Abstracts of the 2022 Banff-CST Joint Meeting

The CST's annual scientific meeting provides a forum for the transplantation community to share ideas, leading practices, innovative science, and educational content in transplant care. This year's meeting brought together members of the Banff Foundation for Allograft Pathology and the Canadian Society of Transplantation for a hybrid event, combining both in-person and virtual experiences, and helping us reach an even wider audience. **The 2022 Banff-CST Joint Meeting was held at the Banff Centre for Arts and Creativity and ONLINE, September 19 - 23, 2022.** With over 600 Canadian and International delegates attending, the 2022 Banff-CST Meeting received outstanding educational programming, but also rare opportunities to connect with Transplantation professionals from all over the world**.**

The Canadian Society of Transplantation may be reached at admin@cst-transplant.ca

ID: 1
Preimplantation Biopsy in Deceased Donor Kidney Transplantation (DDKT)

Raymond Heilman, Mayo Clinic

Abstract Body: Background The value of preimplantation biopsy in selecting kidneys from deceased donors for transplantation remains uncertain. Our aim was to study the impact of preimplantation biopsy findings on the process of selecting kidneys from marginal deceased donors. Methods We conducted a 2-year prospective single center observational study of all preimplant biopsies done on deceased donor kidneys between 6/2019 and 6/2021. Indications for biopsy included donors with acute kidney injury, high kidney donor profile index (KDPI) or other indicators of marginal quality. All biopsies were interpreted by the surgical pathologist on call. The outcomes of interest were glomerular filtration rate (eGFR) at 4 months post-transplant and graft survival for the cohort stratified by the preimplant biopsy status. All continuous data is shown as mean (standard deviation). Results 656 deceased donor kidneys were transplanted during the study period. A total of 530 consecutive biopsies were interpreted of which 235 kidneys (44.3%) were declined. The kidneys declined based on biopsy findings had more chronic changes (figure 1). Among all kidneys transplanted during the study period 295 (45.0%) had biopsy and 361 were transplanted without biopsy. The biopsy cohort had several indicators of inferior donor quality including higher KDPI (55 (25) vs 39 (24), p, donor age (years) (43.4 (14.3) vs 33.1 (14.1), pand donor death from CVA (20.2% vs 10.3%, p. The biopsy cohort had a lower eGFR (ml/min/1.74 m2) at 4-months (51.6 (19.4) vs 58.4 (21.3), pConclusion Graft survival was similar in the cohort of DDKT with preimplant biopsy even though the donor quality was inferior. The utilization of preimplant biopsy in marginal donors is helpful to guide clinical decision making specific to donor-recipient selection and to better maximize post-transplant outcomes.

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ID: 2

Epitope Compatibility to Guide Deceased Donor Kidney Allocation: Recommendations from a Pan-Canadian Online Public Deliberation

Louisa Edwards, University of British Columbia

Abstract Body: Background: The increasing demand for kidneys, coupled with their scarce supply, necessitates finding ways to reduce rejection and improve transplant outcomes. Longer-lasting kidneys might result from greater epitope compatibility – donor-recipient matching on targeted immune system protein molecules. However, adding epitope-based criteria to deceased donor allocation decisions would alter the current waitlist system for recipients, with transplant outcomes prioritized over wait times. We sought public input to identify trade-offs and guide Canadian policymakers and health professionals in deciding how best to allocate kidneys fairly, should epitope compatibility be adopted. Methods: Postal invitations were sent to 35,000 randomly-selected households across Canada, with over-sampling of rural/remote locations. Participants were selected to ensure socio-demographic diversity and geographic representation. Five two-hour online sessions were held from November-December 2021. Participants received an information booklet and heard from expert speakers prior to deliberating. During small- and large-group facilitated discussions, participants deliberated on how epitope compatibility could be implemented fairly for transplant candidates, and governance issues. Participants collectively generated and voted on recommendations on these topics. In a final policy panel session, kidney donation and allocation policymakers engaged with participants. All sessions were recorded and transcribed. Results: Thirty-three participants (18 female, 15 male) took part and generated nine recommendations. There was consensus on adding epitope compatibility to the existing deceased donor kidney allocation criteria. However, participants recommended including safeguards and flexibility around this (e.g., mitigating declining health). They specified that a transition period was needed before implementing epitope compatibility, which included an ongoing comprehensive public education program. Participants unanimously recommended regular monitoring of outcomes of epitope compatible transplants, and noted that this should be publicly shared. Conclusion: Participants supported adding epitope compatibility to kidney allocation criteria, but wanted safeguards and flexibility around implementation. These recommendations can provide guidance to policymakers regarding including epitope-based deceased donor allocation criteria.

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ATN-like ABMR transcriptome is similar to acute active ABMR in early post-transplant period

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Abstract Body: Background: Banff classification describes ATN-like ABMR as an active ABMR with C4d depositions, presence of circulating DSA, and ATN-like minimal inflammation. However, molecular phenotype of ATN-like ABMR remains unclear. Methods: Intragraft transcriptome of ATN-like ABMR (n=8) was compared to active ABMR (C4d and DSA positive, g>1) (n=8), DSA positive pure ATN (n=8) and DSA negative pure ATN (n=8) by RNA sequencing. All biopsies were performed early after transplantation (median 8 days) and all patients received T cell depletive induction treatment. The differential gene expression and gene annotation analyses were performed using DESEq2 and FGSEA, respectively. Results: ATN-like ABMR in the early post-transplant period cannot be distinguished from early ABMR as shown by unsupervised PCA analysis of intragraft transcriptome (Fig.1A). Fast gene set enrichment analyses based on pre-ranked transcripts lists were generated for each group's comparison and intersections among GO terms were displayed using Upset Plot (Fig.1B). ABMR, ATN-like ABMR and ATN DSA positive groups when compared to ATN DSA-negative group showed upregulation of 31 GO terms involved in adaptive immune response, antigen receptor signaling, B cells and complement activation (Fig.1C). ABMR and ATN DSA-positive groups compared to ATN DSA-negative group shared 39 GO terms associated with innate immune response, T cell activation and cytokine production. Conclusion: Transcriptome of ATN-like ABMR is similar to active ABMR with less activation of innate immune response and T cell activation.

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ID: 5

The reverse transcriptase multiplex ligation-dependent probe amplification (RT-MLPA) assay as a simple molecular tool for diagnosis and classification of rejection in formalin-fixed paraffin-embedded kidney transplant biopsies.

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Abstract Body: Background The Banff Classification for Allograft Pathology recommendations for the diagnosis of kidney transplant (KT) rejection includes molecular assessment of the transplant biopsy. However, implementation of molecular tools in clinical practice is still limited, partly due to the required expertise and financial investment. The reverse transcriptase multiplex ligation-dependent probe amplification (RT-MLPA) assay is a simple, rapid and inexpensive assay that permits simultaneous evaluation of a restricted gene panel using paraffin-embedded tissue blocks (abstract image 1) Methods A bicentric cohort of 220 KT biopsies, with 52 antibody-mediated rejection (AMR), 51 T cell-mediated rejection (TCMR) and 117 no-rejection controls was assessed. The RT-MLPA assay allows the simultaneous evaluation of a panel up to 20 genes. Based on the knowledge of pathways involved in the pathophysiology of rejection and previously published data about molecular diagnosis in KT using Affymetrix and Nanostring, 30 genes of interest were selected. A 17-gene panel was identified, including genes significantly associated with at least one of these diagnoses. A support vector machine classifier (SVM) was developed. A subset of 109 biopsies was also assessed using the Nanostring B-HOT panel to compare the two assays. Results The SVM classifier train and test accuracy scores were 0.84 and 0.83, respectively. In the test cohort, the F1-score for AMR, TCMR and control were 0.88, 0.86 and 0.69, respectively (abstract image 2). Using ROC curves, AUC for class predictions were 0.96, 0.89 and 0.91, respectively, with a weight-average at 0.94. Gene expression levels assessed by RT-MLPA or Nanostring correlated: r = 0.68, p Conclusions The RT-MLPA assay is simple molecular tool which can be used on FFPE KT blocks to aid the diagnosis and classification of rejection.

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HLA-II subclasses behave differently between themselves and between humans: cues to understand alloreactivity

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Abstract Body: De novo anti-HLA-II DSAs are associated with ABMR. However, some patients with anti-HLA-II DSAs will not develop rejection, suggesting that the development of antibodies is not sufficient to trigger the process. We hypothesized that a determinant of rejection is the expression of the associated HLA-II antigen on the endothelial cells and that this expression varies between individuals and between subclasses (DR, DP and DQ) within the same individual. To examine the expression of HLA-II antigens on endothelial cells, we generated endothelial-colony-forming cells (ECFCs) from PBMC samples biobanked from patients and healthy volunteers (n=31). ECFCs were activated by 10-day time-course with IFN-γ. HLA-I and II (DR, DP and DQ subclasses) expression was measured by flow cytometry and IF-microscopy for ECFCs and PBMCs from the same individual. The relationship between the level of expression of HLA-II and specific alleles was analyzed by a multivariate model. On ECFCs, we found a high variability for HLA-DQ expression between individuals ranging from 0% to 86% (standard deviation of 28%). HLA-DR and DP expression were more similar (standard deviation of 3% and 8% respectively). In the cohort, the percentage of ECFCs expressing HLA-DQ correlated with the percentage found on CD14+ cells. Analysis of the HLA typing revealed that patients who had the DQ5 and DQ6 alleles had substantially more HLA-DQ antigen expression (13±6 vs. 37±11% positive cells and 10±5% vs. 39±11% for DQ5 and DQ6 respectively; p=0.03 and 0.01 respectively). On the opposite, DQ7-patients had substantially less endothelial surface expression of the antigen (42±10 vs. 7±5%, p=0.03). These data suggest an underappreciated heterogeneity in HLA expression on endothelial cells, which could be predictable by HLA typing. These results are clinically relevant since most anti-HLA antibodies are directed against HLA-DQ. Our observations could explain why some patients do not develop ABMR despite the development of anti-HLA DSAs.

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Cytomegalovirus Infection and Risk of New-Onset Diabetes after Transplantation: A Retrospective Study

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Abstract Body: Abstract: Background: New-onset diabetes after transplantation (NODAT) is one of the common complications reported in patients with kidney transplant and is associated with risk of infection, poor allograft and patient survival. There is conflicting research literature regarding the role of cytomegalovirus (CMV) infection in increasing the risk of NODAT development. Objective: To assess the risk of development of NODAT in kidney transplant patients with CMV infection Methods: A total of 59 kidney transplant patients were studied from March 2017 to February 2019. NODAT was defined as two readings of fasting plasma glucose of ?126 mg/dL at three months post-transplant. CMV viral load was also documented. The 12 months post-transplant allograft and patient survival outcomes were also measured. Results: Mean age was 43.4 ± 6.2 years. Nearly one-fourth, 14 (23.7%), of the patients had NODAT. CMV viral load and viremia were high in NODAT group; however, the result did not reach statistical significance. CMV DNA replication was statistically high during 1-6 months post-transplant for NODAT group (P symptomatic CMV infection. Also, we found that high CMV viremia load was associated with poor kidney allograft function at 12 months. Conclusions: In summary, this study showed that infection with CMV may not be a risk factor to develop NODAT in patients transplanted with kidney. An elevated CMV viral load may decrease the post-transplant allograft function at 12 months. The prompt diagnosis and timely 2 management of CMV infection could substantially lessen the risk to develop NODAT subsequent worsening of allograft and patient survival.

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Meta-analysis of Association between TCF7L2 rs7903146 and Risk of New-Onset Diabetes After Transplantation

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Abstract Body: Abstract Background: Single nucleotide polymorphisms may influence the risk of development of new-onset diabetes after transplantation (NODAT), a post-transplant clinical complication that is often implicated in allograft rejection and mortality. We performed a meta-analysis of association between TCF7L2 rs7903146 and risk of post-transplant diabetes mellitus. Methods: A systematic search was conducted using PubMed and ScienceDirect electronic databases for studies published between January 2001 to January 2021. Case-control or cohort studies reporting association between NODAT (diagnosis based on American Diabetes Association [ADA] criteria) and TCF7L2 rs7903146 were included. MetaGenyo was used for meta-analysis (random effects model). Pooled odds ratios with 95% confidence intervals were reported to evaluate the strengths of association. Results: Two reviewers independently screened for articles. A total of six case-control studies were included for full-text review and quantitative analysis after screening for eligibility. Genotypic distributions were in Hardy-Weinberg equilibrium for included studies. All papers reported statistically significant association of TCF7L2 rs7903146 for risk of NODAT, except for one study. There was moderate heterogeneity among studies (I2 = 60.6%). Pooled analysis revealed 51% odds of developing NODAT with TCF7L2 rs7903146 T allele (Allele Contrast Model: OR = 1.51, 95% CI 1.13 – 2.02, adjusted p = 0.03). Conclusion: The present meta-analysis demonstrated association between TCF7L2 variant rs7903146 and risk of developing NODAT. This finding may have clinical implications for individuals undergoing kidney transplantation. Abstract Background: Single nucleotide polymorphisms may influence the risk of development of new-onset diabetes after transplantation (NODAT), a post-transplant clinical complication that is often implicated in allograft rejection and mortality. We performed a meta-analysis of association between TCF7L2 rs7903146 and risk of post-transplant diabetes mellitus. Methods: A systematic search was conducted using PubMed and ScienceDirect electronic databases for studies published between January 2001 to January 2021. Case-control or cohort studies reporting association between NODAT (diagnosis based

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HLA TYPING USING NANOPORE TECHNOLOGY: A BETA TESTING STUDY

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Abstract Body: BACKGROUND & METHODS: We explored the benefits of nanopore sequencing for HLA typing in a beta testing study in collaboration with Omixon Ltd. and Oxford Nanopore Technologies (ONT) Ltd. Ninety-nine genomic DNA samples extracted from peripheral blood and buccal samples, previously typed at high resolution level using the 2nd generation NGS method, were tested using the Omixon NanoTYPE™ multiplex kit. Protocols with enzyme-based and magnetic bead purification were also compared. RESULTS: Results for class I loci (HLA-A, -B, -C) were 99% concordant at three-field typing. One new allele was detected and one HLA-B locus dropout (HLA-B*51:01:02) was observed. For two samples, typing of HLA-B*44:03:01 was reported as an ambiguous combination with HLA-B*44:336. Results for HLA-DRB1/3/4/5 and HLA-DQB1 were also 99% concordant with previous results. We observed two HLA-DQB1*03:01:01 dropouts, one HLA-DQB1*03:19 dropout, and one HLA-DQB1*04:02 dropout. We observed one instance of an incorrect typing of HLA-DRB1*04:58N, resulting from low amplification of HLA-DRB1*04:01:01. Results for HLA-DQA1, -DPA1, and -DPB1 loci were 100% concordant with previous results. The library preparation time was significantly reduced using enzyme-based purification in place of magnetic beads. We also typed three samples in a mock deceased donor typing scenario, with adjustments to sequencing times, to test the accuracy and reproducibility of the results. NanoTYPE™ was able to deliver three-field, high-resolution typing with 100% concordance for these samples. CONCLUSION: Nanopore-based HLA typing using the NanoTYPE™ kit is advantageous in allowing shorter turnaround times for multiple samples and is more cost-effective than traditional NGS methods. With refinements to the method to prevent allele dropouts, it will constitute a useful tool for HLA high-resolution typing. Reduction of the PCR amplification time would make this a feasible typing method to provide high-resolution HLA typing of deceased donors, resulting in greater availability of organs for highly sensitized patients.

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Apoptotic exosome-like vesicles mediate immune response dysregulation and kidney dysfunction following ischemia-reperfusion injury

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Abstract Body: Background: Ischemia-reperfusion injury (IRI) is integral to kidney transplantation. IRI-induced peritubular capillaries (PTC) rarefaction predicts progressive renal failure, especially in older kidneys. We previously reported that circulating anti-LG3/perlecan autoantibodies in renal transplant patients predict poor graft survival. Also, ApoExo, which are exosome-like vesicles produced by apoptotic endothelial cells and characterized by the LG3 autoantigen, active 20S proteasome, and ability to induce anti-LG3 production, modulate PTC rarefaction and fibrosis post-IRI. Here, we test the hypothesis of an ApoExo-mediated dysregulation of immune response post-renal IRI, enhancing anti-LG3 and tertiary lymphoid structures (TLS) formation and renal dysfunction with age. Methods: Unilateral renal pedicle clamping for 30 minutes with contralateral nephrectomy were performed in young (8 weeks) and old (28 or 56 weeks) mice. ApoExo were purified from serum-free medium conditioned by apoptotic murine endothelial cells and injected to mice every other day. End-points were assessed 21 days post-IRI. ApoExo and anti-LG3 circulating levels were measured by proteasome activity and ELISA, respectively. Splenic follicular helper T (Tfh) and germinal center B (gcB) cells were analysed by FACS. Lymphoid aggregates were assessed by immunohistochemistry for CD3/CD20. Renal damage was monitored by PTC congestion, tubular injury, and BUN level. Results: ApoExo and anti-LG3 circulating levels increased with age post-IRI. After renal IRI, old mice showed enhanced activation of splenic Tfh and gcB-cells, and increased numbers and sizes of intra-renal CD3+aggregates organized into TLS. PTC congestion, tubular damage and renal dysfunction were also worsened by age. ApoExo injection post-IRI further increased splenic Tfh, gcB-cells, and anti-LG3 levels in old mice, associated with further increased and larger CD3+aggregates with TLS formation, and aggravated renal damage. Conclusion: Our results suggest that ApoExo favor progressive renal dysfunction post-IRI, especially in older subjects, at least in part through increased splenic GCs response, intra-renal TLS formation and anti-LG3 production contributing to enhanced microvascular damage.

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ID: 13

Organ Donation Following Medical Assistance in Dying: A Scoping Review

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Abstract Body: Background: While more countries are legalizing Medical Assistance in Dying (MAiD), only Canada, Netherlands, Belgium and mostly recent Spain, allow for controlled organ donation following MAiD. To support updates in the practice guidelines and ensure safety and ethically acceptable procedures for organ donation following MAiD, we examined the current international literature on the existing processes, outcomes and ethical debates regarding organ donation following MAiD. Methods: Scoping review following JBI methodology. Databases included Ovid MEDLINE, Ovid Embase, CINAHL via EBSCOhost, Ovid PsycINFO, Web of Science – Science Citation Index and Social Science Citation Index via Clarivate, and Academic Search Complete via EBSCOhost. Gray and unpublished literature included materials from organ donation organizations. Studies of any design were considered if they discussed organ donation following MAiD at home or in any healthcare setting in any country. Articles were screened, and data extracted and analyzed using a content analysis approach by two independent reviewers. Results: 1879 reports were identified and 121 were included. The reports were in English (n=95), Dutch (n=17) and French (n=9); majority from Canada (n=51), The Netherlands (n=38), and Belgium (n=14), published between 2019-2021 (n=57). Our content analysis identified several major theme areas: the main processes and procedures involved in organ donation after MAiD in the hospital and at home; the main clinical pathways involved in different settings; ethical dilemmas involved in this combined procedure; healthcare professionals' roles and perceptions; impacts on the organ donation system; transplant outcomes; public perceptions; safety processes and tools in place; educational strategies for healthcare professionals involved; and suggestions for future research to address knowledge gaps. Conclusion: The results of this review provide important directions for improvements in the current organ donation after MAiD and the transplantation system. The findings can also be used as a rich source of information for countries with organ donation following MAiD.

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ID: 14
Noninvasive prediction of subclinical graft injury after liver transplantation using peripheral blood microparticles

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Abstract Body: Background Graft biopsies (Lbx) are still the gold standard for identifying graft injury such as acute or chronic rejection. However, Lbx come with a risk of bleeding due to their invasiveness, as well as causing high costs and requiring patients to visit a transplant center. The detection of specific biomarkers could therefore be helpful in diagnosing (subclinical) rejection. Methods This study aimed at comparing peripheral blood levels of microparticles (MP) in patients with clinical overt T cell-mediated rejection (clinTCMR; n=16) in comparison to stable liver transplant recipients (LTR) (liver enzymes Results Frequencies of MP with positivity for CD4, CD39, ASGPR, Cx43, HLA class I, CD39+Annexin V, CD31+Annexin V or Cx43+Annexin V were significantly associated with clinTCMR in comparison to stable LTR. However, only MP with positivity for CD31+Annexin V (AUC .797), HLA class I (AUC .703) or CD31 (AUC .760) were significantly associated with the presence of subclinical TCMR within stable LTR. In addition, only CD4+ MP were significantly associated with the presence of relevant subclinical graft injury according to the 2016 BANFF criteria for immunosuppression reduction (AUC .676) within stable LTR. Conclusion These results match previous studies, indicating that quantification of peripheral blood MP can be useful but is not yet a reliable diagnostic tool for a non-invasive detection of subclinical graft rejection in surveillance biopsies in a cross-sectional approach.

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ID: 15

Prospective comparison of liver stiffness measurement methods in surveillance biopsies after liver transplantation

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Abstract Body: Background Liver stiffness measurements (LSMs) have proven useful for non-invasive detection of fibrosis. Previous studies of LSMs after transplantation were performed in cohorts dominated by hepatitis C reinfections and indication biopsies for the evaluation of graft dysfunction. However, the diagnostic fidelity of LSMs for fibrosis is biased by inflammation e.g., during replicative hepatitis C or rejection. Methods The current study aimed for a head-to-head comparison of two different LSMs, acoustic radiation force impulse (ARFI) and transient elastography (TE), and a determination of cut-off values for the detection of advanced fibrosis (Ishak F?2) in grafts undergoing surveillance biopsies (svLbx) without recurrent hepatitis C. Results 115 svLbx were paired with valid LSMs at time of biopsy. AUROC analyses showed significant positive correlation with fibrosis for both methods (TE: AUROC=0.853 (p Conclusion LSM is a good non-invasive tool to screen for advanced graft fibrosis but not for relevant graft injury in patients with normal/near normal liver enzymes. Fibrosis cut-off values identified and validated in svLbx were lower than in previous cohorts using indication biopsies.

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Evaluation of pediatric kidney biopsies with chronic active (ca) mixed T-cell (TCMR) and antibody mediated rejection (ABMR) by gene expression profiling

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Abstract Body: BACKGROUND: The antibody and T-cell limbs of the human immune system are both capable of mounting an immune response to allogeneic antigens. As a result, biopsies with mixed TCMR and ABMR) are encountered in clinical practice. Histologic assessment of the relative contributions of these two processes is difficult. Molecular diagnostics offers a prospective solution to this problem. METHODS: Five pediatric renal transplant biopsies with mixed caTCMR and caABMR performed 3.48 to 10.03 yeas after transplantation were sent for analysis by the MMDx® Molecular Microscope System. Histologic findings were correlated with molecular features. RESULTS: The pure molecular interpretation of these biopsies was always ABMR (two early stage, 3 full developed, none cg2 or cg3 by histology). No TCMR was detected in any biopsy despite the presence of t2/t3 tubulitis in all biopsies (median t>1 molecular probability 0.10, IQR 0.07). High Banff histologic tubulitis/inflammation scores were not always associated with high molecular scores. The correlation was poor: Linear Trend Function R^2 0.002/0.142 and Pearson R -0.041/-0.377 respectively (Figures 1-3). This poor agreement can be attributed to the 3mm fragment taken for molecular analysis not capturing areas with the worst lesion severity in the biopsy. Agreement of molecular scores with g/ptc scores was better (R^2=0.252/0.643, consistent with more diffuse ABMR lesions being present in the tissue. Bioinformatics noise of upto 0.17 units (on a 0-1 scale) was observed in molecular ABMR scores generated from the same gene expression data analyzed by three ABMR models. CONCLUSIONS: MMDx® did not recognize the TCMR component of mixed caTCMR/ABMR in any biopsy. Potential causes for this finding include sampling issues, thresholding effects, and the use of molecular classifiers for acute TCMR to probe biopsies with caTCMR. Caution is indicated in using molecular lesion scores as a substitute for Banff histology scores, since the coefficients of variations are undefined, and appropriate clinical validation studies have not yet been performed.

