Oral Abstract Presentations

Date: Friday, September 24, 2021, Time: 10:00-12:00ET

Abstract 1

Presenting Author: Rayoun Ramendra **Institution:** University of Toronto

Abstract Title: Donor airway bile acid as a biomarker of aspiration and predictor of post-transplant outcomes

Top 3 - Abstract Award

Abstract Body:

Background: Emesis and aspiration in organ donors contributes to donor lung damage and may promote post-transplant allograft dysfunction. Previous studies have identified total bile acids (TBA) measured in large airway bronchial wash (LABW) to be a marker of aspiration in transplant recipients. Herein, we seek to investigate if donor LABW TBA is associated with suitability of donor organs for transplant and recipient outcomes. Methods: TBA was measured in LABW of 605 consecutive lung donors from 2012-2018. TBA levels were compared in donor lungs deemed unsuitable for transplant, those requiring further assessment on ex vivo lung perfusion (EVLP), and those suitable for transplantation. Associations between LABW TBA and performance of donor lungs on EVLP as well as recipient outcomes were evaluated. Results: Donor TBA was higher in lungs deemed unsuitable for transplant compared to those suitable for direct transplant and those requiring further assessment on EVLP. TBA concentration in donor LABW also correlated with markers of acidemia, lactate levels, and pro-inflammatory cytokines in EVLP perfusate. A TBA cut-off of 1245nM was able to differentiate donor lungs directly declined and those suitable for direct transplantation with a 90% specificity. Based on this cut-off, a high donor TBA was associated with post-transplant recipient outcomes: longer time to extubation (HR=0.48 [95% CI=0.35-0.66]) and shorter time to death (HR=1.84 [95% CI=1.24-2.75]). Conclusion: In a large retrospective cohort we observed that TBA measured in donor LABW was associated with suitability of donor lungs for transplant, performance of lungs on EVLP, and adverse recipient outcomes after lung-transplant.

Abstract 2

Presenting Author: Jillian Oliver **Institution:** University Health Network

Abstract Title: Nintedanib as an anti-fibrotic therapy in a mouse model of chronic lung allograft dysfunction

Abstract Body:

Background Chronic lung allograft dysfunction (CLAD) is the leading cause of lung transplant failure, with 50% of patients developing it by five years post-transplant. CLAD is characterized by progressive fibrosis, and it has no effective therapies. Nintedanib is a multiple tyrosine kinase inhibitor used to treat idiopathic pulmonary fibrosis. Here we assess its efficacy with tacrolimus as a potential CLAD therapy in the heterotopic tracheal transplant mouse model, a model of CLAD-like fibrosis. Methods We performed transplants in major MHC-mismatched mice, using Balb/C mice as donors, and C57BL/6 mice as recipients. To assess nintedanib and tacrolimus alone, we treated six groups of n=10 recipients with one of three doses of tacrolimus (0mg/kg, 1mg/kg, 2mg/kg) or nintedanib (0mg/kg, 25mg/kg, 50mg/kg). Mice were given either drug daily for 28 days. Following sacrifice, tracheas underwent Masson-Trichrome staining, and were graded for luminal fibrotic occlusion and epithelial necrosis. Kruskal-Wallis one-way analyses of variance were performed on both grades within drug treatments. Results Histopathological grading revealed that luminal occlusion and epithelial necrosis were significantly reduced and nearly eliminated in both tacrolimus treatment groups (Figure 1a, c; Figure 2). Further, we found that tracheal occlusion was significantly reduced in both nintedanib treatment groups (Figure 1b) in a dose-dependent manner. Contrastingly, we found no significant difference in epithelial necrosis in nintedanib treatment groups (Figure 1d). Conclusion Our results demonstrate nintedanib's promise as an anti-fibrotic drug in this model. It shows a significant decrease in luminal fibrotic occlusion, but only tacrolimus also shows a decrease in epithelial necrosis. Since both tacrolimus treatments resulted in near elimination of both pathologies, we will explore lower doses of tacrolimus to use with nintedanib. Following this, we will study these treatments in the minor-mismatch mouse orthotopic single lung transplant model, which produces a more clinically relevant CLAD-like pathology.

