2017 CST-Astellas Canadian Transplant Fellows Symposium

Introduction and Overview of the Current Landscape on Organ Donation and Transplantation in Canada

Jag Gill, MD

Dr. Gill graduated from Medicine at the University of BC in 2001 and completed his post-graduate training in Internal Medicine and Nephrology at UBC in 2006.

Dr. Gill completed a post-doctoral fellowship in kidney transplantation at the University of California, Los Angeles as part of the KRESCENT program and obtained a Masters degree in Public Health from Harvard University. He returned to Vancouver in 2008 and has been on staff at St. Paul's Hospital since. His primary clinical focus is in renal transplantation and his research interests are in transplant epidemiology and database analyses, examining access to transplantation, expansion of organ donation, and the impact of donor status on post-transplant health outcomes.

Case Studies
CST Transplant Fellows Symposium

September 25, 2017

Jag Gill

Case 1

Case 1

- 46 yo woman with ESRD from ADPKD
- Family history of ADPKD – father with transplant and sister on dialysis
- Obese
- No other comorbidities; 1 pregnancy
- ROS negative for cardiac, respiratory, hematologic, malignancy, or ID concerns

Case 1

- Preemptive LDKT from her husband
- No noted surgical complications
- ~100cc/hr urine output post transplant
- Pre-op CR was ~330 umol/L
- Hyperkalemic post-op
  - K 6.0 @ 1h→ 7.1 @ 3h → shifted with insulin, etc
- Good UO ~ 100cc/hr → 80cc/hr → given lasix for K and increases to 110cc/hr → K down to 5.8
- What do you do next (if anything)?

Case 1

- Repeat bloodwork at 12 hours post tx
  - K 6.3, Cr 354
- What do you do next?

Case 1

- CR was 333 preop→ 316 @17:21 → 321 @21:57→ 347 @ 03:00 → 354 @ 06:12 → 369 @10:30

- UO ~ 50cc/hr

- Urgent ultrasound gets ordered

Case 1

- Ultrasound
- No hydronephrosis
  - Reversal of flow within main renal artery with no definite flow in main renal vein; loss of flow in the ilac vein → concerning for occlusive thrombosis of main renal vein with extension into the iliac vein

- OR ~ 230pm
  - Poorly perfused kidney with right iliofemoral DVT; entire iliac was filled with clot; some flow still in the kidney
  - No kinking or other technical problems with anastomosis were apparent

Case 1

- Intubated in ICU; maintained on IV heparin
- MMF/Tac held; given additional dose of basliximab + hydrocortisone
- CRRT for lactic acidosis
- POD 3–? bleeding → heparin held
- POD 4 – heparin restarted and extubated
  - US – no venous flow
- POD 5– renogram → no flow
- POD 6 – right transplant nephrouretectomy
- MMF/pred restarted peri-op

Case 1

- Hematology assessment
  - Risk factors:
    - Family history of clotting (dad)
    - Obesity
  - Prothrombin gene mutations, FV Lieden, Protein C and S → all normal
  - Antithrombin III can't be tested on AC
  - Plan for 6 months of AC with followup US and AT III

Case 1

- Immunosuppression
  - Maintained on low dose tacrolimus/MMF/pred

- R/A re repeat transplantation after heme workup completed in 6 months

Discussion point # 1

- What could have been done differently during the assessment
  - Thrombophlic workup not routinely done
  - Family history of clots was negative on history as per patient
- Should we broaden criteria for thrombophilia testing pre-transplantation?

CST Consensus guidelines, 2005

- The routine hematologic assessment of a renal transplant candidate should include a complete blood count, a differential white cell count and assessment of partial thromboplastin time and international normalized ratio. Additional investiga- tions, such as a hypercoagulability screen, bone marrow eval- uation or review by a hematologist, are recommended in cases of thrombophilia or hypercoagulability, monoclonal gammopathy and persistently abnormal blood counts.