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ID: 17

Time to First Cytomegalovirus Viremia Clearance in Transplant Recipients with Refractory Cytomegalovirus Infection With or Without Resistance Receiving Maribavir Versus Investigator-Assigned Therapy: Subgroup Analyses of a Phase 3 Trial

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Abstract Body: Background: In the Phase 3 SOLSTICE study of haematopoietic cell/solid organ transplant (HCT/SOT) recipients with refractory cytomegalovirus (CMV) infection with/without resistance (NCT02931539), maribavir was superior to investigator-assigned-therapies (IAT; val/ganciclovir, foscarnet or cidofovir) for CMV clearance at Week 8 and maintenance of CMV clearance plus symptom control from Week 8 to Week 16. This post-hoc analysis reports time to first CMV clearance in subgroups at study Week 8. Methods: Transplant recipients with confirmed CMV infection were randomized 2:1 to maribavir (400 mg BID) or IAT for 8 weeks' treatment, with 12 weeks' follow-up. Time to first CMV clearance (2 consecutive measurements of plasma viral load[VL] first date of two consecutive CMV DNA results meeting clearance minus the randomization date plus 1 day; patients without CMV clearance by Week 8 were censored on the last CMV assessment date before initiating rescue/alternative anti-CMV treatment. Post-hoc subgroup analyses were performed by baseline resistance status, VL (low, < 9 ,100; intermediate/high, ?9,100 IU/mL [plasma]) and transplant type. Data were summarized using Kaplan–Meier method. Results: 352 patients were randomized (235 maribavir, 117 IAT). Median time (days) to first CMV clearance in patients with baseline resistance was 27.0 for maribavir and 44.0 for IAT; without resistance 17.0 and 22.0, respectively; in patients with low baseline VL, 15.0 for maribavir and 22.0 for IAT; with intermediate/high VL, 43.0 and 44.0, respectively (Table). Median time (days) to first CMV clearance was 25.0 for maribavir and 30.0 for IAT in SOT recipients, and 15.0 and 22.0 in HCT recipients, respectively (Table). Conclusion: These post-hoc subgroup analyses are consistent with the previously reported pre-specified analysis from SOLSTICE, where time to first confirmed CMV clearance was shorter for maribavir than IAT in the randomized set.

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ID: 18

Regulatory Gene Pathways in Quilty Lesions Are Associated With Cardiac Allograft Acceptance

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Abstract Body: Background. Quilty lesions (QL) are sub-endocardial lymphoid aggregates commonly found in biopsies from heart transplants. Their appearance and presence in the cardiac tissue is still a mystery, without clear evidence of their relationship with rejection or acceptance of the allograft. Methods: 42 heart allograft biopsies from one institution were included in the study. Immunohistochemistry (IHC) was performed for the T-cell markers CD4 and CD8, and the immune regulatory markers Fox-p3 and TGFbeta-1. A sub-set of 9 of these biopsies, 5 with QL and 4 without QL were selected for RNA extraction and gene analysis using the Nanostring n-Counter Human Orghan Transplant Immunology Panel (Seattle, WA). Results. Biopsies with TGFbeta-1 (OR 1.4, p < 0 .05) and Foxp3 (OR 1.3, p < 0 .05) positive stain in QL were associated with better allograft acceptance. CD4 and CD8 stain in QL were not associated with rejection, however. interstitial CD4+< 0 .04) and C < 8 + (p < 0 .02) T-cells were associated with rejection.The sub-set of biopsies with QL showed a predominance of adaptive type Th2 response over Th1 genes (3.88x vs. 3.15x). Particular regulatory genes (all p< 0.001) that were higher in biopsies with QL included TGFbeta1, IL10RA, Foxp3 and JAK3. Other pathways analyzed shows anupregulation of genes of cell-extracellular matrix interaction, adaptive immune response, innate immune response, Th17 mediated biology, T-reg differentiation, TGF-beta signaling, TNF family signaling and type I interferon signaling in biopsies with QL. Conclusion. Heart allograft biopsies with QL showed a predominance of regulatory signals by both IHC and RNA gene analysis compared to biopsies without QL. QL, far from being passive bystanders, may have an immunomodulatory function in cardiac allografts.

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ID: 19

Immunemodulation Induced Pleuroparenchymal Fibroelastosis in Lung Transplant Recipients For Usual Interstitial Pneumonia

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Abstract Body: Background: Pleuroparenchymal fibroelastosis (PPFE) is a rare but distinctive manifestation of interstitial lung disease (ILD) characterized by a highly elastotic pattern of lung fibrosis. Its etiology is not known. The purpose of this study was to explore the underling pathogenesis of this condition by looking at an interesting group of patients with Usual Interstitial Pneumonia (UIP) that underwent a single lung transplant, and subsequently developed PPFE in the native lungs left in the recipients. Methods: Cases were identified in our pathology database. Total RNA was extracted from paraffin embedded tissue of explanted native lungs before and after the single lung transplant. Multiplexed mRNA measurement was performed using nCounter and fibrosis panel (NanoString Technologies). Results: Four patients were identified who had unilaterally lung transplantation for fibrotic interstitial lung disease (UIP). In all these patients the 2nd native lung tissue was subsequently analyzed because the patient developed a malignancy (2 patients) or received 2nd lung transplant (1 patient) or passed away (1 patient). The native lungs, initially diagnosed as UIP, showed the phenotype of PPFE. All four patients were taking the same immunosuppressive regimen of tacrolimus, azathioprine, and prednisone. PPFE was diagnosed between 12 to 48 months after lung transplantation. Comparing the mRNA expression in explanted lungs with UIP at transplantation, the lungs with PPFE showed an upregulation of lymphotoxin beta (LTB), CD8A, AMOLT2 (Angiomotin like 2), RAC3 (Rac family small GTPase 3), and BCL2 by 3.83, 2.81, 2.1, 1.93, and 1.72 in log 2 folds, respectively, which are involved in the regulation of NF-kappa B, Hippo, Wnt, and Hedgehog signaling pathways (all $p < 0$ .001). Conclusions: Not reported before, we show here that after following a similar post-transplant immunosuppresion regime, 4 patients initially diagnosed with UIP, developed the phenotype and genotyope of PPFE, indicating therfore a inmmunemodulation mechanisms in the process.

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ID: 21

Risk factors for developing low eGFR and albuminuria in living kidney donors

Anisha Dhalla, University of Calgary

Abstract Body: Background: Chronic kidney disease is associated with significant morbidity and mortality in the general population, but little is known about the incidence and risk factors associated with developing kidney dysfunction in living donors following nephrectomy. Methods: We conducted a retrospective, population-based control study using linked healthcare databases in Alberta, Canada to identify 590 donors who underwent nephrectomy between May 2001 and December 2017. The primary outcome was evidence of sustained kidney dysfunction following nephrectomy, defined as either 2 estimated glomerular filtration rate (eGFR) measurements Results: Over a median follow-up period of 8.6 years (interquartile range [IQR]: 4.7-12.6 years), 47 donors (8.0%) developed sustained kidney dysfunction, with an incidence rate of 9.2 per 1,000 person-years (95% confidence interval: 6.6-11.8). The median time for development of kidney dysfunction beyond the first year after nephrectomy was 2.9 years (IQR: 1.4-8.0 years). After adjustment, an increase in pre-donation eGFR by 5 mL/min per 1.73 m2 decreased the hazard of developing kidney dysfunction in the first four years after donation by 21% (aHR 0.680.790.91). Furthermore, donors were at higher risk of developing kidney dysfunction if they had evidence of pre-donation hypertension (aHR 1.282.555.07) or post-donation diabetes (aHR 1.234.5616.81). Conclusion: A small proportion of kidney donors will develop post-donation kidney dysfunction. Donors with risk factors associated with sustained kidney dysfunction may benefit from more diligent follow-up care.

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ID: 22

Does a higher CO2 concentration during normothermic machine perfusion of the pancreas improve the results?

Catherine Parmentier, University Health Network / Toronto General Hospital

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Abstract Body: Background: Pancreas transplantation is the only curative treatment for patients with diabetes mellitus. However, organs available for transplantation are scarce and the waiting list increases every year. Strategies to preserve, assess and repair pancreas allografts are needed. Our lab has previously proven that normothermic perfusion of the pancreas in swines is feasible and safe. Carbon dioxide is a vasodilator that has proven to be useful to decrease intravascular resistance in the brain. The aim of this study was to analyze the effect of a higher CO2 concentration during normothermic perfusion. Methods. All cases were perfused for 3 hours with identical parameters except for CO2 concentration. Four cases were perfused with a CO2 concentration of 5%, five cases with a CO2 concentration of 9% and 2 cases were perfused with a concentration of 9% and transplanted after the perfusion. Arterial pressure and flow were measured throughout the perfusion and used to calculate the intravascular resistance. Amylase was also measured hourly in all cases during perfusion and once a day for the transplantation cases until POD 3. Results: There was a significant effect of CO2 concentration on intravascular resistance, being lower in the cases perfused with a higher CO2 concentration. (Figure 1) Amylase was also significantly lower during perfusion in the higher CO2 concentration cases (Figure 2). Two grafts were successfully transplanted after the perfusion with a CO2 concentration of 9% with no complications and practically a normal level of amylase on POD3. Conclusions: Higher CO2 concentration appears to be a useful method to decrease intravascular resistance without compromising the pancreas function during perfusion and after transplant. Further studies are needed but the results are very encouraging.

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ID: 23

Clinicopathological and molecular characteristics of plasma cell rich rejection in renal transplant biopsies

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Abstract Body: Background Plasma cell rich rejection (PCRR) is a rare, ill-defined type of renal allograft rejection. It is currently considered a subtype of acute T-cell mediated rejection (TCMR), but research suggested PCRR has poorer clinical outcome and is often refractory to classic immunosuppressive therapy. We studied the clinical course, Banff lesion scores and mRNA expression of PCRR compared to late rejection episodes in large cohort of renal allograft biopsies. Methods We retrospectively scored and reclassified the last known biopsy of N=280 renal transplant recipients, morphologically classified as rejection. Cases were scored according to the 2019 Banff classification for elementary lesion scores and diagnostic classes. mRNA expression analysis was performed with Nanostring B-HOT panel on a subset of cases. PCRR was compared to patients/biopsies with late TCMR, ABMR and mixed rejection for eGFR follow-up and graft survival. Results Nanostring mRNA analysis identified signatures of differentially expressed genes in PCRR versus late TCMR and ABMR including LOX, CPA3, IL4, IL12RB2, IL17F and CH25H. Gene set enrichment analysis suggested that PCRR is enriched for genes related to (activated) mast cells, memory B- and T-cells. Principal component analysis showed large differences in gene expression within the group of biopsies with PCRR (heterogeneity). Pseudotime analysis suggested PCRR might be a late event compared to late TCMR and ABMR, with a higher degree of total inflammation and IFTA. Patients with PCRR did not seem to have a poorer graft survival or decline in kidney function during a 5 year follow-up period after renal biopsy, compared to late TCMR, ABMR or mixed rejection, although anti-rejection treatment was not taken into account yet. Conclusion Our results suggest PCRR is a type of rejection with heterogeneous gene expression patterns different from late TCMR and ABMR, without significant differences in graft survival or eGFR compared to other late episodes of rejection.

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ID: 24
CD163+ M2 Macrophages in Antibody-Mediated Renal Allograft Rejection

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Abstract Body: Background: M2 macrophages are activated by exposure to cytokines as compared to M1 macrophages that are classically-activated. CD163 is a marker of M2 macrophages. We evaluated M2 macrophage infiltration in renal allograft biopsies diagnosed as active antibody-mediated rejection (ABMR) and compared it with levels of urinary soluble CD163. Methods: The study included twenty renal allograft recipients with indication graft biopsies. Ten patients were diagnosed as ABMR and ten as no evidence of rejection (NER) as per the Banff criteria. Immunohistochemistry for CD163 (clone-EP324) was performed on renal allograft biopsies. Quantitative analysis for CD163+ M2 infiltration in glomeruli and tubulointerstitial compartment was performed for the complete biopsy cores using 40x objective and estimated as cells/10 glomeruli and per 10hpf respectively. Urinary sCD163 level was estimated by ELISA as per the manufacturer's protocol. Results: All patients were males; mean age 33.8±9yrs. Graft biopsies with ABMR had significantly higher glomerular infiltration (35.8±34.7/10 glomeruli) of CD163+ macrophages as compared to NER (3.9±3.6/10glomeruli) (Fig 1). The tubulointerstitial CD163+cells per 10hpf was slightly higher in ABMR (100.8±87.2) than NER (92.3±87.4). The mean level of urinary sCD163 in patients with ABMR was 1.48±1.2ng/ml and it was not detected in NER. The degree of tissue macrophage infiltration significantly correlated with urinary sCD163 levels (r=0.886, p=0.045). Conclusion: We found significantly increased glomerular CD163+ macrophage infiltration and elevated urinary sCD163 in ABMR, demonstrating the activation of alternatively-activated macrophages. Our findings suggest that M2 macrophage-targeted therapy may hold therapeutic potential in ABMR. Further studies are required to understand the prognostic significance of M2 macrophage infiltration in ABMR.

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ID: 26
Exploring the ethical considerations of direct contact in pediatric organ transplantation: A qualitative study

Jordan Wadden, Ontario Shores Centre for Mental Health Sciences

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Abstract Body: Background Non-anonymized direct contact between organ recipient and donor families has been explored in the adult context, including the recent development of such a program in British Columbia. However, there is limited discussion about whether direct contact should be extended to pediatric settings due to clinician and researcher concerns of the potential harms to pediatric patients. Methods This qualitative project draws on narrative interviews with pediatric recipients, their families, and organ donor families. Interview questions fell into three broad categories: developing context, determining the harms and benefits of direct contact, and identifying needs and safeguards. Interviews were conducted in two stages: those who were further removed from the transplant process occurred first and informed the approach to interviews with those who more recently went through the transplant process. Results Twenty-nine individuals participated in twenty in-depth interviews, where some interviews included multiple participants from the same family. Participants were pediatric recipients and families who are now in the adult program (n=13), pediatric recipients and families who are still in the pediatric program (n=11), and family members of organ donors (n=5). The study included participants from three major organ systems: kidney (adult n=3, adolescent n=6), heart (adult n=4, adolescent n=2), and liver (adult n=3, adolescent n=6). Only five participants expressed that direct contact might cause harm or discomfort, while twenty-three indicated they saw significant potential for benefits. Nearly half (n=14) focused instead on the harms to others rather than themselves, and nearly two-thirds (n=20) focused more on the benefits for others. Conclusion This study indicates that direct contact in the pediatric transplant community may provide more benefits than harms to both recipients and donor families. Therefore, current practices employed in protecting patients and families from harm may have moved beyond reasonable measures. These results suggest a need to revisit assumptions in our practice as clinicians and researchers.

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ID: 29
Distinct molecular signatures of TCMR and ABMR after liver transplantation

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Abstract Body: Background: Graft fibrosis and subsequent chronic dysfunction affect up to 1/3 of patients after liver transplantation (LTX). Thereby, the relevance of antibody-mediated rejection (ABMR) as a cause of graft injury, has been questioned recently and very few transplant centers routinely quantify DSA. We aimed to decipher a molecular signature for possible ABMR using RNA-seq. Methods: Seventy-one biopsies from 60 patients were retained from a prospectively collected biorepository at Hannover Medical School and analyzed retrospectively. Possible ABMR (n=16) was defined as graft injury according to 2016 BANFF criteria including presence of DSA (MFI>1000). Comparators were clinical and subclinical T cell-mediated rejection (cTCMR n=11; subTCMR n=26) and normal graft function (NGF n=18). RNA-seq was performed on an Ilumina HiSeq System with 50 million reads from freshly cryoconserved liver tissue. Results: Patients with possible ABMR showed no differences in age or sex compared to cTCMR, subTCMR or NGF. Rejection activity index was comparable between subTCMR, ABMR and cTCMR while ABMR had higher fibrosis (ISHAK staging and liver allograft fibrosis score). About half of ABMR patients also exhibited TCMR features in light microscopy demonstrating the difficulty to distinguish the two entities reliably by histology. However, on the molecular level we could identify a distinct pattern of differentially expressed genes (DEGs) in ABMR which was different from cTCMR. Moreover, unsupervised clustering yielded a good match to given phenotypes (Figure 1). KEGG pathway analysis revealed pathways involved in epithelial cell signaling, TNF-alpha signaling and others as unique for ABMR. Pathways related to allograft rejection, interferon signaling and others were uniquely mapped to cTCMR (Figure 2). SubTCMR and NGF were not relevantly different. Conclusion: We identified a unique signature of possible ABMR not being shared with cTCMR or subTCMR. The finding underscores the potential importance of chronic ABMR in graft inflammation.

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ID: 30

Evaluation of virtual care in kidney transplant recipients in the early post-transplant period

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Abstract Body: Abstract Background Though virtual care was widely adopted during the COVID-19 pandemic, evidence to support the practice in kidney transplant recipients early after transplantation is limited. Objective To determine if there was a difference in post-transplant outcomes in patients who received early transplant care before the COVID-19 pandemic (when care was mainly delivered in person) and during the COVID-19 pandemic (when care was mainly delivered virtually). Design A retrospective cohort study of consecutive kidney transplant recipients Setting St Joseph's Healthcare Hamilton, a quaternary kidney transplant centre in Hamilton, Ontario. Patients The usual care cohort received a kidney transplant between March 1, 2019 to September 1, 2019 (n=69) and virtual care cohort received a kidney transplant between September 1, 2020 and March 1, 2021 (n=64). Patients were followed for 6 months. Measurements We evaluated process measures reflecting care provided during the clinic encounter (e.g., blood pressure), outcome measures examining the effectiveness of care (e.g., estimated glomerular filtration rate, eGFR) and balancing measures examining unintended harm (e.g., hospitalizations). Results Overall, 58% of recipients were male, and 32% received a living donor kidney transplant. At 6 months, the eGFR and blood pressure were not significantly different between groups. The eGFR was 52 mL/min/1.73m2 in the usual care group versus 59 mL/min/1.73m2 in the virtual care group (p= 0.046) and the systolic blood pressure was 136 in the usual care group versus 128 in the virtual care group (p= 0.01). There were more hospitalizations in the usual care group but the difference was not significant (57 versus 29 hospitalizations, p = 0.15), 4.1 hospital days versus 3.7 hospital days, p = 0.21). Conclusions Outcomes were similar and there was no signal of harm. Careful recipient and donor selection during the pandemic (when healthcare resources were limited) may have led to unmeasured differences between groups.

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ID: 31

SARS-COV2 Vaccination could induce HLA antibodies and impact the renal transplant

Yayuan Zhao, USASK

Abstract Body: Background: The most common sensitizing events resulting in the production of HLA antibodies are previous solid organ transplantation, pregnancy, blood transfusions, vaccinations, and severe infections. COVID-19 vaccine has been rapidly and widely used to control the spread of SARS-CoV-2 in the general population. However, the side effects of these vaccines such as the generation of HLA antibodies are not completely known. Therefore, there are concerns over the possibility that COVID-19 vaccination could induce the development of HLA antibodies in waitlisted kidney transplant recipients. Most of our patients received at least 2 doses of COVID-19 vaccines. Re-exposure to repeated antigens from vaccines may trigger reactivation of memory B cells and production of anti-HLA antibodies, leading to unsuccessful matching and premature graft injury and loss. In this study, we aim to evaluate the status of HLA antibodies in waitlist renal transplant patients before and three weeks after each COVID-19 vaccination dose. Method: Sixty-three waitlisted kidney transplant patients are included in this study and HLA antibodies were monitored using the HLA single antigen beads (SAB) from One Lambda by Luminex platform. We also followed the HLA antibodies for 6-months after their last COVID vaccination. Result: Our preliminary cases showed an increase in HLA antibodies after the COVID-19 vaccination [Figure 1]. In the next few weeks, further analysis will be provided to identify the specificity of HLA antibodies and to conclude whether these antibodies are persistent or transient in nature. Conclusion: We hypothesize that vaccination could, at least in a subgroup of patients on the kidney transplant waitlist, lead to the generation of anti-HLA antibodies. We anticipated that the finding of this study could guide transplant physicians regarding the need to repeat HLA antibody testing prior to kidney transplantation after COVID-19 infection or vaccination.

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ID: 32

A machine learning time series analysis strategy for informing goal-directed anesthesia in renal transplantation

Rohit Malyala, University of British Columbia

Abstract Body: Background: It is understood that perioperative anesthesia protocols during kidney transplantation may play a role in graft outcomes, but best practices are unclear. We sought to associate features of anesthesia courses, as well as conventional pre-transplant donor/recipient/graft characteristics with DGF incidence, defined as need for dialysis within 1 week of transplant. A machine learning approach was chosen to enable analysis of a high-dimensional dataset. Methods: 306 transplant recipients were included from a single academic medical centre from 2014-2019 by retrospective sampling based on anesthesia record availability. Anesthesia records comprised a time series of medications/fluids administered and intraoperative hemodynamics. We extracted features from the time-courses, summarizing the courses of medications/hemodynamics in tabular format. XGBoost was the selected ML algorithm. 3-fold cross validation was performed on a training split with grid search for hyperparameter tuning. The model accuracy was tested on an unseen validation split. Results: 142 intraoperative and pretransplant features were extracted, with 88 instances of DGF (total: 40.3%; ECD: 57%; SCD: 38.6%). Grid search resulted in a model that predicted DGF with 77.4% accuracy. A SHAP beeswarm plot was generated demonstrating that intraoperative characteristics had an outsized effect on the model, ranking lower late-operative MAP as the most important feature, more relevant to estimates of DGF incidence than live-donor status. Other intraoperative characteristics ranked highly over preoperative characteristics, including low IV fluid infusion pre-vascular clamp, and the use of vasopressors. SHAP dependence plots were generated, illustrating that MAP < 7 5mmHg associated with DGF, and that more crystalloid administered associated with MAP improvement and DGF reduction. Conclusions: Our retrospective study, enabled by an ML approach to account for high-dimensionality in a highly granular time-series anesthesia dataset, indicates that perioperative hemodynamics are a sizeable DGF risk factor, and may inform future investigations to optimize outcomes.

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ID: 33

Characterizing intraoperative hemodynamics and anesthesia-controlled patient factors in renal transplants: an anesthesia course time-series analysis

Rohit Malyala, University of British Columbia

Abstract Body: Background: Perioperative hemodynamics are understood to influence the incidence of delayed graft function (DGF), defined as the need for dialysis within one week of transplant. We aim to characterize features of intra-operative anesthesia courses, with special attention to temporal features of these, in order to determine whether what parameters, if any, associate with DGF incidence. Methods: 306 kidney transplant recipients were included from surgeries performed at a single academic medical centre from 2014-2019 based on retrospective availability of the anesthetic record. Anesthetic records comprised medications and fluids administered (including quantities, timing, and rate of administration), and hemodynamics throughout the procedure, in five minute intervals, along with information regarding major time points such as timing of vascular clamp and anastomosis. Time courses for hemodynamic parameters were plotted as mean values without time transformations. Logistic regression analysis after feature extraction of time-series variables was used for hypothesis testing. Results: 80 DGF events were captured in our cohort after exclusion of 8 DGF events attributable to biopsy-proven rejection. Longer anastomosis times were significantly associated with DGF incidence ($p=0.019$). The rate and total quantity of crystalloid provided, either throughout the operation, or at pre-vascular clamp, post-clamp removal, or end-operation, were not statistically significantly different between recipients with and without DGF. Notably, diastolic blood pressure and mean arterial pressure throughout the operation were substantially lower in DGF recipients (average DBP: $p=0.001$, average MAP: $p=0.002$). Pressors were provided with greater frequency in DGF patients, in particular phenylephrine (44% vs 58%, $p=0.03$). Conclusion: We have collated a highly granular time-series anesthesia dataset, depicting a preliminary view into intraoperative hemodynamics and decision-making in renal transplant surgeries. Future steps include further interrogation of the dataset, and prospective study, to inform optimal goals in transplant anesthesia.

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ID: 34

Histological features in a prospective cohort of transplant patients with screening for development of donor-specific antibodies

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Abstract Body: Background: Donor-specific antibodies (DSA) predispose kidney transplant patients to antibody-mediated rejection (AMR) and accelerated graft loss. We prospectively studied histological features in biopsies taken at the time of appearance of a de novo DSA. Methods: All patients transplanted in our centre between January 2019 and November 2021 were screened (at 1, 2, 3, 6 and 12 months post-transplantation and then every year) for the development of DSA. All patients who developed a de novo DSA were offered a biopsy. Biopsies were analysed using the Banff Classification for Allograft Pathology. Results: Out of 570 consecutive transplant patients, 82 developed DSA at mean 42 days (+/- 106 days) post-transplant (14.4%)(39% Class I, 40% class II, 21% class I + class II). 57/82 patients had a biopsy at a median 33 days (+/- 114) post-DSA detection. 47% did not show any histological features of rejection, 30% showed histological features of AMR (either suspicious for or definite AMR), 16% showed only histological features of T cell-mediated rejection (TCMR) (either borderline and TCMR) and 7% had histological features of both AMR and TCMR . Conclusion In a prospective cohort of patients with de novo DSA, 53% of those investigated with a biopsy showed histological features of rejection (including incomplete/suspicious features). Our next step will be to complement histological analysis with gene expression analysis.