Abstract 3

Presenting Author: Imane Kaci **Institution:** CRCHUM

Abstract Title: Apoptotic Exosome-Like Vesicles Aggravate Inflammation and Renal Injury after Ischemia-Reperfusion

Abstract Body:

Background: Ischemia-reperfusion injury (IRI) is a common cause of acute kidney injury (AKI) and chronic kidney disease (CKD). Damage to microvascular peritubular capillaries (PTC) is a critical determinant of CKD transition after IRI. We previously identified anti-LG3/perlecan autoantibodies in patients with CKD, as a negative prognostic factor for long-term renal function after AKI. We also showed that a new class of extracellular vesicles produced by apoptotic endothelial cells (ApoExo), characterized by the LG3 autoantigen, active 20S proteasome and a specific pattern of immunogenic RNAs, can prompt the production of anti-LG3. Here, we test the hypothesis that ApoExo drive renal inflammation after renal IRI leading to anti-LG3 production, defective microvascular repair and loss of renal function. Methods: ApoExo were purified by sequential ultracentrifugation from serum-free media conditioned by apoptotic murine endothelial cells. Renal IRI in mice was performed with renal artery clamping for 30 minutes and contralateral nephrectomy. ApoExo were injected every other day before IRI and thereafter up to eight injections, and end-points were assessed at day 21 post-IRI. Interstitial inflammation, PTC rarefaction, complement activation, and myofibroblasts accumulation were assessed with immunohistochemistry for CD3 and IL-17A, MECA-32, C4d, and α-SMA. Anti-LG3 titers were measured by ELISA. Results: ApoExo injection enhanced tubular damage and interstitial inflammation with increased CD3+ lymphocytes infiltration and IL-17A staining ($p=0.004$ and $p=0.002$, respectively). PTC rarefaction, C4d deposition and interstitial accumulation of α-SMA+ cells were also increased in ApoExo treated mice ($p=0.01$, $p=0.009$, $p=0.04$, respectively) as were anti-LG3, which correlated with C4d deposition on PTC and myofibroblasts accumulation ($r=0.86$, $p=0.007$ and $r=0.75$, $p=0.03$, respectively). Conclusion: These results identify ApoExo as novel regulators of inflammation after renal IRI, driving anti-LG3 formation, complement activation and fibrosis. These results suggest that autoimmune pathways triggered by ApoExo can contribute to microvascular rarefaction and renal fibrosis.

Abstract 4

Presenting Author: Elizabeth Shin **Institution:** Dalhousie University

Abstract Title: Using the DeRitis Ratio to Predict Graft Dysfunction and Mortality After Liver Transplant: A Novel Scoring Model

Abstract Body:

Background: Early allograft dysfunction (EAD) and mortality are the most severe complications after liver transplantation. Previous attempts to create a scoring model to predict these complications have never considered the longstanding DeRitis ratio (AST:ALT) as one of the components. Methods: A retrospective chart review was conducted in 132 adult patients receiving a whole deceased-donor liver transplant from April 2015 to March 2020 in Atlantic Canada and their matching donors. Donor variables, postoperative liver function test trends, and DeRitis ratio were correlated with the occurrence of EAD, Clavien-Dindo, and 30-day mortality as outcome variables. A comparison was also performed between the predicted outcome by Diaz-Nieto et al. versus the observed outcome in our cohort. Results: EAD was observed in 26.5%, and 7.6% patients died within 30 days post-liver transplant. Patients were significantly more likely to experience EAD if they received a DCD allograft ($p=0.04$), a liver with DRI >2.0 ($p=0.006$), ischemic injury at time 0 biopsy ($p=0.02$), longer secondary warm ischemia time ($p<0.05$), or higher Clavien-Dindo scores (IIIb-V) ($p<0.001$). DRI, total bilirubin and DeRitis ratio on post-operative day (POD) 5 yielded significant associations with EAD, high Clavien-Dindo score, and 30-day mortality, and therefore used to develop the Gala-Lopez score using a weighted scoring model. The score accurately predicted EAD in 75%, 30-day mortality in 64%, and high Clavien-Dindo in 81%. Diaz-Nieto's model did not have similarly accurate predictive value within our patient cohort. Conclusion: The Gala-Lopez score is the first of its kind to use the DeRitis ratio as part of a weighted scoring model for predicting primary outcomes of graft function, 30-day mortality, and high Clavien-Dindo post-liver transplantation. The DeRitis ratio, along with DRI and total bilirubin level on POD 5 can predict all three outcomes to aid in the decision-making process to re-transplant at an early stage.

