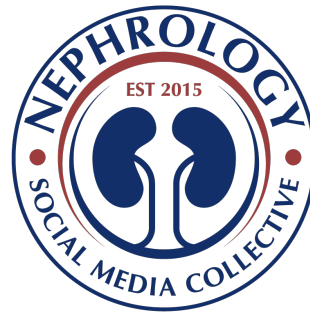
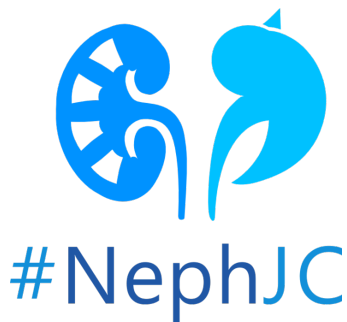




# Nephrology Fellow Clinical Compendium



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*Disclaimer- This guide is intended as an overview with salient details only. In order to provide high quality patient care it is important to maintain close and appropriate supervision.*

**Last update: Dec 24, 2021**

## Chapter 7: Kidney Transplantation

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### Kidney Transplant Note

#### Information needed in notes

Cause of kidney failure, if patient was on dialysis or not, last dialysis session, dialysis access, how much urine made prior to transplant and if yes, amount of proteinuria (to differentiate between origin- native vs transplanted).

- Date, type, and organ or organs transplanted
- Living donor or deceased donor
- Donation after brain death or donation after cardiac death (DCD)
- Organ transplanted
  - DDLT or DDKT (Deceased Donor kidney or kidney transplant)
  - SPK (simultaneous pancreas-kidney)
  - SLK (simultaneous liver-kidney)
  - LUKT or LRKT (living unrelated or living related kidney transplant)
  - SHK (simultaneous heart kidney transplant)
- Allograft function: If a new transplant, is there immediate graft function or SGF (Slow graft function) versus DGF (Delayed Graft Function, means requiring HD in less than 1 weeks), this is impacted by donor factors, cold ischemia time (>24 hrs), intra-op issues, and patient issues including ischemia-reperfusion (warm ischemia time > 45 min).

Here is a review of delayed graft function:

- The AKI of Kidney Transplantation

**Transplant Data:** Try to get as much as you can as the information might not always be easily available, also must be careful not to be specific about donor data due to HIPAA in particular age (e.g for a 35 y/o donor should say mid thirties)

Relevant donor data: age, sex, size, KDPI score, initial/peak/terminal creatinine, HIV/Hep C status urine output, biopsy, relevant history (DM/HTN)

Cold and warm ischemia time (preferred cold ischemia time (CIT) is <24 hours and warm ischemia time (WIT) is <45 minutes)

Public Health Service (PHS) high risk: yes or no (risk factors include prisoner, history of drug use, sex worker, etc)

CMV and EBV status of donor and recipient

HLA cross match and if Donor Specific Antibody (DSA) was present

Induction therapy

Removal of ureteral stent and dialysis catheter (usually to be scheduled post-op so if no date can put to be scheduled)

Relevant surgical details if there were intra-operative complications

- **KDPI** (Kidney Donor Profile Index), not well that a KDPI of over 85% is a risk factor for delayed graft function or DGF.
  - Ten factors affecting KDPI:
    - **Age (very important)**
    - **DCD (donation after circulatory death, important)**
    - Weight
    - Height
    - Race (this is being debated to be removed)
    - HTN
    - DM
    - Death cause
    - Terminal serum creatinine
    - HCV
  - 100% means worst outcome, >85% risky, but still mostly better than dialysis.
  - Baseline serum creatinine (look at the trend not one point in time) if not immediately post-transplant

Native kidney disease to determine recurrence incidence:

- Oxalosis 80-100%
- Diabetic Nephropathy 80-100% (by histology)
- HUS/TTP 50-75%
- IgA 40-60%
- FSGS: 20-40% (can recur within minutes after transplant)
- MPGN-I: 30-50%, II 80-100% (mind new classification)
- Membranous 10-30%
- GPA <20%
- Fabry's <5%, ↓  $\alpha$ -galactosidase enzyme (Tx Fabrazyme)
- SLE 5%
  - Significant post-transplant events including return to the OR, recent biopsies, infections, treatment for rejection etc
  - Immunosuppressive drugs and if any hold try to find out why (commonly due to low white count or infection)

## Human Leukocyte Antigen (HLA) and Basics of Transplant Immunology Review

### HLA in transplantation & Use of HLA Antibody and Mean Fluorescence Intensity (MFI) testing

**Initial immunological assessment of a potential kidney transplant candidate:**

- History of sensitizing events (eg previous transplant, blood transfusion, and/or pregnancy).
- HLA typing of the donor and recipient,
- Screening for alloantibody against HLA

Major histocompatibility complex (MHC) is a family of genes that encodes HLA.