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ID: 35

Discovery, validation and application of antibody-mediated rejection transcripts in a continuous retrospective cohort or kidney transplant biopsies.

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Abstract Body: Introduction: The Banff Classification for Allograft Pathology permits the use of gene expression in the diagnosis of Antibody-mediated rejection (AMR) of kidney transplants, but a predictive set of genes for classifying biopsies with ‘incomplete’ phenotypes has not been studied in clinical practice. We aimed to develop and assess a gene score that could help classify biopsies with features of AMR, and identify biopsies that are at higher risk of allograft loss. Methods: RNA was extracted from a continuous retrospective cohort of 350 FFPE biopsies that were randomised into a ‘Discovery’ (n=221) and a ‘Validation’ (n=129) cohort. The biopsies were divided into three groups: biopsies that fulfilled the 2019 Banff Criteria for AMR (AMR, n=31), those that would meet the criteria for AMR only in the presence of a validated gene signature (AMRsusp, n=50), and biopsies that showed no features of active AMR (No AMR, n=269). Gene expression analysis of 758 genes in the Banff Human Organ Transplant panel was carried out using Nanostring and Lasso Regression was performed to identify a sparse gene set predictive of AMR in the discovery cohort Results: We identified 7 up-regulated genes that were predictive of active AMR (AUC 0.9887, p Conclusion: Gene expression in FFPE biopsy samples can identify an AMR gene signature which can enhance standard histological diagnosis

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ID: 36

Exploring the possibility of developing an advanced and voucher donation program in kidney transplantation in Canada: Transplant professionals' perspectives on ethical and logistical issues

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Abstract Body: Background Advanced and voucher donation has the potential to increase the number of living donor kidney transplantation (LDKTs) performed, by allowing living donors to donate at the most appropriate time for them and receive assurance that their relatives will have priority access, if possible, to a kidney from a living donor if needed in the future. However, this type of program raises numerous issues. The objective of this study is to gather transplant professionals' perspectives on ethical and logistical issues involved with developing an advanced and voucher donation in kidney transplantation in Canada. Methods We conducted semi-structured interviews with 17 transplant professionals across Canada. The interviews were digitally recorded and transcribed. Thematic and content analysis was conducted. Results Transplant professionals had limited knowledge of this type of program, which is already offered in the United States. They were open to advanced and voucher donation as it could increase the number of donors and the willingness to donate. Some characterized this form of donation as a form of a living will to take care of loved ones. They also identified ethical issues related to informed consent, including the need to weigh risks and benefits. Potential donors should be informed about the uncertainty related to this program and that there is no guarantee that the voucher holder will be a suitable candidate for a kidney transplantation when they need it. Participants also recommended including donors' perspectives in the development of an advanced and voucher donation program, including the need to clarify the intent of and logistics related to vouchers. Conclusion This is the first study looking at the Canadian transplant professionals' perspectives on ethical and logistical issues related to advanced and voucher donation. This findings provide empirical data to inform discussions regarding the development and future implementation of this program in Canada.

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ID: 38

Acceptability and feasibility of the Kidney Transplant Physical Activity and Social Club (KEeP ACTIVe Club)

Tania Janaudis-Ferreira, McGill University

Abstract Body: Background We developed the "Kidney Transplant Physical Activity and Social Club" (KEeP ACTIVe Club) to offer support for kidney transplant recipients (KTRs) to improve their levels of physical activity (PA) and knowledge in cardiovascular disease, and to break the isolation and loneliness they may feel after transplantation. The main objective was to assess the acceptability and feasibility of the KEeP ACTIVe Club. We also evaluated pre-post intervention changes in self-efficacy for PA, levels of PA and social support and personal relationships. Methods The KEeP ACTIVe Club lasted six months and offered one educational session about benefits of PA and risk factors for cardiovascular disease, online social networking (via a Facebook closed group led by two patient partners), peer and professional mentorship, and a menu of options for PA. Acceptability and feasibility were measured by the proportion of KTRs approached who participated and the number who completed the intervention. Self-efficacy was measured using a multidimensional self-efficacy scale for exercise, the level of PA was assessed by the the International Physical Activity Questionnaire (IPAQ), and social support was measured by the MOS Social Support Survey. Results One hundred twenty-one KTRs were approached over 15 months (43 initially interested and eligible; 78 refused); 18 (15%) participated in the study (mean age 50.5 ±16.1; 50% female; 7 months – 24 years post-transplant). Forty-four percent of participants chose to do virtual exercises classes led by a kinesiologist and several walked with the patient partner. Eleven KTRs (61% of enrolled) finished the post-intervention questionnaires. Self-efficacy improved by 7.7 points (±16.0), the IPAQ improved by 2,273 MET minutes/week (±4,450) and social support remained stable at 3.5 points. Conclusions The KEeP ACTIVe Club is feasible. Acceptability was low (possibly influenced by the pandemic), however, self-efficacy for PA and level of PA improved in those who participated in the intervention.

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ID: 39

Progression of kidney disease in kidney transplant recipients with a failing graft: A matched cohort study

Ngan Lam, University of Calgary

Abstract Body: Background: Renal function may decline more rapidly in kidney transplant recipients with a failing graft than in people with chronic kidney disease (CKD) of their native kidneys. Methods: We conducted a retrospective, population-based cohort study using linked healthcare databases in Alberta, Canada (2002-2019) to identify kidney transplant recipients with a failing graft, defined as 2 outpatient estimated glomerular filtration rate (eGFR) measurements between 15 and 30 mL/min/1.73 m2 at least 90 days apart. Recipients were compared to propensity-score matched, non-transplant controls with a similar degree of sustained kidney dysfunction who were followed by a nephrologist. We compared the change in eGFR over time (primary outcome) and the competing risks of kidney failure and death without kidney failure (secondary outcome). We used joint modelling to account for possible informative censoring and the association between time-dependent changes in eGFR (eGFR with 95% confidence limits, LCLeGFRUCL) and the competing events (hazard ratios, LCLHRUCL). Results: We matched 575 transplant recipients to 575 non-transplant controls. For the recipients, the median age was 57 years (interquartile range [IQR] 46-67), 39% were women, and median potential follow-up time was 7.8 years (IQR 3.6-12.1). The hazards for both kidney failure (HR 1.101.331.60) and death (HR 1.211.592.07) were significantly higher for transplant recipients. In the joint model, the eGFR decline over time was similar in the two groups (recipients vs. controls: -2.60-2.27-1.94 vs. -2.52-2.21-1.90 mL/min/1.73 m2 per year). eGFR decline was associated with kidney failure but not with death. Conclusion: Although kidney function declines at a similar rate in transplant recipients as in non-transplant controls, people with a failing graft have a higher risk of kidney failure and death. Studies are needed to identify preventive measures to improve outcomes in kidney transplant recipients with a failing graft.

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ID: 43

Autophagy inhibition aggravates ischemia-reperfusion injury-induced microvascular injury

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Abstract Body: Background: Ischemia-reperfusion injury (IRI) is an integral component of kidney transplantation. Programmed cell death (PCD) of endothelial cells (ECs) in peritubular capillaries (PTCs) after renal IRI is a major predictor of long-term loss of renal function. We previously showed that caspase-3 deficient mice show reduced apoptosis of renal PTCs after IRI and preserved long-term renal function. However, the precise role of autophagy on the response of PTCs to IRI remains unclear. Here, we characterize the dynamics of autophagy activation and effect of autophagy inhibition on the renal microvasculature following IRI-induced AKI. Methods: Unilateral renal artery clamping for 30 minutes with contralateral nephrectomy was performed in transgenic GFP-LC3 mice that allow monitoring of GFP+ puncta. Mice were injected intraperitoneally with PBS or Chloroquine (CHQ), an autophagy inhibitor, on surgery day and every day after surgery until sacrifice. Mice were sacrificed at 1, 2, 7, or 21 post-surgery. Kidney function was assessed by measuring the serum creatinine level. Autophagy activation was assessed by confocal and electron microscopy. PTC rarefaction, myofibroblast accumulation, and collagen deposition were assessed by immunohistochemistry for MECA-32 and ?-smooth muscle actin (?-SMA), and Sirius red staining respectively. Results: Autophagy activation was present in PTC ECs following IRI with an increased number of autophagic puncta and formation of large autolysosomes one-day post-surgery. CHQ inhibited autophagic flux and autolysosome formation. Autophagy inhibition aggravated renal function with higher serum creatinine levels one-day post-surgery. In the long-term (21 days), although CHQ injection did not modulate serum creatinine compared to PBS group, microvascular rarefaction was increased in the CHQ-injected group. This was associated with enhanced renal fibrosis, increased ?-SMA, and collagen deposition within PTC. Conclusion: Collectively, these results suggest that IRI induces autophagy activation in PTC ECs. Inhibition of autophagy aggravates renal dysfunction and increases microvascular injury, myofibroblast differentiation, and collagen deposition post-IRI.

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ID: 44

Kidney transplant recipients', kidney transplant candidates and living donors' perspectives on the ethical and logistical issues related to the possibility of an advanced and voucher donation program in kidney transplantation in Canada

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Abstract Body: Background Living donor kidney transplantation (LDKT) is the best therapy for patients with end-stage renal disease. Living donors can donate directly to their recipient, or through the kidney paired donation program (KPD). Recently, the National Kidney Registry (NKR) in the United States implemented an advanced and voucher donation program. This program allows a kidney donor to donate at the most appropriate time for them and to receive vouchers that could be redeemed by a specified person in need of a kidney transplant in the future, if they are a suitable transplant candidate. Advanced and voucher donation programs have the possibility to increase the number of LDKTs performed, but raise numerous ethical issues. The objective of this study was to gather transplant recipients', transplant candidates', living donors' perspectives on advanced and voucher donation. Methods We conducted 17 individual semi-directed interviews with kidney transplant recipients, kidney transplant candidates and living donors from three urban Canadian transplantation centers. Interviews were digitally recorded and transcribed. Thematic and content analyses were conducted. Results Interviewees were enthusiastic about the possibilities of this program to increase LDKTs, and were confident that this type of donation would not change the meaning of donation for kidney donors and recipients. At the same time, participants were concerned about issues of fairness and equity. Whether vouchers can be transferred (or not) and the number of allowed voucher holders were the most important logistical issues identified. During the course of the interviews, participants' perspectives on an advanced and voucher donation program evolved, highlighting further uncertainties and complexities related to this type of LDKTs program. Conclusion Initial results show that the offer of this program could potentially benefit kidney donations in Canada. These results will inform the development of a future advanced and voucher kidney donation program in a way that would be deemed equitable and fair.

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ID: 45

KeEP ACTIVe CLUB Study: Transplant recipients' experience and perspectives on a physical activity club project supported by a private group on an online platform

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Abstract Body: Background It is difficult for kidney transplant (KT) recipients to be physically active after their transplantation. Physical inactivity increases risk of cardiovascular disease which can cause graft loss. In order to help KT recipients start and maintain a physical activity routine, we have developed the KeEP ACTIVe club which is a 6-month online intervention where patients had access to a kinesiologist, a patient partner and a private support group on an online platform (Facebook). The aim of this project was to evaluate the perceptions and opinions of the KT recipients about this club. Methods We conducted 11 individual semi-directed interviews with KT recipients from two urban kidney transplant programs who participated in the KeEP ACTIVe club. The interviews were digitally recorded and transcribed. Thematic and content analyses were conducted. Results Most participants were aware of the importance of physical activity after transplantation and were motivated to improve their overall fitness. Participating in the KeEP ACTIVe club allowed some to develop self-confidence and to find exercises adapted to their reality as transplant patients. However, the small number of participants in both groups limited the schedules of the classes offered, the intensity of the exercises and the number of exchanges on the online group. All participants felt that the Keep Active Club should be offered in transplant centers. Participants mentioned their needs to connect with other transplant recipients, and viewed the club as a good way to meet and share their experiences and meet other KT recipients. Some recommendations were discussed, like prioritizing a club in the fall and winter and to offer outside activities. Conclusion A club dedicated to physical activity and overall wellness for KT recipients is a useful and valuable avenue to offer in the post-transplant care and has the potential to decrease their cardiovascular risk.

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ID: 46

SARS-Cov-2 antibody levels to confer immune protection based on neutralizing antibodies

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Abstract Body: Background: Transplant recipients have a heterogeneous and rapidly vanishing response to SARS-Cov-2 vaccination. The vaccination response is mainly assessed using binding antibody levels. So far, no cutoff value of adequate immune protection has been objectively determined. Eventually, this information might be key to safely individualize the frequency of vaccination. Neutralizing antibodies are the best indicator of immune protection since they block the binding between the virus and the ACE2 receptor used to infect cells. There is little data available to inform about the relationship between binding antibody levels measured by standard serology and the neutralizing effect. Aim: To establish a binding antibody cutoff of immune protection based on a neutralizing assay. Methods: We analyzed the response to COVID-19 vaccination using an anti-spike SARS-COV-2 binding antibody quantitative assay (EUROIMMUN QuantiVac, Germany) and a semi-quantitative surrogate virus neutralization test (sVNT) (Genscript, New Jersey). The sVNT measures the inhibition capacity of the serum for ACE2 – Sars-Cov2 interaction. Dilution analyses using the live virus previously established that reduction of 90% of infected cells (PRNT90) correlates with inhibition of 30% or more. Results: Sera from 75 adult kidney transplant recipients were examined after 2 or 3 doses of vaccine, providing a wide range of binding antibody levels (4.8 – 1790 BAU/mL) for examination. The ROC cruve analysis indicated that positive inhibition was predicted by a binding antibody (BAU) concentration of 74 BAU/mL (sensitivity 100%, specificity 94%). Considering a previously reported 22-fold reduction in vaccine-elicited neutralization by Omicron, we empirically estimated that the BAU required for this variant would be 193 BAU/mL (sensitivity 97%, specificity 96%). Conclusion: This work provides an objective approach to answer the current limitation in the literature regarding vaccine response to SARS-Cov-2. In vitro testing of the neutralization levels required for the Omicron protein is underway.

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ID: 47

Kidney Transplant Candidates' Perspectives on the Implementation of a Canadian Willingness to Cross Program: a Strategy to Increase Access to Kidney Transplantation for Highly Sensitized Patients

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Abstract Body: Kidney transplantation is the optimal treatment for patients with ESKD. Unfortunately, highly sensitized patients (HSPs) have decreased access to transplantation, and increased mortality on the waiting list. In an effort to improve the chance of receiving a kidney transplant for HSPs, the Willingness to Cross Program (WTC) will permit transplantation across preformed donor specific antibodies that are deemed to at low risk of causing rejection. The objective of this study was to gather patients' perspectives on the development of a WTC program. Methods We conducted 14 individual interviews with kidney transplant candidates, highly (cPRA ? 95%) and not highly sensitized (cPRA The interviews were digitally recorded and transcribed. Thematic and content analyses were conducted. Results Although participants' understanding of immunological risk and the WTC program was limited, they were open-minded to WTC because they trusted the judgement of their healthcare providers. HSPs viewed the WTC program as a great opportunity to gain freedom from dialysis and a source of hope for access to kidney transplantation in spite of a potentially increased risk of rejection. Willingness to participate in the WTC program was further influenced by personal considerations. Non-HSPs were concerned about distributive justice issues. They had relative concerns regarding the potential increased waiting time for non-HSP candidates and the possibility that allocating kidneys to WTC patients could compromise the longevity of the kidney allografts due to the potential increased risk of antibody-mediated rejection. Conclusion WTC program is a promising strategy to improve HSPs' access for kidney transplantation. HSPs viewed this program as a source of hope although non-HSPs shared relative concerns about distributive justice issues. These results will help to develop a WTC program that is deemed fair and ethically sounded for all transplant candidates.

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ID: 48

Coping with COVID: A Qualitative Investigation of the Perspectives of Parents of Pediatric Kidney Transplant Patients Concerning Their Pandemic Experiences

Julie Strong, Children's Hospital, HSC, WInnipeg

Abstract Body: Background. Families of children who are waiting for or who have received a kidney transplant deal with very challenging circumstances on a daily basis. The impact of the COVID-19 pandemic on the mental health and well-being of these parents and children is not yet fully understood. The goal of this study was to explore the perspectives of these parents concerning their pandemic experiences. Methods. Seven parents of pediatric kidney transplant patients who had participated in a previous study prior to the pandemic were contacted with a letter of invitation. All caregivers, including fathers and grandparents were invited; however, all participants were mothers, including one foster mother. Interviews were conducted online, except for one interview conducted at the hospital. Parents were asked open-ended questions about how the pandemic affected their child, their family, and themselves; a $75 honorarium was provided. Responses were coded into themes by two independent coders. Results. Seven main themes emerged, along with several subthemes. These included: 1) Family Life (e.g., isolation / remote contact with non-cohabiting family members), 2) Work Life (e.g., remote work), 3) School Life (e.g., stopped or remote schooling), 4) Health & Health Care Systems (e.g., adherence / monitoring), 5) Parenting (e.g., lack of respite), 6) Mental Health & Coping (e.g., mental health issues), and 7) Broader Systems (e.g., public health restrictions). Conclusions. Parents identified both positive and negative aspects of their pandemic experiences; however, the majority were negative. Personal stress and suffering was often downplayed by participants, in contrast to rich detail provided about their family. For some, past trauma related to their child's kidney disease was triggered by pandemic experiences. Results were discussed in terms of lack of resources and barriers to resources for families of pediatric transplant patients.

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ID: 49

Inhibition of calcineurin and mtor pathways synergizes to prevent missing self-induced NK cells-mediated rejection

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Abstract Body: 'Background' Chronic vascular rejection currently represents the main cause of late graft loss. Our group has demonstrated that the inability of donor graft endothelial cells to deliver HLA-I dependent inhibitory signals to circulating recipient NK cells, was the cause of a previously overlooked type of innate chronic vascular rejection. This translational study aimed at investigating the impact of various immunosuppressive (IS) regimen to prevent missing self-induced NK cell-mediated rejection. 'Methods' Purified human NK cells were cocultured with microvascular endothelial cells as to emulate missing self-induced NK cell-mediated rejection. The impact of different IS regimen [a calcineurin inhibitor (CNI); a mTOR inhibitor; or both drugs together] was evaluated in this in vitro model. A pilot clinical study was conducted on 46 kidney transplant patients diagnosed with missing self-induced NK cell rejection while on CNI-based immunosuppression. Among the latter, mTOR inhibitor was introduced in 16 patients, while the remaining 30 remained on the same treatment. 'Results' Both CNI and mTOR inhibitor partially blocked missing self-induced NK cell activation in vitro and the combination of drugs appeared highly potent. In line with these results the adjunction of a mTOR inhibitor to a CNI-based immunosuppression regimen resulted in significant reduction of microvascular inflammation on biopsy and better graft survival as compared with patients that remained on CNI alone, in patients diagnosed with missing self-induced NK cell-mediated rejection. 'Conclusion' The addition of an mTOR inhibitor to CNI-based regimen in patients with missing self-induced NK cell-mediated rejection appears effective to reduce rejection lesions and may improve long-term graft survival.

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ID: 50

The effect of kidney preservation at 10°C with Hemopure and hydrogen sulfide donor, sodium thiosulfate, in a syngeneic rat renal transplantation model

Maria Abou Taka, Western University

Abstract Body: Background: Static cold storage (SCS) at 4°C is the current gold standard for kidney preservation. SCS contributes to renal damage through ischemia-reperfusion injury (IRI). In porcine models of renal transplantation, we added non-FDA-approved hydrogen sulfide (H2S) donor, AP39, to Hemopure at 21°C and 37°C, which improved renal graft quality; though, the experimental setup was costly to meet renal metabolic demand. In rats, we investigated sodium thiosulfate (STS), an FDA-approved H2S donor, at 4°C and observed similar benefits. However, there is still a risk of 4°C cold IRI. Recent studies showed that 10°C human organ graft preservation enhanced patient survival without requiring extensive oxygen during preservation. Therefore, we hypothesize that preservation solutions with STS and Hemopure at 10°C will reduce renal IRI compared to SCS. Methods: Using an in vitro model of rat renal IRI, we evaluated STS use at 4°C, 10°C, 21°C, and 37°C. We treated rat proximal tubular epithelial cells with 150 µM STS in serum-free media for 24 hours in hypoxic conditions to mimic ischemia, and 24 hours in normoxic conditions to mimic reperfusion. To assess cellular viability, we used flow cytometry and stained cells with FITC-Annexin-V and PerCP-Propidium Iodide to determine apoptosis and necrosis levels, respectively. Results: STS treatment significantly enhanced cellular viability at 10°C compared to 4°C, 21°C, and 37°C (p Conclusion: Our findings demonstrate that 10°C STS treatment significantly protects rat proximal tubular epithelial cells from IRI compared to the other temperatures investigated. This suggests that 10°C kidney preservation may enhance renal graft survival compared to other preservation temperatures.

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ID: 51

A Proposal for Grading Peritubular Capillary Basement Membrane Multilayering

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Abstract Body: Background: In this study, we aim to investigate the Banff ptcml1 criteria in the diagnosis of transplant glomerulopathy. Methods: Forty-four renal transplant indication biopsies of 32 patients with available electron microscopic examination between 2013-2018 were re-evaluated. Banff lesion scores were updated according to 2019 classification. Glomerular and peritubular capillaries were reexamined under electron microscopy. A maximum of 10 peritubular capillaries per biopsy were evaluated clockwise, taking the glomerulus as the initial starting point. Statistical analyses were performed using SPSS26®. Results: Clinicopathologic features are listed in the Table. The mean number of layers in the most severely affected three peritubular capillaries (mean±SD=3.67±2.05, median=3.17) most accurately predicted chronic active antibody mediated rejection (caABMR) (AUC=0.756, p=0.012) (Figure1). Cut-off values were determined via ROC analysis and two subgroups were generated: ptcml with = 4 layers. Seventeen cases showed > = 4 layers. Among this group, no cases were diagnosed as borderline changes. There were 2 T-cell mediated rejection (TCMR), and 2 no rejection cases. PRA positivity was detected in one of the 2 no rejection cases (DSA, unknown), and the other had a previous biopsy of ABMR. TCMR cases had both acute and chronic active TCMR components. ABMR related Banff lesions such as, g, ptc, and cg significantly differed among two groups (Figure2). 10/17 cases with > = 4 ptcml layers did not meet Banff 2013 ptcml requirement for the presence of ABMR. Nine among these 10 cases were diagnosed as ABMR, and one as caTCMR. The single caTCMR case were diagnosed as C4d positive ABMR, showing DSA positivity within one year-follow up. Conclusion: We suggest that mean number of basement membrane layers within the three most severly affected peritubular capillaries may be considered as a criterion for ptcml, for it showed the highest correlation with ABMR related lesions.

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ID: 52

The Toronto management of initially unresectable liver metastases from colorectal cancer in a living donor liver transplant program

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Abstract Body: Background Living donor liver transplantation (LDLT) is an attractive potential surgical option for patients with unresectable, bilobar, liver-only colorectal liver metastasis (CRLM). However, it is not yet available in centres beyond clinical trials. This study describes our interim experience with LDLT at a large transplant and hepatobiliary centre in North America. Methods Adults with unresectable bilobar, liver-only CRLM, receiving systemic chemotherapy were recruited. Relevant data on demographics, referral, and clinical characteristics were extracted from study inception in October 2016 to April 2022. Patients were divided into three groups: transplanted, resected, and control (excluded and referred back for systemic chemotherapy). Overall survival (OS) and recurrence-free survival (RFS) were compared. Results 81/85 referred patients underwent assessment and screening, of which 6 were transplanted, 3 pending further transplant evaluations, 21 were resected, and 51 were excluded (control) (Figure 1). No differences in pre-assessment baseline characteristics existed. Median time from assessment to transplantation was 15.5 months (Table 1). The control population had significantly worse post-assessment OS than the transplanted population (p=0.005) (Figure 2). There were no statistically significant differences in post-operative OS (1-year 100% vs. 92.3% and 3-year 100% vs. 73.9%, p=0.46) or RFS (1-year 80% vs. 15.4% and 3-year 80% vs. 7.7%, p=0.13) between the transplanted and resected populations, however the resected population had a higher proportion of recurrences. Conclusion Most patients with unresectable liver metastases from colorectal cancer referred to LDLT are deemed ineligible for study inclusion. However, patients deemed eligible experience excellent oncologic outcomes. LDLT is a viable treatment option in this highly selected population. Future results after trial completion can inform the long-term trial outcomes.