Abstract 5

Presenting Author: Christie Rampersad **Institution:** University of Manitoba

Abstract Title: The negative impact of T-cell mediated rejection on renal allograft survival in the modern era

Abstract Body:

Background: The prevalence and long-term impact of refractory T-cell mediated rejection (TCMR) is poorly defined in the modern era of tacrolimus (Tac)mycophenolate (MPA)-based maintenance immunosuppression. Methods: This single-center observational study evaluated renal transplant recipients transplanted between 2001-2019 with serial histology. The impacts of alloimmune events (e.g., TCMR and antibody-mediated rejection (ABMR)) on subsequent risk for graft loss were assessed in a sequence of models including these events as time-dependent covariates in extended proportional hazards models. Results: 775 recipients had a mean follow-up 6.5 years. TCMR inclusive of Banff Borderline rejection occurred in ~30% of recipients from surveillance or for-cause biopsies. The first biopsy proven rejection (BPAR) was TCMR in 229/232 (99%) patients occurring a median of 6.1 months (IQR 2.6-12.1 months) post-transplant and 62% of these were Banff Borderline. After a first TCMR event, 64% (114/179) of patients with histologic follow-up had either persistent TCMR (89/179, 50%) on first follow-up biopsy or recurrent TCMR (25/179, 14%) after an intervening negative follow-up biopsy. After each additional TCMR event, ≥50% of recipients had another TCMR. Intermediate and high HLA-DR/DQ eplet mismatch alloimmune risk categories correlated with the risk of multiple TCMR events (p=0.008) and more severe Banff TCMR (p=0.007). Whereas the risk of allograft survival was not significantly altered following a first TCMR event, a second TCMR event predicted both death-censored allograft failure (HR 2.98, p=0.001) and all-cause allograft failure (HR 2.30, p=0.001) even after adjustment for ABMR. Designation of clinical or subclinical TCMR using arbitrary thresholds of 10% or 25% rise in creatinine over baseline did not differentiate those at risk for death-censored or all-cause graft loss. Conclusion: Refractory TCMR is predictive of death-censored and all-cause graft loss, which raises the potential for clinical trials evaluating novel agents to decrease rates of refractory TCMR to improve long-term allograft and patient outcomes.

Abstract 6

Presenting Author: Ranie Ahmed **Institution:** University Health Network

Abstract Title: Exploring the information needs of African, Caribbean, and Black Community Members Regarding Living Donor Kidney Transplantation in Toronto, Ontario

Top 3 - Abstract Award

Abstract Body:

Background: In Canada, patients with kidney failure from African, Caribbean, and Black (ACB) communities are 60-70% less likely to receive a living donor kidney transplant (LDKT) compared to white patients. Providing transplant-related information may improve equitable access to LDKT. However, little is known about information needs of ACB communities on LDKT in the Canadian context. In this qualitative study, we aimed to better understand the information needs of ACB communities in Toronto, ON. Methods: Purposive and snowball sampling were used to recruit self-identified ACB participants for in-person and virtual focus groups (FGs) (January-November 2020). In collaboration with community partners, an exploratory qualitative approach was used to guide discussions on racial and ethnic identity, medical experiences, and knowledge and perspectives on LDKT. FGs were audio recorded and transcribed verbatim. Thematic analysis directed the development of codes and themes. Analysis was informed by the tenets of Critical Race theory, which prioritizes racism as an important determinant of health. Results: Of the 81 participants, 48% self-identified as Caribbean, 36% as North American Black/African, 4% as Central/West African, and 6% as North African. One major theme that emerged was a desire for tailored and trustworthy information on LDKT. Participants expressed mistrust in the health care system, rooted in historic and current experiences of racism, and this may impact willingness to engage with information on LDKT typically provided by medical institutions. This may be one reason why some participants described being unaware of the causes, consequences, and treatment options for kidney failure. Participants emphasized that future development of resources on LDKT would require collaboration with ACB communities to incorporate important cultural, preventive, and holistic elements e.g., nutrition preferences and religious beliefs. Conclusion: Future information on LDKT provided to ACB communities must be culturally tailored, trustworthy, and focused on preventive and holistic health.

