of futility and dialysis dependence at 3-months. Results: Of 1546 LT recipients, 529 were on RRT (34%). The mean MELD score was 38. Compared to patients undergoing LT alone (LTA, n=407), SLK (n=94) patients were significantly older and more obese, diabetic, and hypertensive, but less likely hospitalized, on continuous RRT, ventilator-dependent, or on vasopressors. Despite kidney transplantation, 21% of SLK recipients were dialysis-dependent at 3-months, compared to 43% of LTA recipients (P<0.001). Of all futile LTs (n=94, 19%), only 4 patients (4%) became dialysis-independent prior to their death. Futility LT accounted for 43% and 75% of failures to achieve dialysis independence in LTA and SLK, respectively. Multivariate predictors of futility included coagulopathy requiring abdominal packing, pre-transplant length of RRT, mechanical ventilation, recipient and donor age, and hyperlipidemia. In non-futile patients, multivariate predictors of dialysis dependence included non-fulfimental etiology, LT, emergent intraoperative RRT, pre-transplant RRT > 7 days, metabolic syndrome, pre-transplant stay, and gender (Table). Conclusions: We report the largest single-institution experience of LT in patients on pre-transplant RRT. We identified important predictors of post-LT futility and renal recovery that may help to guide the allocation of kidneys in these challenging LT recipients.

Abstract# 453

Therapy (RRT): Predicting Renal Recovery and Post-Transplant Futility. V. Agopian,1 J. Baber,1 A. Dhillon,2 H. Petrowsky, A. Zarrinpars, F. Kaldas, H. Yerusiz,1 D. Farmer,1 J. Hiatt, R. Busuttil,2 Surgery, UCLA, LA, CA; Anesthesiology, UCLA, LA, CA. Background: The Model for End-Stage Liver Disease (MELD) system prioritizes liver allocation to patients in renal failure, increasing the number of simultaneous liver-kidney transplants (SLK). Identifying predictors of post-transplant futility (90-day or in-hospital mortality) and renal recovery could maximize utilization of these scarce resources. Methods: Analysis of adult LT recipients on pre-transplant RRT from July 2004 to September 2012 at a single-institution using 33 recipient, donor, and operative variables. Multivariable logistic regression was used to identify predictors of futility and dialysis dependence at 3-months. Results: Of 1546 LT recipients, 529 were on RRT (34%). The mean MELD score was 38. Compared to patients undergoing LT alone (LTA, n=407), SLK (n=94) patients were significantly older and more obese, diabetic, and hypertensive, but less likely hospitalized, on continuous RRT, ventilator-dependent, or on vasopressors. Despite kidney transplantation, 21% of SLK recipients were dialysis-dependent at 3-months, compared to 43% of LTA recipients (P<0.001). Of all futile LTs (n=94, 19%), only 4 patients (4%) became dialysis-independent prior to their death. Futility LT accounted for 43% and 75% of failures to achieve dialysis independence in LTA and SLK, respectively. Multivariate predictors of futility included coagulopathy requiring abdominal packing, pre-transplant length of RRT, mechanical ventilation, recipient and donor age, and hyperlipidemia. In non-futile patients, multivariate predictors of dialysis dependence included non-fulfimental etiology, LT, emergent intraoperative RRT, pre-transplant RRT > 7 days, metabolic syndrome, pre-transplant stay, and gender (Table). Conclusions: We report the largest single-institution experience of LT in patients on pre-transplant RRT. We identified important predictors of post-LT futility and renal recovery that may help to guide the allocation of kidneys in these challenging LT recipients.