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ID: 54

Lung transplant recipients' perspectives on integration of pharmacogenomic testing to transplant care

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Abstract Body: Background: Pharmacogenomic (PGx) testing allows for individualization of medication therapies based on genetic variations. Patients who have completed PGx testing felt more confident in their prescribed medications and were more likely to take medications as prescribed. PGx testing is not a current standard of care practice in lung transplantation. The perspectives of lung transplant (LTx) recipients on the addition of PGx testing to their post-transplant care will help determine the utility of PGx testing for a LTx program. Methods: This prospective cohort study included LTx recipients who received voriconazole between January 1, 2016, to November 30, 2019. Participants were excluded if they did not read or speak English, did not have access to email or internet, and did not provide consent to PGx testing. Electronic surveys were sent to participants after the completion of an at-home PGx testing kit (Survey A) and after individual PGx test results were returned to participants via a one-on-one online or phone meeting (Survey B). Results: Thirty-four participants were included in the study. Thirty-two (94%) and twenty-four (71%) participants completed Survey A and B, respectively. Prior to the study, greater than 75% of participants were unaware of PGx testing. After PGx testing, 96% (23/24) of participants felt performing an at-home PGx test kit at home was feasible. Seventy-nine percent (19/24) of participants agreed that PGx testing would be helpful to their healthcare decision making, and 92% (22/24) would complete another PGx test if it was recommended for other prescribed medications. Ninety-six percent (23/24) of participants believed if offered, all transplant recipients should receive PGx testing. Conclusion: Lung transplant recipients believed PGx testing is a useful tool for medication decisions and PGx testing should be offered to all transplant recipients. Further studies are needed to determine the implication of routine PGx testing in lung transplant recipients.

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ID: 55

Developing a base editing approach to upregulate IL-10 gene for donor lung immunomodulation

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Abstract Body: Background: Long-term systemic immunosuppression remains a significant burden for lung transplant recipients. We envisioned inducing persistent immunomodulatory capacity in donor organs to reduce the need for systemic immunosuppression. We seek to employ genome editing, which generates permanent changes in genomic DNA sequences, to upregulate the IL-10 gene, an immunomodulatory gene. Particularly, base editing using CRISPR-Cas allows precise and efficient base conversions, thus holding promise in whole organ modification. However, its potential in upregulating IL-10 is uncertain. We hypothesized that base editing at the regulatory region could derepress the IL-10 gene (Figure) and tested this approach in vitro. Methods: We first explored potential repressor binding loci by evaluating a series of mutations upstream of the IL-10 gene. Cas9 nuclease and each of seven guide RNAs (gRNA) were delivered to HEK293 cells by plasmid transfection. The impact of mutation at each locus was assessed by measuring IL-10 expression after 48 h. Next, we designed a gRNA for base editing to install base substitutions at the selected locus. The gRNA and adenine base editor (ABE) were expressed and assessed for IL-10 upregulation. Results: In the screening mutagenesis, three out of seven gRNAs significantly enhanced IL-10 expression compared to the negative control (15.5 ± 6-fold, p=0.0006, 19.3 ± 0.6-fold, p=0.0001, 11.3 ± 2.7-fold, p=0.0074, respectively). We focused on the binding motif of the basic helix-loop-helix family member a15 (Bhlha15), which has an N-terminal repressor domain and binds to an E-box motif, as a target for base editing. Base editing targeting the E-box at the Bhlha15 binding site significantly upregulated IL-10 compared to the negative control (7.6 ± 1.7-fold, p=0.025, Figure). Conclusion: We have developed a derepression base editing method to upregulate the IL-10 gene in a human cell line. This study could lay a foundation for engineering optimized donor lungs using genome editing.

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ID: 56

Utilization of biomarkers for alcohol use in patients with alcohol-associated liver disease

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Abstract Body: Background: Alcohol-associated liver disease (ALD) has become the most common indication for liver transplantation in North America. Although a set period of abstinence is no longer an absolute requirement for transplant consideration, it is imperative to utilize valid monitoring tools alongside clinical interview to detect ongoing alcohol use in potential transplant candidates. Urinary ethyl glucuronide (EtG) testing is an objective measure of ongoing alcohol use and has been an essential tool in the Toronto General Hospital ALD transplant program since its inception in 2018. This study aims to describe the psychosocial characteristics of ALD patients who provided positive EtG tests in the pre-transplant phase in an effort to identify possible risk factors associated with ongoing alcohol use. Methods: Data was collected between May 1, 2018 and November 30, 2021. All transplant candidates were assessed by transplant hepatology, addiction psychiatry and social work. A urinary EtG test was collected at the first point of contact and then subsequently throughout the evaluation and after transplant. Psychosocial characteristics and transplant outcomes were recorded for patients who provided a positive test, which were then compared to a control group of ALD patients who did not provide a positive test. A majority of the patients assessed for transplant (n=497, 95%) underwent full medical and psychosocial evaluation. Of these patients, 48 (9.6%) provided a positive EtG test. This included at initial contact (n=20), during medical evaluation (n=14), while on the waiting list (n=5) and post-transplant (n=8). The group of patients with a positive EtG did not show any significant differences in sociodemographic characteristics when compared to the control group (n=449). A diagnosis of severe Alcohol Use Disorder (AUD) (p=0.018) and consumption of more than 10 drinks per day (p=0.006) were significantly associated with a positive EtG test. Psychiatric comorbidity, previous treatment for AUD and duration of

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ID: 57

Variability in workup and eligibility criteria for adult kidney transplantation among Canadian transplant centers

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Abstract Body: BACKGROUND: All potential kidney transplant recipients undergo rigorous evaluation to rule out or ensure appropriate treatment of conditions that may increase risk of post-transplant complications, but specific recommendations regarding workup and kidney transplant candidacy vary across published guidelines. We assessed current pre-transplant evaluation practices and eligibility criteria for adult kidney transplantation across Canada to elucidate differences in guideline interpretation and identify areas of most uncertainty. METHODS: We compared published guidelines on kidney transplant workup and eligibility in order to create a focused digital survey that included both undisputed and controversial domains. The survey was divided into: referral process, history/physical exam, multidisciplinary assessments, laboratory/imaging, and contraindications. Given the many cancers and different staging for each, malignancy-related inquiries were simplified. The medical directors of all 18 Canadian adult kidney transplant programs were invited to complete the survey. We defined consensus and high uncertainty, respectively, as >90% and RESULTS: Survey completion rate was 100% (18/18). There was consensus on most mandatory pre-transplant viral serology testing and tuberculosis screening, while cardiac evaluation protocols varied considerably. Of 28 questioned conditions, 6 were considered absolute contraindications by >90% of centers (active bacterial infection/malignancy, non-healing ulcer, COVID-19, severe liver disease, untreated multiple myeloma). High uncertainty existed for: medication non-adherence (44%), symptomatic heart failure (61%), recent myocardial infarction (61%), and frailty (39%). Other parameters demonstrating wide variability included latent tuberculosis treatment protocols, and exclusion thresholds for parathyroid hormone, body mass index, left ventricular ejection fraction, and blood pressure. Centers used several guidelines to determine eligibility for patients with treated cancer. CONCLUSION: There is marked variability in evaluation requirements and eligibility criteria for kidney transplantation across Canada. National harmonization of evaluation processes and eligibility criteria may help to ensure more equitable and transparent access to kidney transplantation for Canadian patients with end-stage kidney disease.

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ID: 59
Challenges in deceased donor kidney transplant listing

Helen Mumby, MidCentral health

Abstract Body: Background Kidney transplant offers greater survival benefit and improved quality of life for CKD5 individuals. A transplant survival score (TSS) is used in New Zealand as a standard for acceptance onto the deceased donor waiting list. This score estimates the chance of living for at least five years post-transplant. Patients suitable for acceptance onto the deceased donor waiting list need a TSS greater than 70%. Two years ago, we analysed why a high proportion of our patients had a score greater than 70%, but only 11% of these patients were on the deceased donor waiting list. The findings at that time identified BMI > 40 as the largest contributing factor. Aim Whether the factors that influenced patients eligibility for deceased donor waiting list, had changed over past 2 years. During this period, patients with BMI >40 have been referred to the renal dietitian for weight loss. Method A cross-sectional analysis was undertaken on 6th June 2022, looking at the patients under our service. TSS was used to determine our deceased donor waiting list candidates. Results Total patients: 275 Score >70 136 49% Score 139 51% Of patients with Score > 70% On DDWL 21 16% Being worked up 52 38% Not being worked up 63 46% Score > 70% that are not being worked up BMI > 40 29 46% Cancer 14 22% Compliance 7 11% Cardiac 5 8% Other 8 13% For those patients with BMI > 40 Gender: Female 10, Male 19 Ethnicity: Maori 15, European/Pakeha 12, Pacific Island 2 Conclusion The main reason for our patients being ineligible for transplant work-up continues to be a BMI above 40 though it decreased from 60% to 46%. Further efforts needs to be done on this aspect

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ID: 61
Real world sirolimus prescribing patterns and tolerability after lung transplantation

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Abstract Body: Background: Sirolimus is an immunosuppressant with a high discontinuation rate due to its unique side effect profile. Historically, sirolimus was not routinely used after lung transplantation except in rare circumstances. Recently it has shown to be an effective alternative to antimetabolites as maintenance immunosuppression in the lung transplant population. This report aims to characterize the indications for sirolimus prescribing after lung transplant, as well as the tolerability and outcomes of sirolimus-containing regimens. Methods: All patients followed by the lung transplant clinic between 2010 and 2021 were eligible for inclusion. After screening, a comprehensive retrospective chart review was completed on 54 patients. Paper and electronic charts were manually reviewed to identify transplant indications, maintenance immunosuppression, lung function data, and relevant bloodwork. Clinic transcriptions from lung transplant physicians were reviewed to confirm the indication for sirolimus prescribing, side effects, and discontinuation rationale. Follow-up data was obtained for a minimum of one year after initiation or until May 30th, 2022. The median follow-up was 1.4 years. Results: The standard sirolimus starting dose was 1mg daily and target levels of 6-8ug/L were reached in a median of 30 days. The discontinuation rate was 18%, however, only 4 patients ended therapy due to intolerable side effects. Leading indications for sirolimus initiation were neutropenia secondary to antimetabolite, established chronic lung allograft dysfunction, and malignancy history, primarily squamous cell carcinoma (SCC, Table 1). The neutropenic subset of patients experienced a statistically significant increase of their absolute neutrophil count at both six weeks and 12 weeks after conversion to sirolimus (Fig. 1). No patients experienced recurrent SCC throughout the follow-up period. Conclusion: Sirolimus is a compelling immunosuppressive alternative in patients intolerant to standard antimetabolite drugs used in lung transplantation. With conservative initial dosing and careful therapeutic titration, sirolimus is well tolerated by the majority of lung transplant recipients.

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ID: 62

Examining post-transplant survival in End-Stage Kidney Disease patients – a multivariable prediction model

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Abstract Body: Background Kidney transplantation is a highly effective treatment for End-Stage Kidney Disease (ESKD) and remains the preferred standard of care. Despite this, only a small proportion of dialysis patients (30%) are waitlisted for kidney transplantation. New measures are needed to examine the suitability of non-waitlisted ESKD patients for kidney transplant assessment. We sought to characterise predicted post-transplant survival in patients with ESKD. Methods Adult deceased donor kidney only transplant recipients between 2000-2014 registered in the Australian and New Zealand Dialysis and Transplant Registry were included for analysis. The outcome was time from kidney transplantation to death. The patient population was split 2:1 into derivation and validation cohorts (training and testing). Exploratory univariate and multivariate Cox proportional hazards models were used to examine available covariates in the derivation cohort for inclusion in the predictive model. Model validation, with discriminant statistics and calibration plots, was performed in the internal 2010-2014 validation cohort and a temporal cohort of kidney transplant recipients between 2015-2020. Results 6254 participants were included for analysis. 62.8% were male and 79.2% were Caucasian. Glomerulonephritis was the predominant kidney disease (45.6%). On multivariable analysis, age (HR 1.05, 95% CI 1.04-1.05), peripheral vascular disease (HR 1.47, 95% CI 1.14-1.89), chronic respiratory disease (HR 1.35 95%CI 1.03-1.76), duration of renal replacement therapy & current smoking status (HR 4.22 95%CI1.26-1.88) were associated with an increased hazard of death post-transplant, table 1. Discrimination was adequate in the base model (c-statistic 0.72) and was consistent in the validation (c-statistic 0.70) and temporal cohorts (c-statistic 0.72), figure 1. Conclusion This model identifies and weighs key parameters of prognostic importance in patients undergoing deceased donor kidney transplantation. This model performs well discriminating between surviving and non-surviving patients. This model may allow identification of non-waitlisted ESKD patients with predicted favourable post-transplant outcomes who should be prioritised for kidney transplant assessment and wait-listing.

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ID: 63

Protocol for 24-hour negative pressure ventilation ex-situ lung perfusion with a porcine transplantation model

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Abstract Body: Background: Lung transplantation has a wait-list mortality of 30% due to a shortage of high-quality donor lungs. Ex-situ lung perfusion (ESLP) allows for improved preservation and reconditioning of marginal quality lungs to increase the donor pool. To date, the longest pre-clinical preservation period with favourable transplantation data is 24-hours using positive pressure ventilation ESLP. Negative pressure ventilation (NPV) has been shown to result in reduced lung injury and inflammation, yet reliable 24-hour preservation has yet to be achieved. Objective: Refine our protocol of NPV-ESLP to achieve reliable 24-hour preservation with acceptable in-vivo transplantation data. Methods: Twelve double-lung blocks from 45-55kg pigs were preserved on normothermic NPV-ESLP for 24-hours using a cellular perfusate with autologous packed red blood cells. Six left lungs were transplanted into recipient pigs post-ESLP and reperfused for 4-hours to evaluate the impact on in-vivo post-transplant lung function. Final assessment of the transplanted left lung was performed with the right lung clamped. Lung oxygenation capacity (PF ratio = PaO2/FiO2), dynamic compliance (Cdyn), pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), and lung weight-gain were monitored. Results: All twelve lung blocks demonstrated stable lung function during 24-hours of NPV-ESLP. At 24-hours, PF ratios were 473.9 ± 29.5 mmHg, Cdyn was 20.2 ± 2.8 mL/cmH20, PAP was 15.0 ± 1.1 mmHg, PVR was 570.7 ± 46.9 dynes/s/cm5, percentage weight-gain after ESLP was 54.7 ± 8.0. Acceptable lung oxygenation was demonstrated in all six transplanted left lungs with a mean PF ratio >300 mmHg (329.5 ± 21.7), equivalent to primary graft dysfunction (PGD) grade 0. Isolated left lung weight gain (%) post-transplant was 15.3 ± 39.0. Conclusions: Reliable 24-hour NPV-ESLP is achievable, resulting in acceptable post-transplant oxygenation capacity. Prolonged preservation with ESLP could potentially eliminate geographic barriers for transplant. Future studies will target 36-hours of NPV-ESLP with favourable transplantation data.

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ID: 64

The association between lifestyle behaviours and mental health indicators over the COVID-19 pandemic in an immunosuppressed population

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Abstract Body: Background: Social and physical distancing measures related to the COVID-19 pandemic have adversely affected the mental health of individuals. Lifestyle behaviours such as moderate-vigorous intensity physical activity (MVPA), sedentary time (ST) and sleep duration have also been influenced by the COVID-19 pandemic context. However, little is known on how these changes in lifestyle behaviours may affect mental health among individuals who are immunocompromised. Objective: To examine the association between the pre and post-COVID-19 changes in physical activity, sedentary time, and sleep duration (increase, decrease, and stable) and mental health indicators of stress, distress, resilience, anxiety, and depressive symptoms. Methods: Participants (n = 132) were recruited in a COVID-Immuno Study and completed a baseline questionnaire between May and August 2020. Linear regressions were conducted to assess the associations between changes in lifestyle behavior and mental health indicators, controlling for age, sex, and physical diagnosis. Bonferroni corrections were used to adjust for multiple comparisons. Results: Individuals with decreased MVPA experienced higher distress (p= 0.04), anxiety (p= 0.03), and depressive symptoms (p= 0.04), compared to those who remained stable. Those with increased ST had higher levels of stress (p= 0.03), distress (p=0.005), anxiety (p=0.02) and depressive symptoms (p= 0.03). Those who reported a change in their sleep, both an increase or decrease, had higher levels of stress (p= 0.003; pConclusion: Changes in lifestyle behaviours in the context of a stressful life event, such as COVID-19 pandemic, may impact mental health indicators for immunocompromised individuals. Movement behaviour interventions may help mitigate the natural impacts of a stressful life event on mental health.

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ID: 65

Comparison of surgical outcomes with staged versus simultaneous native nephrectomy for autosomal dominant polycystic kidney disease

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Abstract Body: Background: Bilateral native nephrectomy (BNN) for patients with autosomal dominant polycystic kidney disease (ADPKD) is considered in select cases at or around the time of renal transplant (RT). There is no consensus regarding staged versus simultaneous BNN. The purpose of this study is to compare the surgical outcomes between patients with ADPKD undergoing BNN as a staged or simultaneous procedure with RT. Methods: Retrospective review of patients with ADPKD who underwent RT between 2009 and 2020 at two related academic institutions was undertaken. Clinical records were reviewed to collect data on intraoperative and post-operative details, including graft survival, blood transfusion rates and post-operative complications. Data were analyzed with one-way analysis of variance (ANOVA) or Pearson's chi-squared test in SPSS. Results: Of the 169 patients identified, 65 underwent BNN (38%, 21 simultaneous with RT; 19 prior to RT; 23 post RT). Demographic characteristics between groups were comparable. Patients in the simultaneous group received transplants exclusively from living donors whereas those in the staged groups had a mix of living and deceased donors ($p =< 0.001$). There was no difference in graft survival. There were no differences in postoperative incisional hernias, wound dehiscence, ileus, lymphocele, biopsy confirmed rejection, cardiac event, or readmission between groups (p=NS, Table 1). Median cumulative length of hospital stay was lower in the simultaneous group at 6 days compared to 9 days for staged procedure ($p = 0.0041$) Conclusions: Staged or simultaneous BNN with RT are both feasible and safe. Decreased hospital stay was observed in the simultaneous group, suggesting a potential benefit for carefully selected to patients.

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ID: 70
Reproducibility of rejection classification in human uterus transplants

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Abstract Body: Background: Histological assessment of tissue biopsies remains the gold standard to diagnose rejection after transplantation. A preliminary grading scheme for diagnosis of rejection on cervical biopsies from uterus transplants has previously been reported (Molne, J; Broecker, V. et al. 2017). However, its reproducibility has never been scrutinized. We conducted a multi-center study to test the reproducibility of the grading scheme as well as histological lesions which are currently not considered in the classification. Methods: Five pathologists from 4 centers performed the grading on 145 scanned slides from transplant cervical biopsies according to the proposed grading scheme (no rejection, borderline-changes, mild rejection, moderate, severe). Following group-discussion of controversial cases and identification of histological lesions not currently considered for diagnosis, participants performed a second grading on 48 new cases. Three additional histological lesions were scored as present or absent: perivascular stromal inflammation, endothelialitis and apoptosis in the basal epithelial layer. To measure inter-rater agreement of ordinal grading of rejection weighted kappa was assessed pairwise; Fleiss' kappa was assessed for overall inter-rater agreement for nominal variables. Results: Pairwise inter-rater agreement for grading of rejection on the first set of 145 slides ranged from moderate to substantial (??=0.45-0.74), agreement did dot improve substantially for the second set of 48 biopsies. Overall inter-rater agreement for additional histological lesions was moderate for perivascular stromal inflammation (??=0.513) , fair for endothelialitis (??=0.219) and poor for apoptosis (??=0.197). Conclusions: Grading of rejection on cervical biopsies from human uterus transplants according to a previously proposed grading scheme shows acceptable agreement, but may be improved by sharpening diagnostic criteria and education of pathologists performing the grading. For additional histological lesions such as apoptosis, perivascular stromal inflammation and endothelialitis clear consensus definitions and education of pathologists is required.

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ID: 72

Donor Survey to Assess Satisfaction with Living Kidney Donation and Elicit Ideas for Process Improvement

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Abstract Body: Background: Live kidney donation (LKD) is a critical strategy to address the shortage of kidneys for transplantation. In June 2017, we launched a LKD program to enhance our services through local access to live kidney transplantation. We aimed to evaluate donor satisfaction with the process, as well as identify opportunities for improvement. Methods: We developed an anonymous survey to evaluate donor satisfaction related to education, care and recovery after LKD. This paper survey was sent to all donors 6-12 weeks post-donation from June 2017 to May 2022. Results: Response rate was 59% (19/32). Mean age was 48.9±9.2 years and 57% were Female. All donors were satisfied or very satisfied with the education, care and recovery of LKD (Table 1). Two (10.5%) donors felt unprepared for discharge from hospital related to their mobility post-surgery. Both were older (58- & 62-year-old) and the spouses of their elderly recipients. Two donors expressed concern about recipient rejection and post-donation kidney failure, but none regretted LKD. Conclusion: Our program's survey indicated donor satisfaction with LKD. The main opportunity for improvement involves support of elderly donors, particularly those who are donating to a spouse.

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ID: 73

Use of Pancaspase inhibitor during Normothermic ex vivo liver perfusion: a strategy to reduce ischemia reperfusion injury in pig liver grafts

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Abstract Body: Background: Ischemia-reperfusion injury (IRI) has significant impact in Liver Transplant (LTx) especially for expanded criteria donors, such as cardiac death donors (DCD). IRI is mainly induced by apoptosis which is regulated by caspases cascade. Caspases are proteolytic enzymes responsible for cell death and activation of inflammatory cytokines. Normothermic ex-vivo liver perfusion (NEVLP) emerges as an important tool to reduce the impact of IRI. NEVLP reduces liver tissue damage caused by cold ischemia, but also allows the development of strategies for better organ preservation, such as the use of nutrients, hormones and drugs which, acting directly on the liver, can improve graft function after transplant. In this study we used a porcine model for NEVLP applying Emricasan, a pancaspase inhibitor, during NEVLP to assess its effects on liver function and tissue damage. Methods: A model for Porcine DCD was used with 60 min of warm ischemia followed by 5 hrs of NEVLP. The swine were divided into two groups: the EMRICASAN group (n=4) and the CONTROL group (n=4). Primary endpoint were liver injury and function during perfusion. Results: AST levels were significantly reduced in the Emricasan treated lover vs the control group (p=0.0004).Improvement in liver weight and bile production were observed with Emricasan treatment that did not reach significance. pH levels, hepatic artery and portal vein flow showed no differences during NEVLP period. Conclusion: The pancaspase inhibitor Emricasan demonstrated potential benefit in reducing tissue damage and enhancing liver function during NEVLP in a donor model with increased ishemic damage. Emricasan administration during NEVLP may be a new strategy to reduce IRI after liver transplant.

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ID: 74
Ex Vivo Perfusion De- and Recellularization of Rat Hindlimbs for Vascular Composite Allotransplantation

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Abstract Body: BACKGROUND Vascular composite allotransplantation (VCA) is a promising reconstructive surgical avenue for patients with severe tissue and muscle loss. However, due to high allograft immunogenicity and required long-term immunosuppression, VCA's clinical implications are limited. Engineering acellular composite tissue allografts using de- and recellularization can help circumvent the need for immunosuppression and significantly advance VCA strategies. METHODS Rat hindlimbs were procured from cadaveric male Lewis rats where the common femoral artery was cannulated. An ex vivo perfusion-based, single-pass, closed-system bioreactor was constructed to perfuse 0.25% sodium dodecyl sulfate (SDS) at 1 mL/min. Decellularization was determined by gross examination for systemic white, translucent tissue. The skin, femoral vessels, nerves, muscle, and femur were histologically assessed for preservation of tissue architecture and absence of cellular content. Recellularization was performed using 20 x 106 human umbilical vein endothelial cells (HUVECs) by arterial perfusion and 20 x 106 L6 rat myoblasts by injection. Using the same bioreactor design, scaffolds were cultured and monitored for cell engraftment for 24 hours. RESULTS Gross morphology showed systemic white, translucent appearance of decellularized relative to native by 5 days (Fig 1). The construction of a perfusable, single-pass, and closed-system bioreactor circuit was suitable for both de- and recellularization. Tissue structure of all tissues was maintained. Cellular content was absent across all decellularized tissues (Fig 2). For recellularization, cells could be detected histologically in vessels and muscle tissue after 24 hours of seeding (Fig 3). CONCLUSION The present study offers a proof-of-concept model for applying this tissue engineering technique for composite tissues. 0.25% SDS perfusion, a lower concentration of SDS than commonly used, retained all respective tissue compartments post-decellularization, suggesting a less toxic approach. Initial recellularization showed cell presence within 24 hours. Further work will involve examining long-term culturing of cells to test cell proliferation and survival within the acellular scaffolds.