- Increased graft thrombosis and rejection may be seen in patients with thrombophilia or hypercoagulability.218 Rou- tine screening of all kidney transplant candidates is likely to result in a low yield.219 However, those with a prior history of graft thrombosis, arterial or venous thrombosis, recurrent thrombosis of hemodialysis access (other than central ve- nous catheters) or SLE could benefit from screening.

Screening in non-TX populations

- Isolated provoked VTE – screening not recommended
- Patients with VTE and family history or other risk factors should be screened
- No guidelines recommend routine screening of family members with recurrent DVT
- ? Screening prior to pregnancy on women with family history of DVT

Discussion point #2

- Evaluation of graft function in pre-emptive LDKT recipients
  - Should SCR be tested more frequently in the first 24 hours (esp. preemptive)?

Discussion Point #3

- Would you consider a repeat transplant in the patient?
- What you consider a prioritization for repeat transplantation?
- What do you do with immunosuppression at this time?

Case 2

Case 2

- 27 year old woman with ESRD due to unknown cause
  - Presented with advanced renal dysfunction with a history of hypertension
  - US – bilateral shrunken kidneys – precluded biopsy
  - No other congenital abnormalities, but does have issues with low IQ and poor memory
  - Presents very well; married, strong social supports with her husband and mother
  - Has not had major issues with non-adherence based on her nephrologists assessment

Do you have any concerns regarding her transplant candidacy?

Do you have any concerns regarding her transplant candidacy?

- Unknown primary disease
- Cognitive issues

Case 2

- Blood type B
- 0 PRA
- eGFR 14ml/min
- Potential living donor
  - Friend, blood type O, 0 DR mismatch; DQ mismatch

Case 2

- Preemptive live donor kidney transplant
- What would you give for immunosuppression?
- What mechanisms would you put in place to ensure adherence and monitor this?

Case 2

- Basiliximab induction
- Tacrolimus, MMF
- Steroid free (given young age, 0 PRA)

Case 2

- Well post transplant
- Cr ~300 → 70 umol/L within 2 days; excellent UO
- No adverse reactions
- Tacrolimus levels good in hospital
- 1 week post discharge, tacrolimus levels ranged from 3 to 14
- What do you do?

Case 2

- 10 days post DC
  - Cr increased from baseline of 70-78 to 94

- What do you do now?

Biopsy

- Isolated 2A rejection
  - Focal endarteritis
  - Mononuclear interstitial inflammation; focal tubulitis

- Solumedrol 500mg IV X 3 doses, prednisone
- Cr fell to 75umol/L;
- Stable thereafter
- Tacrolimus was still erratic
- What would you do about the erratic tacrolimus levels?

Tacrolimus variability

- wide variations in trough tacrolimus blood levels are associated with acute rejection and allograft failure

- non-adherence, drug prescription patterns, variability in drug absorption/metabolism, and drug–drug interactions may result in IPV in tacrolimus trough levels

Hsiau, et al. Transplantation 2011; 92: 918–922.
Pollock-Barziv SM, et al. Pediatr Transplant 2010; 14: 968–975.
Borra et al. Nephrol Dial Transplant 2010; 25: 2757–2763.

Table 3 | Relative hazard of primary composite end point (total graft loss, late acute rejection and transplant glomerulopathy) and secondary composite end point (death with function excluded) by TacSD threshold

TacSD threshold	Hazard ratio (95% CI) for primary composite end point[a]	*P*-value	Hazard ratio (95% CI) for secondary composite end point[a]	*P*-value
>1.5 vs. ⩽1.5	1.33 (0.75, 2.37)	0.33	1.23 (0.60, 2.51)	0.58
>2 vs. ⩽2	1.50 (0.89, 2.54)	0.13	1.44 (0.73, 2.86)	0.29
>2.5 vs. ⩽2.5	1.84 (1.04, 3.25)	0.04	1.99 (0.96, 4.12)	0.06
>3 vs. ⩽3	2.56 (1.42, 4.62)	<0.001	2.77 (1.30, 5.89)	0.01

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; ECD, expanded criteria donor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; PRA, panel reactive antibodies; TacSD, standard deviation of tacrolimus levels.