Abstract 7

Presenting Author: David Hartell **Institution:** Canadian Blood Services

Abstract Title: Impact of COVID on the Canadian donation and transplantation system

Abstract Body:

Background: The COVID-19 pandemic caused by the SARS-CoV-2 virus impacted nearly every aspect of global healthcare, including organ and tissue donation and transplantation (OTDT). As a novel virus, OTDT clinicians and administrators were forced to make difficult decisions based on very little scientific evidence regarding risk of donor to recipient transmission or criteria for suspension of transplant programs. In response, a wide range of recommendations were created by individual programs across the international OTDT community, which led to variable slowdowns or complete suspensions of OTDT activity over the course of 2020. Beyond individual decisions made by OTDT programs to suspend or modify activities, many programs reported multiple factors that contributed to decreased OTDT activity such as overwhelmed ICUs, decreases in eligible donors, closed operating rooms, or difficulties approaching families due to COVID-19 infection control policies. Methods: In this analysis, we report OTDT performance metrics for the Canadian system during the COVID-19 pandemic and how these metrics correlate to the response from Canadian programs and stakeholders. The analysis looks at the by-weekly OTDT data submitted by every provincial organ donation organization with a comparison against previous years, the daily OTDT program status, the annual eye and tissue data provided by every eye and tissue bank, as well as the archives of the national consensus guidance on the management of OTDT during the pandemic and how this evolved over the course of the year. Results and Conclusion Initial analysis demonstrates an 11% reduction in deceased donation, a 21% reduction in living donation, as well as a 14% reduction in transplants performed. Further analysis will show the impact of policy and guidance recommendations on missed donation opportunities, the impact of how OTDT programs responded in subsequent waves and how certain programs across the country managed to have record numbers of donations and transplants in-spite of the pandemic.

Abstract 8

Presenting Author: Anna Lee **Institution:** University Health Toronto

Abstract Title: The Real-World Effectiveness of COVID-19 Vaccines in a Large Renal Transplant Cohort: An Observational Cohort Study

Abstract Body:

Despite emerging evidence that kidney transplant recipients mount a markedly diminished antibody response to available COVID-19 vaccines, there is minimal data on its real-world effects. Therefore, we conducted an observational cohort study of kidney transplant patients followed by the St. Michael's Hospital Renal Transplant Clinic. COVID-19 vaccination and infection status were recorded for the period between January 2020 and July 2021. Two email surveys and/or a phone survey of all patients followed by the Renal Transplant Clinic were performed from late-May to mid-July 2021. The surveys assessed the following: (1) vaccine awareness, (2) vaccination status (dates of 1st/2nd dose of COVID-19 vaccine and manufacturer type), and (3) COVID-19 infection and outcomes (if yes, date of infection, hospitalization, ICU admission, intubation, and death). Demographic information and patient characteristics likely to influence COVID-19 infection and severity were collected. Preliminary data on 1798 of a total of 1803 renal transplant recipients (99.7%) has revealed that as of July 2021, 86% had received a 1st dose of a COVID-19 vaccine, and 78% had received a 2nd vaccine dose (Figure 1). A total of 123 patients had a documented SARS-CoV2 infection. The vast majority of COVID-19 infections in our renal transplant cohort to date occurred amongst unvaccinated patients or those ≤14 days after their 1st dose (Table 1). The occurrence of COVID-19 infections amongst transplant patients mirrored trends amongst the larger Toronto and Ontario communities. As of July 2021, the third wave of infections in Ontario is receding and most patients have received their second dose. Further time-varying-covariate analyses are planned to determine whether the observed decline in COVID-19 infections in our cohort result from declining community infection rates, or also reflect COVID-19 vaccine-conferred protection.