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ID: 75

Turf Wars: Divisive renal governance in Canada and its consequences for living donor kidney transplantation

Anna Horton, McGill University

Abstract Body: Background: Living donor kidney transplantation (LDKT) is considered to be the most optimal therapy for patients with kidney failure, particularly when done pre-emptively. Nevertheless, instead of receiving transplantation, about 75% of the incident dialysis patients in Canada are started on haemodialysis and another 24% on home dialysis therapies. Once on dialysis, many patients are not considered as transplant candidates and from those who are evaluated, only about 20% receive LDKT and the rest receive deceased donor transplantation. We aimed to explore the extent to which current governance of renal care in Canada supports the delivery of LDKT. Methods: This study drew on data from three Canadian provinces – BC, ON and QC – which vary in the success of LDKT rates. We analysed 91 interviews with key stakeholders across these provinces, using an established theoretical framework for systems w systems with multiple centers of decision-making or control. We applied this framework to map and describe how LDKT is delivered in Canada and the complex relationships between governance bodies. Results: As shown in figure 1, we identified four main, interconnected categories (nodes) of governance that influence LDKT delivery: public organizations; financing; professional culture; independent organizations. Our findings demonstrate that the multiplicity of organizations and mechanisms involved in renal governance, with various, at times competing, loci of control impede LDKT access and delivery. The following issues emerged as major themes: 1) jurisdictional divisions; 2) ineffective resource transfer; 3) converse financial incentivisation; 4) rigid governance structures that have difficulty adapting. Conclusion: We report several macro-level issues with LDKT delivery and demonstrate how current governance structures fail to optimize LDKT delivery due to inter and intra-organizational divisions and incompatibilities. This analysis sets foundations for our future work, developing strategic implementation for system-level change to enhance the delivery of LDKT. It therefore holds significant implications for practice and policy.

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ID: 77

Can we predict graft function and graft survival rate using hypothermic machine perfusion parameters from donors after cardiac death?

Juliano Chrystian Mello Offerni, Western University

Abstract Body: Background: The shortage of kidneys limits access to transplantation. The increment of donors after circulatory death (DCD) increased the availability of the organs. DCDs may have a higher risk of delayed graft function (DGF). However, DCDs can have decent long-term survival compared to a donor with brain death (DBD). Although these results are acceptable, we must look for features to help us in the process of accepting and allocating a DCD kidney. We aimed to use pump parameters for graft function and DCD kidneys' long-term outcomes. Methods: Between January 2016 and November 2019, we analyzed 86 single DCD transplants divided into standard criteria donor (SCD) and expanded criteria donor (ECD) due to the way kidneys were allocated by the timeframe of transplantation. All kidneys were pumped into a hypothermic machine (LifePort®- kidney Transporter machines). Donor and recipient demographics were performed. We assessed the overall graft and patients' survival rate. Outcome variables such as creatinine, clearance of creatinine (eGFR), and DGF were analyzed. Results:47% experienced DGF. (Table1) In the ECD group, those with an average resistance of The average flow had a significant impact on the ECD group. ECD group with an average flow of more than 150ml/min had better kidney function on D30 after transplant than less than 75 ml/min (p There was no difference in patient or graft survival between groups after a mean of 3 years (1-5 years). (p=0.6 and 0.3, respectively). (Figure 3) Conclusion: Overall, DGF did not impact graft or patient survival rate. We showed that either average resistance or flow could be used to determine the short-term outcome and, overall, the quality of the kidney. Therefore, this study highlighted the benefit of using multiple pump parameters to predict the outcomes in donors after circulatory death.

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ID: 78

COVID-19 hospitalizations and hospital outcomes among transplant recipients in Canada

Katrina Sullivan, Canadian Institute for Health Information

Abstract Body: Background: Solid organ transplant recipients are at increased risk for morbidity and mortality due to COVID-19, yet to best of our knowledge, an evaluation of the risk of hospitalization and in-hospital outcomes (including intensive care unit (ICU) transfer and mortality) has not been conducted for a national cohort of Canadian transplant recipients. Methods: All patients registered in CIHI's Canadian Organ Replacement Register (CORR) who received an organ transplant in Canada as of December 31, 2020, were linked to CIHI's Discharge Abstract Database (DAD) to obtain hospital admissions, ICU transfer and in-hospital mortality with a COVID-19 diagnosis between Jan-Dec 2021. These same outcomes for all Canadians without transplants were obtained for the same time-period from the DAD. Data from Quebec and Manitoba were excluded due to inability to link to DAD. Comparative outcomes were analyzed using Poisson regression to estimate unadjusted risk ratios with 95% confidence intervals (CI). Results: Canadian transplant recipients (N=23,497) were at a substantially higher risk of hospitalization outcomes with COVID-19 when compared to Canadians without organ transplants (N=22,690,130). The risk was generally higher for transplant patients in the 18–49-year age group (N=6,014) versus those aged 50+ (N=17,483), with an up to 25 times greater risk of hospitalization with COVID-19 and 57 times greater risk for ICU transfer with COVID-19 (Table 1). Risk ratios (RR) were similar between males and female. Patients with lung transplant (N=1,785) and a COVID-19 diagnosis experienced the greatest risk of ICU transfer (most notably for patients aged 18-49; RR 57.3, 95% CI 42.1-77.9), and in-hospital mortality (age 50+, RR 18.1, 95% CI 11.7-27.8). Conversely, liver transplant patients (N=4,531) had a lower RR of hospitalization, ICU transfer, and in-hospital mortality (Table 1). Conclusion: Canadian transplant recipients with a COVID-19 diagnosis are at a substantially higher risk of hospitalization and poor hospital outcomes when compared with Canada's non-transplant population.

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ID: 80

Humoral Responses in the Omicron Era following Three-Dose SARS-CoV-2 Vaccine Series in Kidney Transplant Recipients

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Abstract Body: Background: Kidney transplant recipients (KTR) have a diminished response to SARS-CoV-2 vaccination in comparison to immunocompetent individuals. Deeper understanding of the antibody response in KTRs following third-dose vaccination would enable identification of those who remain unprotected against Omicron and require additional treatment strategies. Methods: We profiled antibody responses in KTRs pre- and at one and three months post-third-dose SARS-CoV2 mRNA-based vaccine. Anti-spike and anti-RBD IgG levels were determined by ELISA. Neutralization against wild-type, Beta, Delta and Omicron (BA.1) variants was determined using a SARS-CoV-2 spike pseudotyped lentivirus assay. Results: 44 KTRs were analysed at 1 and 3 months (n=26) post-third-dose. At one month, the proportion of participants with a robust antibody response had increased significantly from baseline, but Omicron-specific neutralizing antibodies were detected in just 45% of KTRs. Median anti-spike and anti-RBD antibody levels declined at 3 months, but the proportion of KTRs with a robust antibody response was unchanged. 38.5% KTRs maintained Omicron-specific neutralization at 3 months. No clinical variables were significantly associated with detectable Omicron neutralizing antibodies, but anti-RBD titres appeared to identify those with Omicron-specific neutralizing capacity. Conclusion The majority of participants had detectable anti-spike and anti-RBD antibodies at one and three months following the third vaccine dose. Our principal findings are: 1) the proportion of patients whose antibody titres were consistent with a robust immune response rose significantly following a booster dose; 2) those who responded robustly at Month 1 had a preserved humoral response at Month 3; 3) over 50% of KTRs lack an Omicron-specific neutralization response 1 month following a third mRNA-vaccine dose and 4) we define anti-RBD and anti-spike antibody levels that may aid in the identification of patients lacking neutralizing antibodies against Omicron, the current dominant variant worldwide.

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ID: 81

The Canadian Anatomic Kidney Score (CAKS) : quantitative macroscopic assessment versus histological grading in pre-transplant evaluation of donor kidneys

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Abstract Body: Background: Quantitative gross assessment of a kidney has not been used to influence the evaluation to utilize a kidney for transplantation. The Canadian Anatomic Kidney Score (CAKS) is a novel grading system standardizing an objective gross description of the donor kidney that allows communication between clinicians and centres. We hypothesize that the CAKS score can independently predict renal graft performance and corresponds with KDPI and histologic assessments. Methods: Between 2018-2020, one hundred forty-seven patients underwent renal transplants (n=174). Prospective macroscopic examination of the kidney was determined via CAKS by set criteria evaluating the aortic vessels, anomaly (cysts/scars), sticky fat, and tactile assessment of structural rigidity (each 2). Furthermore, a renal implantation core biopsy was performed and histologically graded by Remuzzi score (RS). Neither CAKS nor RS was used to determine donor utility. Pre-operative donor score was also obtained using KDPI. GFR and graft function were tracked post-operatively for one year, with outcome failure defined by graft loss or GFR Results: There was a good correlation between the CAKS and RS, with an R-squared value of 0.03. (Figure 2) Importantly, CAKS correlated better with KDPI vs. RS (Figure 2). Independently, the CAKS effectively predicted poor renal allograft outcomes with an odds ratio of 1.48 for every 1-point change in total score (p=0.029)(table1). In contrast, RS was also effective at predicting renal allograft outcomes with an odds ratio of 1.55 for every one-point change in total score (p=0.010). When used as an adjunct to the RS, the CAKS independently increased the predictability of outcome failure to 60% (p=0.075) (Table1). Conclusion: The novel CAKS can be used to predict graft outcomes and correlates well with histologic assessment and KDPI scores. We will evaluate the replicability of the CAKS in other surgeons' hands and develop a composite score to better predict functional donor capacity in the future.

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ID: 82

Development of a simulated ischemia reperfusion injury model to study donor kidney preservation at 22°C

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Abstract Body: Introduction: Ischemia reperfusion injury (IRI) causes inflammation and cell death in kidneys obtained from donation after circulatory death (DCD) donors. This leads to poor organ function posttransplant. Therapeutics that prevent such damage, caused by hyperactive Toll-like receptors (TLR) systems, should be helpful in preserving organ quality pretransplant. We have previously reported that perfusion of porcine DCD kidneys with an oxygen carrier at 22°C significantly reduces TLR-induced inflammation and injury. To further improve this method, and therefore facilitate a high-throughput screening of a drug library, we have developed a simulated ischemia reperfusion injury (sIRI) model in human kidney tubular HK-2 cells. Methods: To mimic clinical IRI conditions, HK-2 cells are subjected to hypoxia for 1h at 37°C in a hypoxia chamber, sealed in a bag for 24h at 4°C (anoxia), and reoxygenated at 37°C for 24h. Cell supernatants are tested for injury markers (KIM1, NGAL), TLR ligands (damage associated molecular patterns; DAMPs) and inflammation markers (IL-6, TNF-? etc.) by ELISA. Cell death and viability are also assessed. For drug repurposing, THP1-Blue™ cells are incubated with DAMPs+drug simultaneously for 24h. NF-?B-inducible alkaline phosphatase reporter gene products are measured by Quanti-Blue. Optimization of discarded human kidney perfusion methods are currently underway. Results: Our results show sIRI condition increases cell death by both necrosis and apoptosis. DAMPs such as HMGB1, which activates the innate immune system through TLRs, and other predominant cytokines, are present in sIRI cell culture supernatants, as indicated by bead-based high throughput Multiplex ELISA assays. Conclusion: Our model provides the foundation for future research aimed at improving organ preservation. The identification of a drug candidate that can ameliorate the damage from IRI will help optimize current organ preservation conditions. Additionally, repositioning of existing clinically-approved drugs will allow for the rapid translation of therapeutics to clinical use.

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ID: 83

Risk of hospitalization, ICU transfer, and in-hospital death with COVID-19 in dialysis patients compared to kidney transplant recipients: A national cohort study

Katrina Sullivan, Canadian Institute for Health Information

Abstract Body: Background: While it is known that patients with kidney failure are at a higher risk of morbidity and mortality due to COVID-19, it is not well known whether there are differences in outcomes comparing dialysis patients and kidney transplant recipients. This study aims to compare the risk of hospitalization, intensive care unit (ICU) transfer, and in-hospital mortality between dialysis patients and kidney transplant recipients who had a hospital admission that included a COVID-19 diagnosis. Methods: To establish the cohort, all patients registered in CIHI's Canadian Organ Replacement Register (CORR) with kidney failure as of December 31, 2020, were linked to CIHI's Discharge Abstract Database (DAD) to obtain hospitalizations that included a diagnosis of COVID-19 between Jan-Dec 2021. Data from Quebec and Manitoba were excluded due to an inability to link to the DAD. Outcomes included hospitalization, transfer to the ICU, and in-hospital mortality. Comparative outcomes were analyzed using Poisson regression to estimate unadjusted risk ratios with 95% confidence intervals (CI). Results: Overall, 21,736 dialysis patients and 15,695 kidney transplant patients were included. The risk of hospitalization or in-hospital mortality with COVID-19 was not significantly different comparing these two groups (Table 1). In contrast, the risk of ICU transfer with COVID-19 was significantly higher in kidney transplant recipients compared to dialysis patients. This held true regardless of dialysis modality, with kidney transplant patients facing 1.4 [95% CI 1.1-1.7] and 1.8 [95% CI 1.2-2.6] times greater risk for ICU transfer with COVID-19, compared to patients receiving in-centre dialysis and home dialysis, respectively (Table 1). Conclusion: Kidney transplant patients with COVID-19 are at a higher risk of ICU transfer compared to dialysis patients with COVID-19, even in unadjusted analyses. These results have implications for the management of kidney transplant recipients who are admitted to hospital and are confirmed to have COVID-19.

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ID: 84
Banff Classification for Polyomavirus Nephropathy: A Single Center Experience

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Abstract Body: Background: We applied the PVN classification presented by Banff Working Group in 2018 to our cohort. We also tested the implementation of Banff i-IFTA score into the PVN classes in combination with polyomavirus load (pvl). Methods: We evaluated 60 indication biopsies with PVN and classified as described in Banff's proposal. We analyzed clinicopathologic differences between PVN classes by: 1) including cases with concurrent acute rejection, 2) excluding cases with rejection. An alternative classification model consisted of i-IFTA (instead of ci) and pvl was additionally tested using the same Banff classification criteria. Results: The median duration from transplantation to PVN diagnosis and the median follow-up was 10 and 23 months, respectively. There were 13, 43 and 4 cases in Banff classes 1, 2, and 3. During follow-up, 35% had biopsy-proven acute rejection or acute rejection suspicion. Median time from transplantation to PVN was 8, 10 and 13 months in class 1, 2 and 3, respectively (p=0.066). Banff scores i, ti, i-IFTA, t, and ct gradually increased from class 1 to 3 ($p < 0$ .05). Two-year graft survival were highest in class 1 and lowest in class 3, both when cases with concurrent rejection were included and excluded ($p < 0$ .05) (mean 22.5, 17.1 and 7.7 months in class 1, 2 and 3, respectively). Serum creatinine levels at the initial PVN diagnosis and at 1st, 3rd, 6th, and 12th months were lowest in class 1 and highest in class 3. Two-year graft survival differed significantly also in classes according to the tested "alternative" i-IFTA/pvl classification model ($p < 0$,05) (mean 17.7 and 10.4 months in class 2 and 3). In this model, 7 cases (4 of which had graft loss) were up-classified. Conclusion: Banff 2019 PVN Classification succesfully stratifies patients in terms of clinical presentation, disease progression, and graft survival. A PVN classification comprising i-IFTA+pvl score may better predict graft survival.

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ID: 85

Validation of the Canadian Anatomic Kidney Score (CAKS): Assessment of Reproducibility Among Surgeons and Trainees

Juliano Chrystian Mello Offerni, Western University

Abstract Body: *Background: The Canadian Anatomic Kidney Score (CAKS) is a novel grading system to standardize the gross description of the donor's kidney. We have shown that CAKS corresponds with KDPI scores and independently predicts allograft performance. To validate the reliability and reproducibility of CAKS, we surveyed transplant surgeons, fellows, and urology residents across Canada. *Methods: CAKS evaluates the vessels, anomaly (cysts/scars), sticky fat, and tactile assessment. In order to assess the reproducibility of the CAKS, we submitted photographs of six kidneys with two pictures each, exposing different anatomical parts (renal artery patch and dissection of fat around bare parenchyma) to respondents, as well as a scorecard to a list of Canadian renal transplant surgeons, fellows (obtained from the Canadian Society of Transplantation), and urology residents through Survey Monkey. We also obtained demographic information from the respondents. *Results: Out of 104 surveys sent, 45 respondents filled out the survey (27 transplant surgeons, six fellows, and 12 residents) (Table1). Overall, Kruskal-Wallis test showed that there were minimal differences in the CAKS assigned to kidneys between those who developed the score and the respondents with various levels of transplant expertise (Table 2). However, in 2 of 6 photographs, scores assigned to the characterization of sticky fat differed between residents of the other groups; $p=0.011$ and $p = 0.020$, respectively (Figure1). The Cronbach's alpha inter-rater reliability after pair-wise exclusion resulted in overall alpha - 0.98, vascular alpha- 0.95, anatomic alpha- 0.99, and structural alpha- 0.98. *Conclusions: The novel CAKS showed to be reproducible among surgeons regarding the visual assessment of kidneys from 2 photographs. The Cronbach's alpha test confirmed the reproducibility of CAKS. As this has also been shown to predict graft performance, this score aids in communication between physicians and surgeons concerning donor kidney assessment.

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ID: 87
Preservation of human kidneys with subnormothermic machine perfusion

Patrick Luke, University of Western Ontario

Abstract Body: Background: While cold static preservation at 4ºC is the conventional method of organ preservation in clinical practice, we observed superior renal graft protection following preservation at 22ºC. Hence, we re-designed a pulsatile perfusate pump, which is used predominantly for preservation of porcine kidneys. However, its application and benefit in human renal grafts is unknown. In this study, we tested the impact of providing oxygenated pulsatile ex vivo perfusion of human donation after circulatory death (DCD) kidneys for 12h at 22ºC. Methods: Human DCD kidneys were obtained in pairs with matching blood (~ 1L) from the same donor or Canadian Blood Services. Suitable donors are HIV (-), Hepatitis B/C (-), diabetes mellitus (-), normal terminal serum creatinine, warm ischemia time of 90-120 min, and no longer than 10h to reach our laboratory, during which time the organs will be stored in cold temperature. Organs were flushed with cold HTK solution and subjected to cold storage at 4°C or pulsatile blood perfusion at 22°C for 12h with hemoglobin-based oxygen carrier solution. Thereafter, kidneys are reperfused with normothermic (37°C) oxygenated blood for 4h. Blood and urine were collected every hour for biochemical analysis. Total urine output, urinary protein, albumin/creatinine ratio, and flow rate are measured. The kidneys were examined for acute tubular necrosis (H&E), apoptosis (TUNEL) and inflammation. Results: Kidneys preserved at 22°C had greater creatinine clearance and urine production compared to 4°C cold storage. Also, ischemia reperfusion injury-induced inflammatory markers were markedly reduced at 22°C compared to 4°C preservation. However, H&E and TUNEL scores may require further modification of evaluation. Conclusion: Our findings indicate that human DCD kidneys can be preserved at 22°C for 12h, with better outcomes than conventional storage. Importantly, our pulsatile pump model allows addition of pharmacological therapy for further improvement, as drugs metabolize better near body temperature.

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ID: 88

Do virtual health appointments impact travel-related greenhouse gas emissions in Solid Organ Transplant patients?

Christopher Buckland, Pediatrics/Cardiology

Abstract Body: Background: The Multi-Organ Transplant (MOT) Program serves children of British Columbia and the Yukon. Families may travel upwards of 2,500km several times a year to attend in-person clinical appointments. The COVID-19 pandemic required a change in healthcare practices, with some in-person appointments replaced with virtual appointments. We sought to estimate the potential reduction in patient travel and greenhouse gas (GHG) emissions that accompanied this change in clinical practice. Methods: Our study cohort included all heart, kidney, liver and lung transplant patients currently followed by our program. All patient appointments between April 1, 2020 and March 31, 2022 were reviewed. Driving distance, driving time and GHG emissions were estimated using specialized geocoding software. Carbon dioxide equivalents (CO2e) were used as a surrogate for GHG emissions and estimated for five motor vehicle fuel efficiencies. We report the results for a fuel efficiency of 10L/100km. Results: The study cohort included 148 (57% male) patients. There were 29 (20%) heart, 66 (45%) kidney, 51 (34%) liver and 2 (1%) lung transplant recipients who were transplanted at a median age of 4.8yrs. Of the 1035 MOT appointments recorded during the study period, 194 (19%) were held virtually. The median travel distance and travel time from home to MOT clinics were 43.2km and 42.5min, respectively. Cumulative driving distance and time during the study period would have been 306,729km and 3,978hrs, respectively, if all appointments were held in-person. Virtual appointments would save 90,549km and 1,092hrs of travel. If all appointments were held in-person, the cumulative CO2e would approximate 124.839 tonnes (t). Virtual appointments would save 36.853t, a 30% reduction in CO2e. Conclusion: While patient travel to MOT clinics is essential for some appointments, others may be held virtually. These virtual appointments significantly reduce patient travel and GHG emissions.

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ID: 91

The Case for Disruptive Innovation in Solid Organ Transplantation: Optimizing Organ Utilization in Canada

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Abstract Body: Background: One in five kidneys from deceased donors are discarded. Kidneys at risk of discard (KARD) are commonly from donors of increased age, comorbidities, and/or impaired renal function. When appropriately transplanted, KARD can improve the life expectancy of older patients with end stage kidney disease (ESKD) who may have fewer opportunities to receive a transplant. The perception of 'wastefulness' in the organ donation process may reduce trust in the system. We hypothesize that a strategy to rationally expand the use of KARD will improve access to transplantation and the outcomes of an unserved population of ESKD patients. Methods: Canadian Blood Services assembled a steering committee of Canadian transplant nephrologists, transplant surgeons, and donation administrators in 2019. The project adopted an approach informed by disruptive innovation (DI) theory to increase access to transplant in unserved patients with ESKD. DI theory is used in various industries to develop breakthrough strategies targeting consumers that may be missing out or overlooked. The goal is that every kidney donated in Canada will be transparently, equitably, and safely transplanted into a suitable recipient. Results: Background information was presented via two webinars, covering topics including donor decline data from Ontario and Manitoba, a donor deferral survey of Canadian transplant clinicians, systematic review of the literature on graft outcomes, qualitative study on patients and family's perspectives, and data from the McGill program on outcomes of KARD. A virtual forum of over 50 stakeholders developed a framework to improve the utilization of KARD including donor and recipient eligibility, accountability, allocation, guarantees, patient education, and outcome measurement. Conclusion: Kidneys at risk of discard are an underused source of organs available for transplantation into recipients who may be unserved by the current system. Improving KARD utilization has the potential to be a DI improving the Canadian organ donation and transplantation landscape.

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ID: 92

Donor-derived cell-free DNA (dd-cfDNA) for detection of allograft rejection and monitoring treatment response in pediatric kidney transplants

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Abstract Body: Background: While donor-derived cell-free DNA (dd-cfDNA) is an established tool for monitoring rejection and treatment response in adult kidney transplants, less data is available in children. Methods: All patients 1000) and dd-cfDNA >1%, but there was no correlation between level of dd-cfDNA elevation and Banff lesions, proteinuria, or eGFR percent change. Post-treatment biopsies showed persistent but reduced microvascular inflammation (MVI). In all but one patient, dd-cfDNA remained >1% at 1 month post-treatment and throughout available follow-up (mean follow-up 8 months, range 3-20 months). There was no correlation between dd-cfDNA and DSA type or level; in 4/12 patients DSA became undetectable, while dd-cfDNA remained >1%. In contrast, only 3/6 patients with TCMR had dd-cfDNA >0.5% at diagnosis. By 1 month post-treatment, dd-cfDNA was 1% identified all cases of ABMR and mixed rejection and did not correlate with treatment or post-treatment DSA levels, but did correlate with persistent MVI. Although only identifying 50% of patients with TCMR, dd-cfDNA returned to baseline after treatment, paralleling histologic resolution of TCMR.