Sapir-Pichhadze, et al. KI 2013

Case 2

- 2 months later, Cr increased to 148 umol/L
- Repeat biopsy
  - 2A rejection
  - Evidence of glomerulitis; no peri-tubular capillaritis, C4d negative;

- No anti-HLA antibodies found
- How would you treat?

Diagnostic criteria for acute ABMR

- Histologic evidence of acute tissue injury
  - MVI (glomerulitis and/or peritubular capillaritis
  - Intimal or transmural arteritis
  - Acute TMA without other cause
- Evidence of current or recent antibody interaction with vascular endothelium
  - Linear C4d staining in peritubular capillaries
- Serologic evidence of DSA

Non-HLA antibody associated AMR

- Typically have C4d positivity
- AMR reported with the following antibodies
  - Angiotensin II receptor antibody (HTN)
  - Anti-endothelial antibodies
  - Major histocompatibility complex class I chain related gene A (MICA)

Case 2

- rATG (6.5mg/kg) + steroids
- Had a modest improvement in renal function (Cr decreased to 80s)

- What next?

Case 2

- Cr stayed at 80 and then climbed to low 100s
- Repeat biopsy
  - 2A rejection with glomerulitis
  - C4d positive
  - Peritubular capillaritis
- DSA to DQ4 MFI 2800
- What next?

Case 2

- Treatment for ABMR
- PLEX/Rituximab/low dose IVIG
- Renal function deteriorated over 1 week and became dialysis dependent
- Continued ABMR treatment for 3 weeks
- How long would you continue treatment?

Diagnostic criteria for chronic ABMR

- Morphologic evidence of chronic tissue injury
  - TG, severe peritubular capillary basement membrane multilayering
  - Arterial intimal fibrosis
- Evidence of current or recent AB interaction with vascular endothelim (C4d)
- Serologic evidence of DSA

Repeat Biopsy

- Acute tubular injury
- Ongoing glomerulitis
- Double contouring of glomeruli (suggestive of chronic active ABMR)

- Continued treatment for 2 weeks
- Tacrolimus level still extremely variable
- Admitted with urosepsis and pneumonia
- Feeling unwell on dialysis

Case 2

- Discontinued PLEX
- Repeat biopsy 1 month later
- Significant interstitial fibrosis
- Dialysis dependent for 7 weeks now

- What next?

Is she a re-transplant candidate?

Case 3

Case 3

- 23 yo woman presents as a potential living kidney donor for her brother
- ABO compatible
- Brother has type I diabetes - has advanced CKD (eGFR 14ml/min) due to DMN
- Family history of diabetes nil except brother
- Medical history is otherwise benign
  - No renal issues, no risk factors for kidney disease
  - Cr 73, eGFR 84ml/min
  - Nuclear renogram – GFR 89ml/min; normalized for BSA 94ml/min

- What do you tell her about the risks of kidney donation and what are her specific risks?

Would you accept her as a donor?

- What considerations do you have?
  - Size
    - her BMI is 19 – ht 5’ wt 100lbs
    - her brother’s BMI is 24 ht 6’ wt 175lbs
  - Level of HLA MM
    - 1 haplotype match
  - ABO
    - Both are blood type O
  - Other options
    - There is another blood type incompatible donor (ABO A) - willing to go in KPD

What options would you present?

What options would you present?

- Would you recommend she donate directly?
- Would you recommend she not donate?
- Would you recommend the other donor donate through KPD?
- Would you recommend she donate through KPD?

Case 4

Case 4

- 74 yo man previous living kidney donor
- Donated to his brother (had ESRD from HTN) when he was 48 yo
- Baseline assessment at time of donation was benign
  - No HTN; family history of HTN and ESRD
  - no diabetic risk factors
  - Slightly overweight
- Pre-donation Cr ~ 80; post donation Cr ~ 120

How would you follow this donor?