Abstract 9

Presenting Author: Stefani Mihilli **Institution:** University Health Network

Abstract Title: Post-transplant diabetes mellitus (PTDM) is associated with distinct risk factors based on timing of onset in kidney transplant recipients (KTRs)

Top 3 - Abstract Award

Abstract Body:

Background: The relative impact of traditional risk factors for post-transplant diabetes mellitus (PTDM) may vary depending on the timing of PTDM development. The aim of this study is to determine the incidence, risk factors, and outcomes of early and late PTDM in kidney transplant recipients (KTRs). Methods: A single-centre, observational cohort study was conducted among adult KTRs (≥18 years) transplanted from January 1, 2000 to December 31, 2017. PTDM was defined as early if it occurred within 3-months post-transplant and late if it occurred between 3 to 36 months post-transplant. The incidence of early and late PTDM was quantified using the person-time approach. Multivariable Cox proportional hazards models were fitted to evaluate the independent risk factors for early and late PTDM. Results: A total of 1364 KTRs were included in the analysis. The incidence rates of early vs. late PTDM were 56.5 (95% CI: 48.7, 65.6) vs. 7.4 (95% CI: 6.4, 8.5) cases per 100 person-years, respectively. Every 1-year increase in age was associated with a comparably increased relative hazard of early (HR 1.06 [95% CI: 1.04, 1.07]) and late PTDM (HR 1.05 [95% CI: 1.03, 1.06]). Non-white KTR race significantly increased the relative hazard of late (HR 1.74 [95% CI: 1.20, 2.51]) but not early (HR 1.25 [95% CI: 0.86, 1.82]) PTDM. Interestingly, KTRs transplanted from 2013 to 2017 were less likely to develop early PTDM, but more likely to develop late PTDM, vs. KTRs transplanted from 2000 to 2007. Conclusion: The results suggest recent improvements in preventing early PTDM, yet there exists a need to address late PTDM. Furthermore, the risk factors for early versus late PTDM may differ. A better understanding of these risk factors can inform more targeted preventive interventions.

Abstract 10

Presenting Author: Faisal Jarrar **Institution:** Dalhousie Medicine

Abstract Title: The Impact of Donor and Recipient Body Mass Index on Graft Survival Outcomes after Kidney Transplantation

Abstract Body:

Background: Obesity is becoming increasingly prevalent in the renal transplant population and amongst waitlisted transplant candidates. Recipient obesity is a risk for adverse outcomes after transplant including delayed graft function, graft failure, and increased healthcare expenditure. However, the potential interaction between kidney transplant donor and recipient (DR) obesity on graft outcomes is unknown. Methods: We used the SRTR to identify recipients of a kidney transplant (live or deceased) from January 2000-December 2016. We dichotomized DR obesity status at a BMI cut point of 30 kg/m2 to identify four DR pairings: i. non-obese DR (NOD-NOR), ii. obese donor-non obese recipient (OD-NOR), iii. non obese donor-obese recipient (NOD-OR), iv. obese DR (OD-OR). We used multivariable Cox proportional hazards models to determine the relative hazard for death-censored graft loss (DCGL) and all-cause graft loss, for each DR obesity pairing. We used multivariable logistic regression to determine the odds ratio for delayed graft function and early (≤30 day) graft survival. Finally, we determined if there was an interaction between donor and recipient obesity for each outcome. Results: 153,737 transplant recipients were included in the analysis; 19.6% developed DCGL. 40.0% and 49.7% of donors and recipients were noted to be obese, respectively. The adjusted relative hazard for DCGL was highest in the OD-OR pairing (HR 1.26, 95% CI 1.22-1.32) relative to NOD-NOR. Time to DCGL is shown in Figure 1. The adjusted risk for all outcomes by DR obesity pairing is shown in Table 1. Donor obesity modified the association between recipient obesity and both DCGL ($p=0.001$) and all-cause graft loss ($p<0.001$). Conclusion: Both donor and recipient obesity are associated with adverse outcomes after kidney transplant (obese donor-obese recipient combination highest risk for all outcomes). Donor obesity modifies the association between recipient obesity and risk of both DCGL and all-cause graft loss.