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ID: 93

CD34 recipient chimerism is an early and accurate predictor of acute myeloid leukaemia relapse After allogeneic HCT

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Abstract Body: Introduction: Allogenic hematopoietic cell transplantation (HCT) is the most successful treatment for acute myeloid leukemia (AML). However, AML relapse continues to be the foremost cause of posttransplant mortality. Approximately 25% of HCT recipients die due to AML relapse. This poor long-term survival is primarily linked to late detection of relapse. Myeloid cell (CD13+/CD33+ cell) chimerism is routinely used for monitoring engraftment but fails to detect relapse within a clinically actionable lead-time (typically 2-3 months prior to relapse). In the present study, we investigated whether a modified approach based on chimerism assessment in CD34+ cells could provide an early and accurate prediction of posttransplant relapse Methods: 165 PBMNC specimens from 77 allogeneic HCT recipients transplanted for AML (20 relapsed and 57 relapse-free) were analyzed at four-time points (from 3+ months to relapse to relapse onset). A highly sensitive method to purify CD34+ cells by flow cytometry-based cell sorting and subsequent extraction of DNA from sorted cells was developed. Sorted cell DNA was then amplified using a panel of 16 Short Tandem Repeat (STR) loci and size fractioned using capillary electrophoresis. Informative markers were used to calculate recipient chimerism. Results: Chimerism was detected in 15 out of 17 patients at 2-3 months prior to relapse (Figure 1). The CD34 chimerism assay showed a clinical sensitivity of 88% and specificity of 96% at predicting relapse ($p = 1.831e-10$) with a 2–3-month lead time to relapse. Conclusion: A modified chimerism assessment approach using CD34+ cells is a highly sensitive and specific method for detecting AML relapse with a significant lead time. Through early detection, this modified chimerism approach will allow for prophylactic treatment of high-risk HCT recipients to decrease the incidence of relapse and allow more patients to stay in remission, improving the overall survival and quality of life for AML patients.

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ID: 94

Discovery of pro-inflammatory and pro-fibrotic macrophage subsets in chronic lung allograft dysfunction using single-cell RNA-sequencing

Allen Duong, University Health Network

Abstract Body: Background: Lung transplant recipient survival is severely limited by chronic lung allograft dysfunction (CLAD) which manifests as two main clinical phenotypes with distinct presentations: bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). Pulmonary macrophages are an immune cell population of interest due to their ability to perform pro-inflammatory and pro-fibrotic functions when activated, however their contributions to CLAD have not been studied. We used single-cell RNA-sequencing (scRNAseq) to identify and characterize unique macrophage subsets in BOS and RAS explanted. Methods: 9 fresh lung samples (6 BOS, 3 RAS) from re-transplant or autopsy cases were collected, processed, and subjected to 10X Genomics 3' chemistry for scRNAseq, and were compared to 5 control donor lung samples. Analysis was performed with R packages: Seurat, ClusterProfiler and CellChat. Results: There was a large variety of immune and parenchymal cell types in the lung. Macrophages were subsetted and reclustered, identifying 21 unique clusters (Figure 1A). Both BOS and RAS lungs had a high proportion macrophages expressing peripheral blood marker FCN1 and pro-inflammatory gene AIF1 (Figure 1B), annotated as AIF1+ macrophage. Gene set enrichment analysis revealed increase in "positive regulation of cell-cell adhesion" and "T cell activation" sets. RAS lungs specifically show an enrichment of macrophages expressing fibrosis-associated genes annotated as SPP1+ macrophage (Figure 1C). Cell-cell interaction analysis revealed that the SPP1+ macrophage have inferred interactions with fibroblasts and type I alveolar cells (Figure 1D). Conclusion: Through scRNAseq, we have identified two unique macrophage clusters associated with CLAD. Pro-inflammatory AIF1+ macrophage are recently differentiated monocytes that may be supporting the T cell alloimmune response, whereas the pro-fibrotic SPP1+ macrophage may contribute to parenchymal lung fibrosis in RAS. To further characterize the function of these macrophage subsets, we plan to sort the subsets and perform in vitro functional assays in future studies.

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ID: 95

Perspectives and experiences of patients with kidney transplant failure: systematic review and meta-synthesis

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Abstract Body: Background: Graft failure is now the fourth leading cause of kidney failure needing dialysis. One in five patients who received a kidney transplant will lose their allograft within five years and over half within ten years. These patients experience fragmented transitions of care between the transplant and dialysis teams and have poor outcomes when compared with transplant naïve dialysis patients. We aimed to 1) synthesize existing evidence on the experiences of patients who have sustained renal graft loss, and 2) isolate critical primary and secondary Patient-Reported Outcomes (PROs) to be integrated into systematic assessment of patient outcomes. Methods: We undertook a systematic literature review of personal experiences of patients with renal graft failure. Six databases were searched systematically. We included empirical qualitative studies published in peer-reviewed journals. Thematic synthesis was used to combine data. Methodological quality of studies was assessed using the Critical Appraisal Skills Programme checklist. Results: We noted a dearth of patient perspective. PROs and the decision-making surrounding re-transplantation are largely unexplored. Of the 4,214 studies screened only five studies met our inclusion criteria. As shown in Figure 1, we identified three interconnected phases as patients transition through renal graft loss. Each phase is fraught with a complex interplay of challenges and requires tailored multi-disciplinary intervention approaches. Critical factors affecting coping include gradual physical health improvement and the availability of professional and social support. Additional complexity arises when support is provided by an informal caregiver who is the living donor. While clinical transplant care is evaluated positively, there are gaps in the provision of information and psychosocial support related to transplant failure. Conclusion: There is limited evidence exploring the perspectives of patients who experience renal graft failure. We report an important knowledge gap in the care of patients with graft failure which has research and practice implications.

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ID: 96

"I feel more comfortable this way": Relationship between African, Caribbean and Black kidney transplant candidates and recipients and their healthcare providers in living donation - a qualitative analysis

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Abstract Body: Background: African, Caribbean, and Black (ACB) patients with kidney failure are ~60% less likely to receive living donor kidney transplant (LDKT) compared to White patients in Canada. The relationship between ACB patients and their healthcare providers (HCPs) is integral to their decisions about LDKT. In this qualitative study we aimed to understand the nature of this relationship. Methods: Snowball and purposive sampling were used to recruit self-identified ACB adult kidney transplant candidates and recipients to participate in semi-structured interviews. Participants were asked about their ethnocultural identities, and their experiences with the healthcare system, specifically along the nephrology pathway. Data were analyzed via reflexive thematic analysis and using tenets of Critical Race Theory. Results: 10 participants (age: 21-69, 6/10 female) were included. The central theme of this analysis was the participants' desire for an open, honest, and collaborative relationship with their HCPs. Our analysis suggests that these expectations are more frequently met if HCPs are also from ACB communities. Several sub-themes were also developed: desire for a person-centered approach, respect for patients' health-related preferences, and their perspectives; desire for judgment-free interactions with their HCPs. Participants felt judged by their non-ACB HCPs which caused them to withhold potentially important information from them; desire for greater representation and diversity within the healthcare system as participants felt more comfortable with HCPs from ACB communities. Conclusion: This study highlights that ACB patients expect a respectful, open, trustworthy, and collaborative relationship with their HCPs and the healthcare system. The absence of this relationship may be an important barrier to decision-making regarding LDKT in this population. We will use this understanding about experiences, expectations, and desires of ACB patients to develop interventions to improve access and utilization of LDKT for these patients.

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ID: 97

Stigma as a potential barrier to living donor kidney transplant (LDKT) for African, Caribbean, and Black (ACB) patients in Toronto, Ontario, Canada

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Abstract Body: Background: Patients from ACB communities are much less likely to receive live donor kidney transplant (LDKT) than White patients. In the context of health and illness, stigma (a pattern of stereotyping) can be defined as “labelling or associating an individual's health practices and lifestyle to their cultural beliefs”. In this preliminary qualitative analysis, we explore how stigma may influence access to LDKT in ACB communities in Toronto. Methods: Self-identified ACB participants (individuals with and without lived experience with kidney failure and health care professionals [HCPs]) were recruited using purposive and snowball sampling. Semi-structured in-depth individual interviews (IDIs) and focus groups (FGs) were conducted, audio-recorded, and transcribed verbatim. Reflexive Thematic Analysis was utilized, also drawing on the tenets of Critical Race Theory (CRT) and Intersectionality. Themes were developed, refined, and finalized by the research team. Results: We conducted 6 community FGs (n=81), 7 IDIs with HCPs, 9 patient IDIs, and 2 FGs (n=6) with patients with kidney failure. Participants both anticipated and had experienced stigma around kidney disease. Participants with kidney failure feared judgment from HCPs (e.g. due to anticipated assumptions about their health beliefs and behaviours) as well as from family, friends, and their community (e.g. due to anticipated assumptions about lifestyle choices). This experienced and anticipated stigma contributes to the hesitancy about communicating the need for a potential donor, which is an essential step towards LDKT. Conclusion: Stigma, stemming from both the racialized status and from the chronic illness, is a potential important barrier to LDKT as it limits the readiness to engage in discussions about kidney failure and treatment options, therefore may reduce the chance of identifying potential living donors. Culturally tailored, competent resources, co-developed with ACB communities, may help reduce stigma and may improve equitable access to LDKT.

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ID: 98

Canadian community pharmacists' management of solid organ transplant recipients: a survey-based characterization of confidence and care roles

Jessie Hallett, Nova Scotia Health

Abstract Body: Background: Immunosuppressant medications prevent allograft rejection following solid organ transplantation (SOT). While little is known about the involvement of community pharmacists in SOT patient care, studies from hospital and transplant clinic settings demonstrate that pharmacist participation in transplant recipient care is associated with improved graft survival. The objective of this study was to describe the care activities that Canadian community pharmacists perform for SOT recipients, the frequency of those care activities, and pharmacists' self-reported confidence in performing them. Methods: A two-part electronic survey was developed. Quantitative questions asked pharmacists to self-report the frequency and confidence with which they perform specified patient care activities. Open-ended qualitative questions allowed pharmacists to comment on their experiences providing care to SOT recipients. The survey was open from March 16 to April 14 2020 and was electronically distributed to pharmacists through national and provincial pharmacy associations. Results: 27 Canadian community pharmacists completed the survey. Pharmacists reported performing specified care activities for SOT recipients "less than monthly". Pharmacists described their confidence in performing a majority of activities as "not at all" to "somewhat" confident. Care activities that pharmacists reported performing more often and with higher confidence were most similar to activities performed for the general population. Pharmacists reported a lower frequency and confidence in performing SOT specific care activities, including differentiating between immunosuppressant formulations, assessing for vaccines and minor ailments, and assessing patients for adverse effects or infectious complications of immunosuppressants. Qualitative responses demonstrated a poor understanding of local dispensing practices, a desire for more communication from transplant clinics, and more SOT specific references. Conclusion: Canadian community pharmacists responding to this survey reported providing care to SOT patients infrequently and with low overall levels of confidence. Pharmacists appeared to be aware of this gap, requesting more quick reference resources and more frequent communication from transplant clinics. Background: Immunosuppressant medications prevent allograft rejection

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ID: 99

Non-A1 blood group to B/O kidney transplantation: A single centre experience

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Abstract Body: Background: In Canada, blood type B kidney transplant candidates have a lower transplantation rate and longer wait times than other blood type candidates. Blood type O candidates have the second longest wait times. One strategy to shorten wait-times for blood group B/O patients is to use kidneys from non-A1 blood group donors. In this study, we analyzed our center's data from non-A1 blood type kidney transplants to B/O transplant recipients to determine what their long-term outcomes are. Methods: This is a single-center retrospective case series. Adult kidney and simultaneous pancreas-kidney (SPK) recipients were included in this study to analyze the outcomes in non-A1/non-A1B to B/O deceased and living donor transplants. Results: Between November 1st 1990 and March 14th 2022, our center has performed 78 non-A1 to B/O kidney transplants and 3 SPK transplants. Of the total cohort of 81 recipients, 55 were non-A1 to A, 13 were non-A1B to AB, and 13 were non-A1 to O. Twelve transplant recipients received living donor organs and the remaining 69 received deceased donor organs. The patients were followed for a mean of 2113 days. In total, 43 patients received induction with rabbit anti-thymocyte globulin (ATG), 8 received equine ATG, and 30 were induced with Basiliximab. Average wait time for B and O recipients was 245 and 307 days, respectively. Two patients had primary non-function (2.4%), and 17 of the 81 patients (21.0%) had delayed graft function. There were 8 cases of antibody mediated rejection, and average time to onset was 8.7 days. There were 11 cases of T cell-mediated rejection, with mean time to onset being 40.7 days. Of these, 4 occurred in the first 10 days post-transplant. Conclusions: Non-A1 into B/O transplantation was well tolerated in this large cohort, and wait-times were lower than the average provincial wait-times in Ontario.

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ID: 102
Symptom experiences of heart transplant recipients and caregivers

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Abstract Body: Background: Heart transplant (HT) recipients experience significant physical symptoms and psychosocial concerns after transplant. These symptoms often remain unmanaged and may reduce their quality of life. In this preliminary qualitative analysis, we wanted to gain a better understanding of the symptom experiences and perspectives of HT recipients and caregivers. Methods: Adult (?18 years) HT recipients and caregivers were recruited using purposive and snowball recruitment. A qualitative description framework was utilized to explore and understand post-transplant symptom experiences and perspectives of HT recipients and their caregivers. A semi-structured interview guide was utilized, interviews were audio-recorded and transcribed verbatim. Directed content analysis with both deductive and inductive coding strategies was used. Emerging themes were co-generated by the research team. Results: Five HT recipients (age: 39-81 years, 12-24 years post-transplant, 4/5 female) and one caregiver (age: 53) reported significant physical, emotional, and social challenges. Theme 1 pertains to overall physical functioning. Participants described an improvement in physical functioning after transplant; however, limitations are experienced in the context of more intense activities (e.g., sports). Fatigue, muscle weakness and side effects attributed to immunosuppressive drugs contribute to limitations even with routine tasks (e.g., taking the stairs) and self-care. This, in turn, leads to emotional distress. Theme 2 pertains to emotional trauma after transplant, anxiety, depressive symptoms, fear of rejection and thinking about the donor and their family. Theme 3 pertains to anticipated and perceived limitations on social life (transitioning back to work or school) and the associated financial constraints. Finally, physical, emotional, and social challenges identified by participants were interlinked to shape the overall transplant symptom experience. Conclusion: This study characterized the physical and psychosocial symptom experiences of HT recipients. This understanding may allow us to provide care and support that is more tailored to patient needs.

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ID: 103

Novel Artificial Intelligence Algorithm Using Donor/Recipient Factors Outperforms Existing Methods in Predicting Kidney Transplant Outcome: A Study of 142,971 Transplants from the SRTR

Mohammad Shafiee, University of Toronto

Abstract Body: Background: Commonly used medical decision-making tools in transplantation generate a risk score considering almost donor factors only. We aimed to introduce a novel Artificial Intelligence method that generates individualized predictions on the outcome of transplantation by learning from complex dynamic interactions among donor's and recipient's variables simultaneously. Method: The transplant outcome is predicted by a DNN model through estimating a Probability Distribution Function (PDF). KDRI score, an established clinical decision-making tool in kidney transplantation, was also calculated for all matches. We compared the accuracy of the expected value of PDFs to KDRI scores using the Concordance Index (CI) score (the proportion of correct ordinal predictions divided by the total number of predictions) in three cumulative post-transplant follow-ups of 60, 120 and 228 months. Results: The DNN tool was trained on 142,971 records of donor-recipient pairs and 472 kidney-related variables from the SRTR, the US kidney transplant dataset. In this dataset, the transplant period was from 2000 to 2019, and transplant follow-up was from 2001 to 2020. The CI scores of the DNN tool in post-transplant times of 60, 120 and 228 months were 0.86 (95% CI: 0.79-0.87), 0.87 (95% CI: 0.83-0.89) and 0.86 (95% CI: 0.82-0.87), respectively. The CI scores for KDRI were 0.54 (95% CI 0.53-0.55), 0.59 (95% CI: 0.57-0.60) and 0.61 (95% CI: 0.60-0.63) in the same follow-up periods, respectively. The comparison between the CI score estimates shows that the DNN tool has significantly higher prediction capability in all follow-up times ($p < 0 .05$). Conclusion: This model enhances insightful compatibility, leading to better outcomes of transplantation and efficient utilization of the scarce organ supplies. Considering donor and recipient variables and analyzing complicated relationships among numerous match variables may explain this tool's superiority. Future studies are needed to validate the performance of this tool further.

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ID: 104

Transcriptomic profiling of small airway epithelium club cells in chronic lung allograft dysfunction

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Abstract Body: Background. The major barrier to long-term survival following lung transplantation is progressive scarring, termed chronic lung allograft dysfunction (CLAD). Two main phenotypes of CLAD have been identified: bronchiolitis obliterans syndrome (BOS) characterized by obliterative bronchiolitis fibrosis and inflammation of small airways; and restrictive allograft syndrome (RAS) defined by pleural and parenchymal fibrosis. Ongoing rejection mediated by alloimmune responses along with repeated injuries and loss of epithelial club cells are hallmarks of CLAD pathogenesis. Club cells are thought to have protective and anti-inflammatory roles. We hypothesize that CLAD is associated with an aberrant transcriptomic profile in club cells related to differential cell death, proliferation, and senescence gene expression. Methods. We used single cell RNA sequencing (scRNAseq) to establish transcriptomic signatures of allograft airway club cells in single cell suspensions generated from lung allografts affected by CLAD (6 BOS, 3 RAS), explanted during autopsy or lung retransplant surgery, and from control donor lung samples (n=5). The scRNAseq dataset was processed, explored, and visualised using Cellenics® community instance hosted by Biomage. Results. Our findings show profound loss of epithelial cells, including club cells, in RAS compared to BOS and controls (Fig. 1A). Further, genes related to I) extrinsic apoptosis (TNFSF10), II) intrinsic apoptosis (BAG1, BIK), III) autophagy (ATP1B1, PRKAA2), IV) mucin, and V) growth factors were preferentially/relatively upregulated in BOS and RAS club cells compared to control club cells. VI) Proliferation-related gene (MCM2) was downregulated and VII) senescence-related genes (CDKN2A, CDKN1A) were upregulated in RAS club cells compared to BOS and control club cells (Fig. 1B). Conclusion. Our data show a disruption of the transcriptomic profile of club cells found in lung transplant recipients affected by CLAD, especially RAS, suggesting increased cell death and senescence processes and reduced proliferation compared to controls. Thus, this study provides insight into potential mechanisms underlying CLAD.

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ID: 105

Automated histology lesion interpretation in kidney transplant biopsies –how using strict decision trees differs from practical application of Banff 2019 guidelines

Philip Halloran, University of Alberta

Abstract Body: BACKGROUND: Standard-of-care (SOC) diagnoses of kidney transplant biopsies requires an expert pathologist interpreting features following Banff guidelines. While many of the Banff 2019 criteria provide clear direction, some require subjective interpretation which can result in discrepancies. We created an "AutoBanff" algorithm that strictly applies Banff 2019 guidelines to recorded lesions (adapted from a prior algorithm following Banff 2015/2017) and assessed the relationship between strict guideline application and SOC diagnoses, as well as an exploration of the relationships between the guidelines and disease states as represented by molecular diagnoses (MMDx). METHODS: We studied 1679 prospective indication kidney transplant biopsies with locally-assigned lesion scores and clinical data (Clinical trials.gov #NCT01299168). AutoBanff converted Banff 2019 guidelines into programmed decision trees (Figure 1), checked by expert pathologists. Automatically-assigned diagnoses from the algorithm were compared to recorded local histologic diagnoses and molecularly-assigned diagnoses (MMDx), using a six-class model (ABMR, possible ABMR 'pABMR', TCMR, possible TCMR 'pTCMR', Mixed rejection, or No rejection 'NR'). RESULTS: AutoBanff diagnoses disagreed with local histology in 484 biopsies (28%, Table 1). Discrepancies were increased in biopsies with molecular abnormalities (p 0 (p=0.002); or with positive BK virus (p=0.03). Many disagreements were not 'boundary disagreements' (i.e. pABMR vs. ABMR), but rather between clear diagnostic categories (i.e. ABMR vs. NR). Local SOC histology diagnoses agreed more with MMDx than did AutoBanff following 2019 guidelines, but this was not significant (a prior algorithm following Banff 2015/2017 agreed significantly less, p=0.002). CONCLUSIONS: Histology lesions can be interpreted by a computerized algorithm to characterize interobserver variation and/or provide unbiased assessment. Discrepancy between AutoBanff and local histology reflects intrinsic noise in histology, ambiguity in guideline interpretation, professional opinion, and/or problematic guidelines. The experience and skill of the professional pathologist using Banff 2019 to interpret biopsies is likely adding value not completely captured in a rigorous algorithm.

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ID: 106

Deep neural network model to determine and rank the predictors of failure time in kidney transplantation in patients younger than 18

Mohammad Shafiee, University of Toronto

Abstract Body: Background: We aimed to use Deep Neural Network (DNN) models to determine factors impactful on graft failure from donor-recipient pairs, which generate individualized predictions to optimize compatibility outcomes for patients of < 1 8 years. Methods: The DNN was trained on 10,788 records of recipients aged < 1 8 years and their donors with 322 variables from the SRTR, the U.S dataset (kidney transplant period 1995-2019, follow-up from 1996-2020). Two DNN models were jointly trained to predict kidney allograft failure and rank donor-recipient variables. While the first DNN model was trained to predict the allograft failure time using survival analysis, the second model learned the importance of donor-recipient pairs factors before and after transplantation by learning the weights of each variable ranking. Kolmogorov–Smirnov test determined to rank the significance of the variables for the goodness of fit considering p-value < 0 .05. Results: The DNN tool identified the most significant covariates (n=28) among 322 donor-recipient pair variables affecting the failure time without pre-selecting assumptions. These covariates were consistent with other human-driven statistical models reported in numerous studies. However, this model ranked these covariates based on the gratitude of their impact on graft failure. The recipient's latest hospitalizations during follow-up, functional status, pulmonary embolism, treatment for BK virus, pre-transplant dialysis, physical capacity, patient non-compliance, rejection events and presence of vascular disease were ranked as the crucial factors in graft failure. BUN, death due to stroke, Hypoxia, HLA-DR51 locus, HCV antibody status, and meeting CDC guidelines for a high-risk donor were found to be significant co-variants from the donor side. Conclusion: DNN could productively develop a predictive model and rank the covariates by their impact on graft failure. The accurate prediction provided by DNN is superior to traditional predictive methods optimizing the quality of organ transplantation. Thus, future studies focusing on the high-ranking covariates could potentially improve graft outcomes.

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ID: 107

Construct validity of the PROMIS® preference-based summary score (PROPr) in patients with liver transplant

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Abstract Body: Background: PROPr is a preference-based health state summary score calculated from Patient Reported Outcome Measurement Information System (PROMIS®) domain scores. We aimed to assess the construct validity of PROPr among liver transplant recipients (LTR) using the EQ-5D-5L and Short-Form Six Dimension (SF-6D®) as legacy instruments. Methods: A cross-sectional, single-center convenience sample of adult LTRs completed the PROMIS-29+2 short form or PROMIS-Computer Adaptive Tests, the EQ-5D-5L, and the Short Form-12 (SF-12) questionnaires. The SF-6D was calculated from SF-12, the PROPr from PROMIS domain scores. EQ-5D-5L utility score was calculated using the Canadian value set. Convergent validity was assessed using Pearson's correlation between PROPr vs EQ-5D-5L and SF-6D. Construct validity was further evaluated using "clinical condition impacts", that is the coefficient for patients with versus without health conditions in linear regression models with preference-based scores as dependent variables. PROPr and legacy measures were compared between groups formed by clinical variables (i.e., comorbidity, symptom burden, anemia) expected to impact health-related quality of life. Results: Mean (Standard deviation) age of the 205 participants was 56 (15) years, 67% were male and 73% Caucasian. PROPr and SF-6D scores were less subject to ceiling effects than the EQ-5D-5L. Strong correlations were observed between PROPr and EQ-5D-5L (r=0.68) and SF-6D (r=0.79). Condition impacts for PROPr were: moderate/severe vs no/mild depressive symptoms (-0.33, P < 0 .001), none/mild vs moderate/severe symptom burden (-0.31, P < 0 .001) and anemia vs normal hemoglobin level (-0.09, P=0.027). Condition impacts for SF-6D were: depressive symptoms (-0.24, P < 0 .001), overall symptoms (-0.20, P < 0 .001) and anemia (-0.01, P=0.711). For EQ-5D-5L, condition impacts were: depressive symptoms (-0.31, P < 0 .001), overall symptoms (-0.23, P < 0 .001) and anemia level (-0.04, P=0.017). Conclusion: These results support the validity of PROPr among patients with liver transplant.