- How frequently
- What would you check?
- For how long?
- Who would coordinate this?

KDIGO (draft)

- **18.1: Living kidney donors should be monitored long-term for hypertension, CKD, and overall health status and well-being. Blood pressure, eGFR based on serum creatinine, and urine albumin testing are particularly important parameters to follow in kidney donors due to concerns for the impact of donation on long-term risk for development of hypertension and CKD. Assessment should include not only the absolute level of eGFR but also its trajectory over time.** ***(Not Graded)***

- **18.2: The following specific practices should be performed annually for each donor as part of post-donation follow-up care:** ***(Not Graded)***
  - **Blood pressure measurement**
  - **Body mass index measurement**
  - **Serum creatinine testing with estimation of GFR (eGFR)**
  - **Evaluation for albuminuria**
  - **Evidence of diabetes**
  - **Review and promotion of healthy lifestyle practices including exercise, diet,**
  - **avoidance of smoking**
  - **Review of psychosocial health and well-being as it relates to their donation**
  - **experience.**

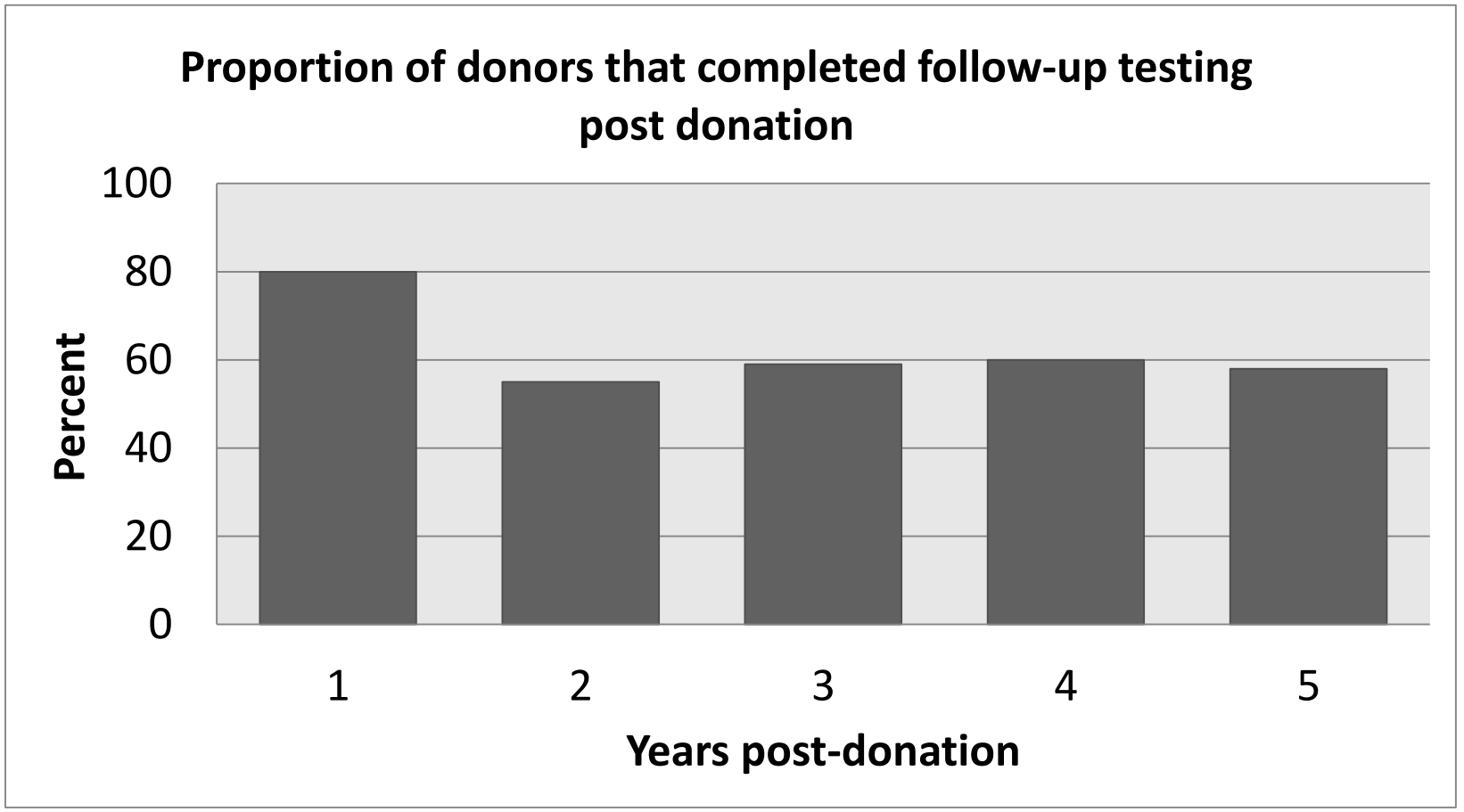
- **18.3: Follow-up information should be reported to national and/or regional registries to facilitate aggregation, assessment and dissemination of current donor outcomes data. *(Not Graded)***
- **18.4: Donors who develop hypertension or CKD should receive appropriate medical treatment for these conditions according to clinical practice guidelines for the conditions. *(Not Graded)***
- **18.5: Donors should receive age-appropriate healthcare maintenance according to clinical practice guidelines for the regional population. *(Not Graded)***
- **18.6: Metabolic conditions (e.g., diabetes), cardiovascular diseases (e.g., coronary artery disease, congestive heart failure), and cardiovascular risk factors (e.g,. hyperlipidemia, obesity) or risk behaviors (e.g., smoking, sedentary lifestyle) should be evaluated during post-donation healthcare maintenance assessments and managed according to general population guidelines. *(Not Graded)***
- **18.7: Donor education provided prior to and at the time of donation should be reinforced by post-donation educational contacts from the transplant center such as newsletters, links to transplant center health recommendations or national guideline website documents to promote sustained healthy lifestyle choices and behaviors. *(Not Graded)***
- 128
- **18.8: When important new information becomes available on the long-term outcomes of living kidney donors that differs from what a donor was told prior to donation, the transplant program should use reasonable efforts to contact past donors and provide this information. *(Not Graded)***