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ID: 108

How does anti-Human Leukocyte antigen class I antibody signal in human glomerular endothelial cells to increase LGALS1 expression

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Abstract Body: Background. Antibody-mediated rejection (AMR) accounts for >50% of premature kidney graft loss. AMR is caused by donor specific antibodies (DSA) against human leukocyte antigens (anti-HLA) on the graft endothelium. DSA can directly injure the endothelium via extracellular signal-regulated kinase (ERK) and mammalian target of rapamycin (mTOR) signaling, activate complement and immune cells. Since HLA does not have a signalling domain, direct injury by the anti-HLA antibody remains poorly understood. We have previously identified galectin 1 (LGALS1), an immunomodulatory and extracellular matrix-associated protein, as significantly increased in laser-captured glomeruli of 7 clinical biopsies with AMR compared to 23 matched "non-AMR biopsies". Glomerular endothelial cells (GMECs), in response to anti-HLA class I antibody excibited increased expression of LGALS1 and the expected phosphorylation of ERK. Endothelial cells are the main parenchymal kidney cells expressing LGALS1, as evidenced from our dataset of single cell RNA sequencing from 19 living donor biopsies. We propose to define the signal transduction induced by anti-HLA antibody class I in GMECs through phosphoproteomic profiling. Methods. To assess our ability to isolate phosphopeptides from our cells, we initially applied our phosphoproteomics protocol to our cultured GMECs (figure 1). Following cell lysis and digestion, peptides were applied on to TiO2 resin under acidic conditions. Supernatants containing non bound, unphosphorylated peptides were saved while bound phosphorylated peptides were eluted under basic conditions. All samples were using Q Exactive HFX mass spectrometry (MS) instrument, and data were analyzed using MaxQuant software. Results: MS analysis of unbound to TiO2 peptides and phosphorylated eluted peptides revealed 5900 proteins and 9579 phosphosites, respectively, with a false discovery rare smaller than 1%. Phosphoserines, phosphothreonines and phosphotyrosines accounted for 85.5%, 13.6% and 0.9 % of total phosphosites, respectively. Conclusion: With these encouraging results we will proceed to decipher signaling cascade following treatment of our GMECs with anti HLA antibody.

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ID: 109

AT1R antibody ELISA assay: Naturally-occurring antibodies as a source of interference

Anne Halpin, Alberta Public Laboratories, University of Alberta, Department of Laboratory Medicine and Pathology University of Alberta, Department of Pediatrics Canadian Donation and Transplantation Research Program

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Abstract Body: Background An ELISA assay (CellTrend GmbH) is used for detection of antibodies (Abs) to angiotensin II type 1 receptor (AT1R). Anti-Neu5Gc antibodies (Neu5Gc-Ab) have been proposed as a potential test interference. Chinese hamster ovary (CHO) cells that over-express AT1R are used for antigen procurement; CHO cells express Neu5Gc sialic acid. Humans lack endogenous Neu5Gc and produce 'natural' Neu5Gc-Ab. Adsorb Out™ (AdsOut), used to remove non-specific reactivity in HLA assays, appears to also reduce AT1R-non-specific reactivity in this ELISA. Our aim was to investigate what antibodies are removed by AdsOut. Methods Assay-provided positive control, 20 and 40 U/mL calibrators were treated with AdsOut by manufacturer protocol. Pediatric heart transplant patient sera (n=52) were tested with and without AdsOut; AT1R ELISA was performed by manufacturer protocol. Neu5Gc glycans on AdsOut particles were detected by flow cytometry; latex beads coated with human albumin were tested in parallel. Results AdsOut did not remove AT1R-Ab reactivity from the positive control or calibrators (Figure 1). 75% of positive AT1R sera were reduced to negative levels following AdsOut (Figure 2). Although Neu5Gc glycans were not detected on the human albumin-coated beads, they are clearly present on AdsOut (Figure 3). Conclusion It is essential that assays demonstrate specificity and that interferences are known. The CellTrend AT1R-Ab ELISA assay lacks a 'blank' (no antigen) control making it difficult to rule out non-specificity in clinical specimens. The AdsOut product is described as "microparticles without antigen treated with blocking solution". Most blocking solutions contain bovine serum antigen (BSA), which is reported to have Neu5Gc. The finding that Neu5Gc is detected on AdsOut identifies anti-Neu5Gc-Ab as a possible source of false positive AT1R-Ab. Additional interferences such as anti-BSA or anti-polystyrene antibodies may contribute. Use of AdsOut mitigates the lack of specificity due to interference of anti-Neu5Gc-Ab and could be used to improve assay specificity.

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ID: 111

Rejection rates of lung transplant patients with reduced renal function on a sirolimus based immunosuppression regimen: A cohort characterization study

David Fung, University of Alberta

Abstract Body: Background: All lung transplant patients require immunosuppression to prevent graft rejection. Calcineurin inhibitors (CNIs), are commonly used for maintenance immunosuppression, but have associated side effects including nephrotoxicity. Sirolimus is used as a renal-sparing agent but there is little literature examining adverse event rates of CNI versus sirolimus in the context of a regimen that includes mycophenolate mofetil and prednisone. This study aims to characterize the outcomes of patients switched to a sirolimus-based regimen. Methods: A retrospective chart review of lung transplant patients on sirolimus at our institution between August 2011 to August 2021was performed. Primary outcome was acute cellular rejection rate as defined by clinical judgment and use of pulse steroids. Secondary outcomes included trajectory of renal function, proteinuria, and hypertriglyceridemia. Results: Eleven patients were placed on a sirolimus only regimen, while 16 patients on a tacrolimus/sirolimus combination. The median age at transplantation was 45 years. Median time post-transplant until sirolimus start was 378 days. The median creatinine (Cr) at time of transplant was 80 umol/L (estimated glomerular filtration rate (eGFR) 85 mL/min/1.73m2) and at sirolimus initiation was 215 umol/L (eGFR 25 mL/min/1.73m2). Mean follow up was 5.95 years, during which time 22% of patients had an episode of treated acute cellular rejection and 30% developed chronic lung allograft dysfunction. Improvement in creatinine at 6 months was seen in 28% of patients and persistent long-term Cr improvement was seen in 31% of patients. However, 15% of the cohort required dialysis. Worsening proteinuria occurred in 47% of patients and worsening triglycerides in 56% of patients. There were no noted cases of drug-induced pneumonitis. Conclusions: Improvement in renal function occurred in 30% of patients after switching to sirolimus, however rates of rejection, worsening proteinuria and triglyceridemia remain substantial and highlight the need for close monitoring of these patients.

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ID: 113

Use of cell free DNA to guide immunosuppression minimization in a patient with a donor derived cancer

John Gill, University of British Columbia

Abstract Body: Background: There is limited experience using donor-derived cell-free DNA (dd-cfDNA) to guide immunosuppression reduction in the early post-transplant period. A 77 year-old male without prior sensitizing events, a pre-transplant cPRA of 0%, and negative T and B cell cross-match, underwent a first living unrelated donor kidney transplant (KTx). He was treated with basiliximab induction, tacrolimus, mycophenolate mofetil and rapid steroid elimination as per our centre protocol. Pathology from a routine post perfusion allograft biopsy reported 10 days post KTx unexpectedly revealed a clonal B cell cellular infiltrate of donor origin. The donor underwent extensive testing including full body imaging and bone marrow biopsy and has not developed clinical evidence of cancer. The recipient underwent comprehensive evaluation including allograft ultrasound, total body CT, and positron emission tomography (PET). No evidence of clinical disease was found. In a shared decision with the patient, we began a program of surveillance and immunosuppression minimization. Methods: Mycophenolate mofetil was withdrawn 14 days after transplantation, and the patient was maintained with tacrolimus monotherapy and low dose prednisone. The patient was monitored monthly using cell free DNA testing (the ProsperaTM test, Natera Inc.), as well as DSA testing, monthly ultrasound imaging of the renal allograft, and bi-annual PET. Results: The patient had significant fluctuations of his kidney function (serum creatinine >10%; Figure 1) but cfDNA testing remained (i.e., below the threshold for rejection) DSA remained negative. There was no change in allograft size or evidence of cancer from serial ultrasounds or PET scans. The patient is now 15 months post-KTx with stable kidney function, free from clinical evidence of cancer and has not required a kidney biopsy. Conclusion: The use of cfDNA facilitated successful early immunosuppression minimization in a patient with donor-derived malignancy. cfDNA monitoring should be considered when early reduction of immunosuppression is necessary.

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ID: 114

PROMIS physical function scores are associated with health-related quality of life among solid organ transplant recipients

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Abstract Body: The ability to perform activities of daily living is a critical outcome for solid organ transplant (SOT) recipients. Many SOT recipients have low physical function (PF) which is associated with poor quality of life. In this study, we assess the association of PF with health-related quality of life among SOT recipients. A secondary analysis was conducted with data obtained from a cross-sectional convenience sample of SOT (kidney, kidney-pancreas and liver) recipients. Participants completed PROMIS PF item bank, EQ-5D-5L and sociodemographic questionnaires. PROMIS PF T-scores were categorized: 'no/mild' (> = 45), 'moderate' (40-45), and 'severe' (Of 692 participants, mean(SD) age was 52(15) years with 63% male. Median (Interquartile Range(IQR)) years since transplant was 6.5(12.1). 53% of the sample had no/mild PF impairment, 20% had moderate, and 27% were severely impaired. Median(IQR) PF T-scores were higher for patients who reported 'no problems' vs those who indicated moderate or severe mobility problems on the EQ-5D-5L mobility domain: [50(11) vs 40(7) vs 33(6)]. PROMIS PF showed excellent discrimination for impaired mobility (ROC=0.86,95% CI: 0.83-0.89). Median(IQR) EQ5D utility scores were higher for patients with PF T-scores > = 45 vs those with scores 40-45 and The PROMIS PF T-score is a valid measure of self-reported physical function. After longitudinal validation it may be a feasible tool to monitor physical functioning in SOT recipients.

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ID: 115

Quantitation of mitochondrial damage-associated molecular patterns in perfusate and bile for analysis of donor liver quality during ex-vivo NMP

Lauren Westhaver, Dalhousie University

Abstract Body: Background: Tissue damage during liver transplantation (LT) results in expulsion of mitochondrial damage-associated molecular patterns (mitoDAMPs), including mitochondrial DNA (mtDNA), into the extracellular space. High mtDNA levels positively correlate with negative clinical outcomes, and mtDNA is emerging as a predictive biomarker for a variety of disease processes. Normothermic machine perfusion (NMP) has emerged as an attractive alternative to traditional static cold storage (SCS), yet there remains an unmet need for an agile and universal marker of graft function during NMP. We hypothesized that mtDNA could be quantitated in perfusate and bile collected during ex vivo NMP of donor livers prior to transplant and would correlate with other metrics of graft quality. Methods: DNA was isolated from perfusate (n=29) and bile (n=18) collected from donor livers undergoing NMP. MtDNA levels were measured via quantitative polymerase chain reaction (qPCR) using primers specific to mtDNA gene targets (COXI, CytB, ND1, ND6) and standard curves generated by commercially available synthetic oligonucleotides of primer-specific amplicons. Results: MtDNA can be quantitated in both perfusate and bile samples collected during NMP. MtDNA quantitation via qPCR with an amplicon-specific standard curve accurately reproduced values measured by droplet digital PCR (ddPCR). Concentration of mtDNA in perfusate was positively correlated with warm ischemia time (COXI, p=0.042; CytB, p=0.041) and donor lactate (CytB, p=0.012; ND1, p=0.040). Donor international normalized ratio (INR) showed significant positive association with mtDNA in both perfusate (CytB, p=0.003; ND1, p=0.048) and bile (CytB, p=0.048; ND1, p=0.049; ND6, p=0.032). Conclusion: Here, we demonstrate the feasibility and reproducibility of mtDNA quantitation in both perfusate and bile via qPCR and show association with clinical parameters. We anticipate that mtDNA will serve as a stable and inexpensive marker for liver function during NMP, which may inform the expected course of disease and illuminate opportunities for precision medicine in patients undergoing LT.

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ID: 117

Differences in Medication Adherence between Preemptive and Post-dialysis Young Kidney Transplant Recipients

Yulia Vaisbourd, Mcgill university, MCH

Abstract Body: Background: The mechanisms underlying the superior graft survival associated with pre-emptive kidney transplantation, compared with transplantation following a period of dialysis, are unknown. Selection for pre-emptive transplantation of a group biased to better treatment adherence is possible. We aimed to compare medication adherence between pre-emptively transplanted young kidney transplant recipients and those who received a transplant after an interval of dialysis. Methods: This was a secondary analysis of the Teen Adherence in Kidney transplant Effectiveness of Intervention Trial (TAKE-IT), in which adherence was assessed with electronic monitors over a 15-month period among 11–24 year-old kidney transplant recipients. Adherence scores were calculated daily as 0%, 50%, or 100%, depending on whether the patient took none, half, or all prescribed doses. We used ordinal logistic regression to estimate the association between pre-emptive transplantation and adherence, with generalized estimating equations to account for repeated measures within each participant. The model was adjusted for sex, age at transplant, time since transplant, primary kidney disease, race, donor source, medication insurer, household income, and adherence intervention (time-varying). Results: There were 43 pre-emptive transplant recipients (median age 15.8 [IQR 13.7-17.6]; 60.5% male) and 103 who has been treated with dialysis (median age 15.7 [IQR 13.3-17.4]; 60.2% male). The mean adherence score was 85.1% (IQR 81.3-88.9) for those pre-emptively transplanted, and 80.0% (IQR 76.7-83.4) for those transplanted after dialysis. Table 1 shows the results of the unadjusted and adjusted logistic regression models. Preemptively transplanted recipients were significantly more likely to be adherent than those dialyzed before transplantation (OR 1.76 95%CI 1.21-2.55; p=0.003). Conclusions: Pre-emptively transplanted patients showed significantly better adherence than those treated with dialysis before transplantation. This suggests that the superior outcomes observed among preemptive kidney transplant recipients likely reflect selection of patients more likely to adhere to therapy.

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ID: 118

Comprehensive immune profiling of SARS-CoV-2 infected kidney transplant patients reveals a distinct immunophenotypic signature

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Abstract Body: Background: SARS-CoV-2 infection leads to worse outcomes in kidney recipients maintained on immunosuppression compared to the general population. We aimed to characterize the immune responses in non-vaccinated kidney transplant recipients vs. non-immunosuppressed individuals diagnosed with SARS-CoV-2 infection. Methods: We used a multi-omics approach to profile the immunity of n=9 kidney transplant recipients (KTx) and n=12 non-immunosuppressed individuals (non-Tx) to SARS-CoV-2 infection. The immune assays included: quantification of serum antibody levels and their isotypes, immunophenotying; serum cytokine profiling and T cell receptor (TCR) sequencing. Results: Immunophenotyping revealed that effector memory T cells were increased in the KTx patients while naïve T cell frequencies were diminished. Additionally, the KTx patients had a strong reduction of CD28+ T cells, particularly in the effector memory subset of both CD4 and CD8 T cells (Fig. 1a). TCR sequencing demonstrated that the KTx cohort showed a higher productive clonality, signifying a repertoire dominated by fewer rearrangements compared to a more polyclonal repertoire in non-Tx patients (Fig. 1b). Together, these immune signatures are consistent with previously reported findings of transplant recipients on immunosuppression and could be used to discriminate against the immunity of non-Tx individuals (sensitivity = 0.92, specificity = 0.89). Interestingly, the KTx group produced lower levels of SARS-CoV-2-specific antibodies compared to the non-Tx cohort while antibodies against other coronaviruses were similar between the two groups (Fig 1c). Furthermore, serum cytokine profiling showed that MIP-1? (CCL4) levels were reduced in the sera of KTx patients (Fig. 1d). These effects have been found to correlate with severe COVID-19 infection and suggest that the KTx group is at an increased risk of severe outcomes. Conclusion: KTx recipients with SARS-CoV-2 infection exhibit an immunosuppressed phenotype with features that are reminiscent of severe COVID-19 patients, particularly reflected in their decreased antibody response and lower concentration of serum cytokine MIP-1? (CCL4).

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ID: 119

Virtual healthcare during the Covid-19 pandemic: are there financial benefits for Solid Organ Transplant families?

Pearl Waraich, Pediatrics/Cardiology

Abstract Body: Background: Patient travel to attend Multi-Organ Transplant (MOT) clinics can be onerous in terms of time, travel costs, and lost wages. Frequent in-person appointments are routinely scheduled. At the onset of the COVID-19 pandemic we made changes to our healthcare practice by replacing some in-person appointments with virtual appointments. We sought to evaluate whether this change in clinical practice significantly reduced travel-related costs and estimate the relative percentage of family income spent on travel. Methods: Our study cohort included all heart, kidney, liver and lung transplant recipients currently followed by our program. All MOT appointments between April 1, 2020 and March 31, 2022 were reviewed. Total costs were calculated using an algorithm that included automobile, ferry, hotel, meals, and parking costs, with travel distance and time built into the costing estimates. Low, moderate and high cost estimates were projected for the number of visits and compared with after tax median household income. Income was based on 2016 census data. Results: The study cohort included 148 (57% male) patients. There were 29 (20%) heart, 66 (45%) kidney, 51 (34%) liver and 2 (1%) lung transplant recipients who were transplanted at a median age of 4.8yrs. Of the 1035 MOT appointments recorded during the study period, 194 (19%) were held virtually. The median travel distance from home to MOT clinics ranged from 3.6km to 1,414km. Estimates for low, moderate and high median travel costs ranged from $64 to $26,670. Virtual appointments reduced costs by 70% across all costing scenarios. The range of household income spent on travel were 0.2-37.5% for virtual and 0.1-62.7% for in-person appointments, respectively. Conclusion: Families may potentially spend up to 63% of their income traveling to appointments. Virtual appointments may lower the financial burden of travel and financial aid is available from governmental and philanthropic programs as well.

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ID: 121
Symptom recovery after kidney transplantation – through the PROMIS (®) lens

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Abstract Body: Background: Kidney transplant candidates want to know how long it takes for their symptoms to improve after transplant. Here we report longitudinal data obtained during the first 20 post-operative weeks that describe the time-course of several patient valued physical and emotional symptoms. Methods: A longitudinal, single-center convenience sample of adult kidney transplant recipients (KTRs) completed the Patient Reported Outcome Measurement Information System® (PROMIS ®) computer adaptive tests (CAT) on tablets in the hospital 1-2 days prior to discharge (baseline) and remotely, every 2-4 weeks thereafter. The following domains were assessed: anxiety, depression, sleep disturbance, fatigue, pain interference and physical function. All PROMIS CAT domains are scored on the T score metric, which is calibrated to a standard score mean of 50 based on the US general population. In general, a 3 to 5 point change is considered clinically relevant. Repeated measures ANOVA was used to analyze the change in symptom scores during the follow-up. Results: Mean (standard deviation [SD]) age of the 54 participants was 50 (15) years, 61% were male. The median time between transplant surgery and baseline questionnaire completion was 4 days. All symptoms and physical function improved significantly by week 8-12 post enrollment: e.g., mean (SD) T score at baseline, 8 and 12 weeks were: anxiety 57(7), 49(6), 49(6); fatigue 57(8), 48(8), 46(7); pain interference 58(9), 50(7), 48(9); and physical function 41(7), 46(6), 47(5), respectively. These changes were all statistically significant (p Conclusion: Emotional and physical symptoms improve to the level of the US general population in many KTRs by 8-12 weeks after transplant surgery and improve further until week ~20 after transplant. These data will better inform patients about the expected trajectory of recovery after kidney transplant surgery.

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ID: 122

Histological changes on renal allograft biopsy in patients with recurrent and new onset diabetic nephropathy

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Abstract Body: Background: Post-transplant diabetic nephropathy (PTDN) can be recurrent or new onset of diabetes after transplantation (NODAT). Renal biopsy for graft dysfunction may have features of DN along with coexisting other etiologies of graft dysfunction. Methods: A total 1815 indicated renal allograft biopsies secondary to graft dysfunction or proteinuria between 2010 to 2021 were retrospectively analyzed for the morphological changes of DN with Tervaert classification and for coexisting lesions. Based on clinical details, laboratory records and histopathology findings, 47 biopsies from 45 patients had PTDN. Results Seventeen patients with recurrent DN had mean age of 58.6 years as compared to 28 patients with NODAT mean age of 47.3 years. Average time from transplantation to detection of DN on biopsy was 89 months with recurrent DN compared to 111 months in NODAT. The patients with recurrent DN had mean S. creatinine of 2.26mg/dl at biopsy (range 0.96-3.9mg/dl) and mean proteinuria of 4.9g/day (range 1.4–11g/day). In recurrent DN morphological lesions comprised DN-NOS, DN-II, DN-III (nodular glomerulosclerosis) and DN-IV in 3, 9, 3 & 2 patients respectively. Four patients of recurrent DN had in addition CNI toxicity (1), TG (1), recurrent IgAN (1) and Chronic TIN (1). The patients with NODAT had mean S. creatinine 2.6mg/dl at biopsy (range 1.0-5.1mg/dl) along with proteinuria of 4.5g/day (range 1.0 -10.1g/day). In NODAT lesions comprised DN-NOS, DN-II, DN-III and DN-IV in 4, 15, 6 & 3 patients respectively. Eight patients of recurrent DN in addition also had border line change(1), acute TCMR with TIN(1), Active ABMR(1), Chronic Active ABMR with TG(3) CNI toxicity(2). One patient of each recurrent DN and NODAT group progressed to DN III from DN II in repeat biopsy. Conclusion: PTDN is uncommon cause of graft dysfunction. Recurrent DN patient present earlier as compared to NODAT

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ID: 123

Pain and depressive symptoms among solid organ transplant recipients – assessment with PROMIS tools

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Abstract Body: Background: Pain contributes to poorer quality-of-life amongst solid organ transplant (SOT) recipients. In addition, a complex, bidirectional relationship exists between pain and depression. We assess the association between pain intensity (PI) and pain interference (PIF) while controlling for co-variables, including depressive symptoms, among SOT recipients. Methods: Secondary analysis of a single-centre, cross-sectional convenience sample of adult SOT recipients. Participants completed the Patient-Reported Outcome Measurement Information System (PROMIS)-29 item profile or PROMIS computer adaptive tests (CATs). Pain intensity was assessed using the single 0–10 numeric item (PI) and PROMIS Pain Interference (PIF) T-score. PI was categorized as: No=0; Mild=1-3; Moderate/Severe=4-10. Multivariable-adjusted regression was used to assess associations between PI, clinical, socio-demographic variables, depression and PIF. We also assessed associations between these variables and moderate/severe PIF (T-score>60). Results: Of 685 participants, 424 were kidney (KT), 67 kidney-pancreas (KP), and 194 liver (LT) transplant recipients. Mean(SD) age was 53(15), 61% were male. Mean(SD) depression score was 49[9]. KP and LT had higher median(IQR) depression scores compared with KT (51[9] and 51[9]vs.48[9], p Conclusion: The relationship between PI, PIF and depression is complex. These results may inform the design of comprehensive symptom management support for transplant recipients

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ID: 124

Views on Deemed Consent for Organ Donation from Indigenous and Racialized Communities in Canada: Results from Multi-ethnic Interviews and Focus Groups

Jagbir Gill, St. Paul's Hospital

Abstract Body: Deemed consent is a legislative strategy that presumes all members of a jurisdiction have consented for deceased organ donation unless they have explicitly registered their non-consent. Public engagement on deemed consent has rarely examined the views of Indigenous and racialized communities in Canada. The aim of this study was to gather views on deemed consent from a multi-ethnic Canadian population. Methods: Focus groups and interviews were conducted with participants recruited through community-based organizations in BC. Information on deemed and voluntary consent was provided to study participants using case vignettes. Participants' views on deemed consent were obtained, considering their cultural background, family traditions, and beliefs around organ donation. A thematic analysis was conducted. Results: 48 participants included Indigenous (n=7; 14.5%), African/Caribbean/Black (n=6; 12.5%), South Asian (n=14; 29.1%), East Asian (n=6; 12.5%), Southeast Asian (n=3; 6.3%), Middle Eastern (n=5; 10.4%), Caucasian (n=6; 12.5%) and mixed race (n=1; 2%) Canadians with a mean age of 41.6 years. 56.3% were female (n=27), 39.5% were male (n=19), 4.1%, were nonbinary (n=2), 14.5% identified as LGBTQ2S+ (n=7) and 66% were born outside of Canada. Most participants (84%) preferred a voluntary consent system or were unsure about deemed consent. Concerns with deemed consent included discomfort with its mandatory nature, concern that members of cultural and ethnic groups and those less knowledgeable about organ donation may be more vulnerable, and concern that a mandatory system may be less acceptable given the cultural diversity in Canada. Some participants compared deemed consent to COVID-19 mandates, citing concerns with public acceptance of such mandates. Those in support of deemed consent cited the need for increased donation and simplification of the consent process as strengths. The need for public engagement and education was highlighted by most participants. Conclusion: Concerns about deemed consent and implications for vulnerable populations to further understand the acceptability of deemed consent policies in Canada.

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ID: 125

Gender dynamics among South Asian Living kidney donors and kidney transplant recipients in Canada

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Abstract Body: Background: The Canadian South Asian (SA) community includes communities with ethnic lineage in the Indian subcontinent and constitutes 25% of Canada's visible minority population. Longstanding inequities in access to living donor kidney transplantation (LDKT) have been reported for SA Canadians. This study aims to identify culturally relevant barriers to LDKT in SA Canadians. Methods: In depth interviews were conducted in English and Punjabi with SA LDKT recipients, deceased donor kidney transplant recipients, and living kidney donors (LDs). Focus groups were conducted with general SA community members. Results: 30 interviews and 6 focus groups were conducted in 2020-21 with 71 participants (52.5% female), with a mean age of 50.6 years. Hesitancy to approach potential donors and feelings of guilt were noted as important barriers for recipients, particularly among elderly and female participants, while information gaps were cited as the primary barrier for potential donors. Patriarchal family units and gender dynamics were identified as important barriers for recipients and donors. Women reported limited opportunities to find LDs due to cultural expectations of marriage and childbearing, with additional challenges for women that were elderly or financially dependent on their spouse. Community members constructed women as more "altruistic" and more likely to donate, specifically mothers and sisters. LDs who were married at the time of their donation and community participants discussed expectations to seek approval from their husband and/or in-laws if donating to someone outside of their husband, children, and in-laws. Conclusion: Gender specific challenges for SA women may limit their opportunities for LDKT and living donation. Understanding potential gender dynamics for SA transplant candidates and potential donors may help better support patients in their pursuit of LDKT.

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ID: 126

Incidence of Polyomavirus Nephropathy in renal allograft biopsies using clinical and histological parameters and Banff 2019 working group classification to assess clinical outcomes.

Aisha Memon, Aga Khan University

Abstract Body: Background: Polyomavirus nephropathy (PVN) has a biopsy-proven incidence of 5-6%. Banff working group on PVN has developed a morphological classification that groups together histologic changes, clinical parameters and facilitates comparative outcome analysis. Material and Methods: This is a retrospective 5-year study conducted from June 2017 to May 2022. A total of 301 cases of renal allograft biopsies were reported. Only the cases diagnosed as PVN were included. Histopathology slides were reviewed and classified according to the Banff 2019 Working Group Classification. Clinical and histological parameters in the three PVN classes are tabulated in Table. Results: Out of 301 renal allograft biopsies reported during the study period, 06 patients (2%) were diagnosed with PVN based on histology and SV40 immunohistochemistry. All patients were male and median age of diagnosis was 34 years (range 27-47 years). The median period of diagnosis of viral infection after transplantation was 14.8 months (range 4.3 – 49.6 months). Serum creatinine level at the time of biopsy ranged from 1.8 to 3.05 mg/dl. BK viral load in serum was positive in only 3/6 cases (50%). Histological grading according to Banff 2019 revealed one case (16.7%) in PVN class 1 (Figure A-C), three cases (50%) in PVN class 2 (Figure D-F) and two cases (33.3%) in PVN class 3 (Figure G-I). PVN class 1 presented early and was associated with only type 1 viral inclusions and had better clinical outcome as compared to PVN class 2 and 3. Associated diseases include Active and chronic- active T-cell mediated rejection (TCMR) and interstitial fibrosis/tubular atrophy (grade1-3). One patient of PVN class 2 and One of PVN class 3 expired, while the rest had functional grafts on follow up. Conclusion: Banff 2019 morphological classification for PVN can be useful for diagnostic purpose and in assessment of clinical outcomes.

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ID: 127

A 5-year retrospective study of spectrum of histological diagnoses in Renal allograft biopsies from a tertiary care hospital

Aisha Memon, Aga Khan University

Abstract Body: Background: Despite the recent advances in diagnostic procedures, renal biopsy remains the gold standard for the diagnosis of renal allograft dysfunction for optimum management. Material and Methods: This is a retrospective study carried out over a period of 5 years from June 2017 to May 2022. Relevant clinical details including age, sex, biopsy duration post-transplant, pre-biopsy renal function tests were recorded. All biopsies were studied according to updated Banff 2019 diagnostic categories and frequencies of various etiologies are tabulated (Table). Results: Out of a total of 301 renal allograft biopsies received during the study period, 242 (80.4%) were males and 59 (19.6%) were females with a male to female ratio of 4:1. Mean age for males was 37.4 years (range 13.8-73.2 years) and for females was 31.7 years (range 13.1-51.6 years). The biopsy duration post transplantation ranged from 0 days to 9 years. Serum creatinine level at the time of biopsy ranged from 1.2 to 11.84 mg/dl. Rise in serum creatinine was the most common clinical presentation (74%) followed by decrease in urine output and proteinuria. The highest frequency was of T-cell mediated rejection reported in 128 cases (42.5%) followed by Antibody mediated rejection in 94 cases (31.2%). Interstitial fibrosis and tubular atrophy (IFTA) was noted in 33% of cases. Data included 04 graft nephrectomy specimens, two showed Hyperacute rejection, 01 showed surgical complications with massive sub-capsular hematoma and 01 showed invasive fungal infection with extensive necrosis and anastomotic rupture of graft. Recurrent glomerulopathy constitute 5% of the graft dysfunction while viral infection was present in 3.6% of cases. Detailed frequencies are presented in the table. Conclusion: TCMR still remains the major cause for graft dysfunction (48.5%) followed by ABMR (30.7%) and IFTA (33%). Recurrent glomerulopathy constitute 5% of the graft dysfunction while viral infection was present in 3.6% of cases.

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ID: 128

Treatment of antibody mediated rejection after liver transplantation. A single Canadian centre experience

Andres Gomez-Aldana, fellow

Abstract Body: Background:Antibody mediated rejection (AMR) is an important factor of graft inflammation, rejection and graft dysfunction in kidney, lung, and heart transplants.While DSAs in liver transplant (LT) have been associated with inflammation and fibrosis, the clinical importance of antibody mediated rejection after liver transplantation and, the therapeutic options remain unclear. Methods: We report 4 patients with AMR according to Banff consensus criteria (B-AMR). In addition, we describe a group of 8 patients with clinical AMR (C-AMR) with histology of T-cell mediated rejection (TCMR), non-responsive to steroids and thymoglobulin, accompanied to class II positive DSAs. Infectious and biliary causes for inflammation were excluded in all patients. All 12 patients received 5 plasmapheresis sessions followed by IVIG.Results:All 4 patients with B-AMR significantly reduced the ALT and AST, and 3 out of 4 patients reduced them to normal limits after 6–12 months.3 of 4 patients normalized the bilirubin, 1 patient developed graft cirrhosis and was relisted for transplantation. In patients with C-AMR,5 out of 8 patients normalized the ALT and 3 out of 8 reduced to 2 times the normal limit. All of them normalised the bilirubin. Graft survival was 100% over 12 months.In the B-AMR group, 1 patient cleared DSAs and 3 out of 4 decreased DSAs prevalence. In the C-AMR group, 4 out of 8 completely cleared DSAs and 2 significantly decreased prevalence of DSAs. Conclusions: B-AMR showed no response to treatment with steroids and thymoglobulin, yet plasmapheresis and IVIG showed a lasting treatment response and the clinical resolution in 3 out of 4 patients. In addition to the classical B-AMR, we describe a new entity of rejection classified as T-Cell mediated rejection by histology with high DSAs, resistant to steroids and thymoglobulin (C-AMR), which can be successfully treated with PLEX and IVIGi n all cases with a long-lasting remission.

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ID: 129

POSITIVE FLOW CYTOMETRY CROSSMATCH IN THE ABSENCE OF DONOR-SPECIFIC ANTI-HUMAN LEUKOCYTE ANTIGEN ANTIBODIES: discordant results in 3 kidney transplant recipient cases

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Abstract Body: FCXM assay is the most sensitive cell-based method to detect DSAs and its prognostic value in a pre-transplant screening is well established. SPA are more sensitive for lower titer antibodies and are better at distinguishing between specific HLA antigens. Complimenting FCXM with SPA offers the potential to better discriminate immunologically relevant positive FCXMs from false-positive results. This is key to maximize the number of safe, compatible transplants to occur. There are still challenges, in their interpretation. In this report, we present 3 cases of discordant testing results in potential kidney transplant recipients: positive B cell FCXM and lack of detectable DSAs using routine SPA testing. Methods: A total of 3 recipient samples and their respective donors were used in analysis. Samples were collected from peripheral blood draws. CDCXM, FCXM, HLA typing, and HLA antibody screening was performed on samples accordingly. Results: Auto-crossmatches for all 3 potential kidney recipients were negative. Serial dilution of serum samples also had no effect on HLA antibody testing. Other trouble shooting, namely DTT, absorb out, increased EDTA volume, and heating serum 56oC, all resulted in negative antibody screening. The Luminex assay was also run using our institution's usual protocol and using manufacturer's protocol, and all were negative. Finally, we analyzed recipients' serum for potential non-HLA antigens using One Lambda's available kits, which were also negative. One Lambda performed SAB testing and ExPlex. Using their ExPlex kits, they identified previously unidentified DSAs. Surrogate crossmatches using these DSAs for each recipient yielded a clinically significant DSA for one recipient and insignificant for another, who proceeded to successful crossmatch with his unrelated living donor. Conclusion: A positive FCXM in the context of a negative HLA antibody screen can be interpreted as 'false positive', but these cases demonstrate that sometimes routine testing or one test protocol is not enough for all cases.

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ID: 131

Supplementation of organ preservation solution with sodium thiosulfate prolongs renal graft and recipient survival after syngeneic orthotopic kidney transplantation in rats

George Dugbartey, University of Western Ontario

Abstract Body: Introduction: Static cold storage (SCS) at 4°C is the current clinical standard procedure to preserve organs for transplantation. It minimizes ischemic injury of organ grafts. However, prolonged SCS obviates the benefits of organ preservation and increases post-transplant complications. In this study, we used a murine model of syngeneic orthotopic kidney transplantation to determine whether pharmacological modification of standard preservation solution with sodium thiosulfate (STS), a major metabolite of hydrogen sulfide, will provide renal graft protection beyond that offered by standard preservation solution alone. Method: Bilateral nephrectomy was performed in 30 Lewis rats and the left kidneys were preserved in University of Wisconsin (UW) solution at 4°C with or without STS (150?M) supplementation. Following 24 hours of SCS, and bilateral nephrectomy in recipient rats, syngeneic orthotopic kidney transplantation was performed. Sham-operated rats (n=5) were used to establish a baseline for survival and analysis of histological and renal function parameters. The transplant recipient rats were monitored from the time of transplant to post-transplant day 14 and then sacrificed and kidneys harvested. The kidney sections were examined for acute tubular necrosis, apoptosis, macrophage and neutrophil infiltration. A subset of rats in the UW+STS group had grafts removed pre-emptively on post-operative day 3 (n=5) for histological comparison with UW grafts of recipients that were sacrificed at this time point. Result: Compared to UW grafts, renal graft function was significantly improved in UW+STS group immediately after transplantation evidenced by markedly reduced levels of serum creatinine and BUN and high urine output, which positively correlated with prolonged recipient survival ($p < 0.05$). Also, acute tubular necrosis, apoptosis, macrophage and neutrophil infiltration were markedly reduced in UW+STS grafts along with downregulation of pro-inflammatory and pro-apoptotic genes compared to UW grafts ($p < 0.05$). Conclusion: Supplementation of standard organ preservation solution with STS improved overall graft quality and function and prolonged transplant recipient.

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ID: 132

COVID-19 Vaccinations and mortality in transplant patients during the OMICRON era: time to shed vaccination mandates?

Patrick Luke, University of Western Ontario

Abstract Body: Background: There is controversy with regards to vaccine mandates and access to transplantation. With each mutation of COVID-19, a new dominant strain emerges with changes in infection-related mortality rates in the community. We perform re-evaluation of the death rates of infected transplant recipients in each era. Methods:As a quality measure, our thoracic and abominal teams from our Multiorgan Transplant Centre report COVID-related infections and deaths at our program. Chart review was performed to delineate vaccination status. The Fisher's exact test was used to evaluate differences between groups. Results: Between February 1-May 31, 2022, 146 cases of COVID-19 were reported to our program. We obtained vaccination status in 139 pateints. Of the patients who had 3 vaccinations or greater, 0.8% (1/118) died from COVID-190. Of those who had 1-2 vaccinations, no deaths were reported (0/11). Of those unvaccinated individuals who had COVID-19 infections, 20% (2/10) died from the disease ($p = 0.014$ compared to vaccinated individuals). Conclusion: Despite a reduction in ICU admissions and death in the community during the recent era of COVIA-19, unvaccinated transplant recipients had a far greater risk of dying from COVID compared to vaccinated patients. This should be factored into decisions that affect vaccine mandates in transplant centres.

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Impact of Early Outpatient Remdesivir on COVID-19 Outcomes in Organ Transplant Recipients During the Omicron BA.2 Wave

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Abstract Body: Background Solid organ transplant recipients (SOTR) are at high risk for complications from COVID-19 and vaccine breakthrough infections are common. Previous early therapies such as sotrovimab are no longer effective against new circulating variants. We determined the effectiveness of 3 doses of intravenous remdesivir in reducing the hospitalization rate during Omicron BA.2 wave. Methods Prospective cohort study of consecutive SOT recipients with SARS-CoV-2 infection diagnosed as outpatients during the Omicron BA.2 wave (April-May 2022), referred to our transplant center, who were followed for at least 30 days. The primary outcome was hospitalization. The effectiveness of remdesivir was estimated using adjusted hazard ratios (HR). Results One hundred ninety-four adult SOTR were included. The median age was 55.3 years (IQR: 43.9 to 63.8), 62.3% were males, and the most common transplant was kidney (50.2%), followed by lung (20.6%), liver (19.1%), and heart (7%). Most of the patients (90.5%) had 3 or more doses of the COVID-19 vaccine. Twenty-two patients (11.1%) were hospitalized, 9 (4.5%) required supplemental oxygen, 4 (2%) were admitted to the ICU, 3 (1.5%) required MV, and 2 (1%) died. On multivariate analysis, lung transplant, age, and multiple comorbidities were risk factors for hospitalization. Three doses of intravenous remdesivir as outpatient were associated with a significant reduction in hospitalization: adjusted HR 0.12 (95% CI: 0.02 to 0.63), figure 1. The adjusted number needed to treat to prevent one hospitalization was 7.6 (95%CI: 5.0 to 15.3). Patients that receive remdesivir also had a trend toward reduction in requirement of supplemental oxygen (1.2% and 7.3% in those without treatment, p=0.08). No patients in the remdesivir group required admission to the ICU, mechanical ventilation, or death (table 1). Conclusion In a cohort of SOT recipients with Omicron BA.2 variant COVID-19 infection, administration of early outpatient intravenous remdesivir was independently associated with a reduction in disease severity.

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Patient and health systems costs associated with eplet compatibility-informed kidney transplantation.

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Abstract Body: Background Every year, more than 500 Canadians with end-stage kidney disease (ESKD) prematurely lose their graft due to antibody-mediated rejection (AMR). Donor-recipient compatibility of targeted HLA-DR and -DQ genes is hypothesized to mitigate AMR risk, potentially reducing downstream costs to patients and healthcare systems. Methods A patient-informed cost analysis was undertaken, comparing the lifetime costs ESKD in British Columbia (BC). Nine patients/family members contributed to the development of a costing methodology using BC renal administrative data, with results incorporated into the KidneyTx-SIM discrete event simulation model (https://www.youtube.com/watch?v=PQJNqGDK5G8). Total costs were analysed from the universal healthcare payer and the societal perspectives—the latter specifically capturing lost productivity, informal caregiving and out-of-pocket expenditures incurred by patients and their families. Results At an additional cost of $198CAD per deceased donor kidney, high-resolution sequencing of HLA genes in the DR and DQ regions that reduces premature graft loss is likely to save costs from the societal perspective. Patients on hemodialysis pay 20-30% of the total costs for ESKD themselves, often exceeding the World Health Organization's recommended threshold for protection against catastrophic healthcare spending. Costs are driven by productivity losses, estimated to total up to $58,365 per year while on dialysis and up to $11,682 following a transplant. Informal caregiving costs families nearly $9,862 annually for patients on dialysis, and decrease substantially, to $1,180 per year after a successful transplant. Approximately $10,870 is paid out-of-pocket to receive a transplant in Vancouver, while annual out-of-pocket spending for patients on dialysis often exceeds $10,020 despite re-imbursement grants and insurance coverage. A detailed breakdown of the costs related to additional testing, patient-borne or "societal costs" and the direct medical costs will be provided. Conclusions High-resolution sequencing that successfully reduces premature graft loss has potential to offset the high costs families pay to manage ESKD.

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Wait-time distributions for deceased donor kidney transplantation: Simulation model of current allocation criteria versus eplet compatibility-based allocation

Mohammad Asgharzadeh, Research Scientist

Abstract Body: Background: Improving post-transplant graft survival is one of the main objectives of contemporary research in transplantation. Kidney allocation based on donor-recipient HLA compatibility is expected to benefit patients, as well as health systems. However, the effects of an allocation strategy optimizing molecular HLA compatibility on the distribution of candidates' wait time is unknown. Purpose: To compare the wait time distribution of simulated kidney transplant candidates between the current deceased donor kidney allocation system and allocation guided by on donor-recipient eplet compatibility. Methods: A Discrete Event Simulation model (KidneyTx-SIM) was developed using data collected from ~1550 waitlisted candidates, 760 deceased donors, and 1400 transplants performed in British Columbia, Canada from 2008 to 2018, spanning both pre- and post-transplant phases. Cox-proportional hazard models were used to predict the times to different events, such as leaving the wait list, graft loss and death. Three allocation rules were considered: 1) by overall dialysis time; 2) by number of antibody-verified eplet mismatch (EMM) scores for any donor-candidate pair; and 3) considering both rules in combination. The EMM matrix was calculated based on high-resolution genotypes across DQ genes (DQA1+DQB1 genes) of all candidates and donors. Results: The wait time distribution of simulated kidney transplant candidates was calculated and presented using Kaplan-Meier graphs. The table shows the quartiles of time on dialysis, extracted from the Kaplan Meier curves. The average mismatch score for the current allocation, eplet compatibility-based allocation and the combined allocation were 9.7, 1.5 and 2.2, respectively. Conclusions: Compared to the current allocation system, incorporating HLA-DQ eplet compatibility could reduce waiting times for more than 25% of candidates and increase it for another 25% of candidates. However, the average mismatch score is significantly improved in new allocation strategy. It is important to develop strategies that ensure equitable access to transplantation.

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Association of BKV viremia/nephropathy and adverse alloimmune outcomes in kidney transplant recipients

Christie Rampersad, University of Manitoba

Abstract Body: Background: Reduction of immunosuppression in kidney transplant recipients who develop BKV viremia/nephropathy must be balanced with the increased risk of adverse alloimmune events.Methods: This single-center observational study evaluated 487 kidney transplant recipients transplanted 2010-2021 on tacrolimus/mycophenolate-based maintenance therapy. BKV status established at 6-months post-transplant was correlated with time to primary composite outcome of de novo donor specific antibody (DSA), rejection, or graft loss, and also to T-cell mediated rejection (TCMR), de novo DSA, death-censored graft loss, and all-cause graft loss. Recipients were stratified by HLA-DR/DQ mMM category. Impact of BKV status on risk of primary composite outcome and TCMR were assessed in Cox proportional hazards models.Results: 487 recipients had a mean follow-up of 5 years. At 6-months post-transplant, 63 (12.9%) recipients had BKV viremia alone and 11 (2.3%) had biopsy-proven BKV nephropathy. The primary composite outcome occurred in 123/487 (25%) recipients. BKV nephropathy correlated with shorter time to primary composite outcome (pConclusion:BKV nephropathy was associated with a shorter time to primary composite outcome of DSA, rejection, and graft loss. Recipients with high HLA-DR/DQ mMM experienced worse alloimmune outcomes after BKV nephropathy, suggesting they are less able to safely tolerate immunosuppression reduction. Future studies on developing optimized immunosuppression reduction strategies for treatment of BKV viremia/nephropathy should stratify by HLA-DR/DQ mMM immunological risk and monitor for subsequent alloimmune events to improve long-term patient and graft outcomes.

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ID: 137

MELD policy, evidence based medicine and implications for liver transplant patients.

Anita Slominska, Western University

Abstract Body: Background In the mid-1980s, the liver transplant community sought to create an allocation system that was efficient and fair and based on a rigorous way of determining the medical status of waitlisted patients so that organs could be distributed to those who need them the most. Eventually, this led to adopting MELD (Model-End-Stage-Liver-Disease), an algorithm that calculates three biochemical indicators to predict 3-month mortality risk. MELD identifies which patients have a more medically urgent need for transplantation using evidence-based analysis of objective data to define disease severity systematically and allocate livers according to greatest need. Methods My study is an autobiographical work of narrative medicine that explores my sister's wait for a liver transplant that ended in her death. I examine the effects of MELD policy in her personal story. Results My examination of MELD in the context of my sister's story demonstrates how generalizable research evidence can be at odds with clinical and patient experience (that "illness as lived" can differ from "the risk state in the evidence-based guideline.") The "fairness" of the system is also compromised by the allocated MELD points for HCC candidates and a gender bias in accurately capturing disease severity. MELD's narrow focus on measuring mortality endpoints also does not consider quality of life for liver transplant candidates - their symptom burden, functional decline, pain and other suffering. It also avoids other complicated factors such as the question of utility and transplant benefit in allocation policy. Conclusion Through my research and retrospective narrativization, I observe how the objectivity and standardization in evidence-based allocation policy contrasts with the variations and uncertainty of lived patient experience. I highlight the way the pursuit of more efficiency can strangle out personal stories and limit understanding of waiting for a liver transplant from the patient's perspective.

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Functional analysis of alveolar macrophages associated with acute lung allograft dysfunction

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Abstract Body: Purpose: Acute lung allograft dysfunction (ALAD) is a risk factor for reduced graft survival in lung transplant (LT) recipients. The contribution of lung macrophages (Mac) to ALAD is yet to be fully studied. Using single-cell RNA sequencing (scRNAseq), we recently identified two unique Mac subsets – TRAIL+ CXCL10+ interferon-stimulated (IS) and metallothionein-expressing (MT) Mac – that are uniquckly present in bronchoalveolar lavage (BAL) cells of patients with ALAD. Here, we report on the functional phenotype of Mac isolated from ALAD BAL samples. Methods: BAL cells from stable or ALAD LT patients were collected and cultured overnight. Culture supernatants were analyzed using muliplex assay. IS Mac were sorted based on TRAIL expression and cultured with IFNγ, LPS, and specific inhibitors of pathways identified using scRNAseq. We employed an imaging flow cytometry (IFC)-based assay to assess the ability of Mac from ALAD BAL to activate alloreactive T cells. Results: Proinflammatory cytokines were released in significantly greater quantities by Mac from ALAD compared with stable patients (Fig 1A). LPS stimulation was unable to enhance cytokine release. Among sorted TRAIL+ Macs, CXCL10+ cells were present in greater frequencies in ALAD BAL and were further increased after IFNγ (but not LPS) stimulation. Both dexamethasone and anti-VEGF decreased the frequency of CXCL10+ IS Macs to the level seen in stable BAL (Fig 1B). Our IFC assay, which is based on the identification of immune synapses between Macs and T cells, showed that ALAD BAL Mac supernatants augmented T cell alloreactivity to allogeneic monocyte-derived macrophages from healthy control blood (Fig 1C). Conclusion: ALAD-associated Mac secrete inflammatory cytokines and enhance T cell alloreactivity. Our data suggest that targeting VEGF and TIMP1 may limit these responses. Future work will determine whether IS Macs are responsible for these phenomena. This work may have important prognostic and therapeutic implications for LT recipients in the future.

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