Follow-up of living donors

- Extremely variable between regions

- OPTN (2013)
  - Mandatory 6 month, 1 year and 2 year follow-up

Adherence to follow-up is poor



O'Brian, Gil J

Case 4

- Did not adhere to follow-up and presented with hypertension at age 58
- Reviewed by nephrologist
- Poorly adherent with follow-up;
- Contracted hepatitis C in his 60s

- 7 years later found to have renal dysfunction – not biopsied, but believed to be hepatitis related→ treated with IFN for HCV with good response but renal function continued to deteriorate
- Followed by nephrology since then
- eGFR is now 17ml/min; somewhat symptomatic

Case 4

- Requesting transplant assessment
- Undergoes transplant assessment and is felt to be suitable to receive a kidney transplant; no potential donors
- He does not want to do dialysis; will only consider a transplant
- He asks if he gets a priority on the wait-list since he is a prior living kidney donor

Priorities for prior living donors?

Would you list him preemptively?

- What are the considerations?

Would you deviate from routine allocation policies

- Would you allocate and ECD kidney to him?
- Would you prioritize an SCD kidney for him?

- What are the considerations?

What we did (and our rationale)

- We prioritized him for an SCD kidney and preemptively listed him
- Rationale: prior living donors have contributed to the health of kidney patients and society and are therefore owed a prioritization
- There is a need to standardize what we mean by “prioritization for transplantation” and be transparent about the rules of application