**HLAs:** Glycoprotein encoded by genes on chromosome 6. Unique like fingerprints. Immuno-dominant antigen for both humoral and cellular alloreactivity.

**MHC I -> HLA Class I:** HLA-A, HLA-B, HLA-C On all nucleated cells (also platelets). Not on RBCs

**MHC II -> HLA Class II:** HLA-DRB1, DRB3,4,5, HLA-DPB1, DPA and HLA-DQB1, DQA on B and certain T lymphocytes and Myeloid cells (antigen presenting cells (APC), Macrophages, Dendritic cells, activated human endothelial cells, Bly).

**Epitopes:** Hypervariable regions in the HLA distal domains and are recognized as foreign.

**Non HLA:** Eg: Angiotensin type 1 receptors, endothelial cells, Agrin, glutathione-S-transferase T1, GBM, Protein kinase, CXCL9,11, IFN-g, glial cell-derived neutrophilic factor. Have a role in AMR, detected by cell-based assays of endothelial cells (IF and Flow cytometry)

**ABO Ags:** on ALL cells.

Barrier to transplantation exception:

-A2 (donors) - low A Ags & develop tolerance.

-Rh present only on RBCs.

## Understanding Cross-match

**Panel Reactive Antibodies (PRA) score:** This estimates the level of sensitization. PRA is the percentage of samples from different individuals in a cell panel with which a patient's serum reacts. Calculated PRA can be expressed with four significant figures beyond the decimal point, which permits more accuracy.

**Donor Specific Antibody (DSA) testing:** Class II is more significant than Class I in rejection. Antibodies to HLA may be present pre-transplant or formed post-transplant (*de novo* DSA).

Anti-HLA Antibody detection techniques:

- Solid phase assay, Multiple / Single Ag Beads (SAB): Immobilized protein/peptides
  1. ELISA-PRA
  2. Flow cytometry
    - Flow screen PRA
    - Luminex Multiple/Single Ag cPRA/DSA
- HLA antibody characterization using a multi-analytic bead method.
  - Recipient serum + Fluorochrome-infused beads coated with soluble HLA molecules.
  - If anti-HLA antibodies are present, they bind to the corresponding HLA molecules on the surface of the microbeads.
  - Multi-antigen beads contain Class I and Class II antigens from a single cell line, while each single antigen bead (SAB) contains a single HLA antigen. If multi-antigen beads in screening are positive, do SABs to accurately identify the HLA-antigen to which the patient has alloantibody to.
  - SAB is a semi-quantitative measure of the amount of antibody referred to as mean fluorescence intensity (MFI), yet only approved as a qualitative assay (negative or positive).

## Cell-based assays complement dependent techniques PRA

### Lymphocytes (HLA Abs, DSA, limited in non-HLA abs detection, validated):

- Complement Dependent Cytotoxicity Cross-match
- Flow Cross-match
  - T cutoff < 60 Median Channel Shift (MCS) considered negative cross-match
  - B cutoff < 100 MCS considered negative cross-match

### Complement-dependent cytotoxicity Cross-match (CD-XM)

- Recipient serum + exogenous complement + Donor lymphocytes
- If donor-specific anti-HLA antibodies are present in the recipient serum, they bind to HLA molecules on the surface of the donor lymphocytes and activate complement, leading to cell lysis. The strength of the cross-match is graded according to the proportion of lysed cells. Both T cell and B cell cross-match assays are performed (different HLA expression). Increase sensitivity of the cross-match by the addition of anti-human globulin (AHG).

### Flow cytometry Cross-match (Flow-XM)

- Recipient serum + Donor lymphocytes + Fluorescent labelled anti-human immunoglobulin.
- If donor-specific anti-HLA antibodies are present in the recipient serum, they bind to HLA molecules on the surface of donor T or B cells and detected using flow cytometry.
- The strength of the flow cytometry cross-match is measured as the number of '**channel shifts**' above the control sample.
- The strength of any antibodies detected is measured as the MFI. MFI cutoff significance is variable between centers, some consider it significant if >2000 and very significant if >10.000. MFI < 1000 is considered negative.

**Flow-XM** compared to **CD-XM**, less subjective and associated with the CDC-XM because it is reported as **mean channel shift** rather than positive or negative result based on visual interpretation.

### Virtual Cross-match:

- Flow-cytometric screen results + sophisticated HLA typing techniques to predict the result of a cell-based cross-match in a clinical scenario.
- Not a substitute for a physical cross-match test unless the recipient does not have anti-HLA antibodies.

Treat antibody mediated rejection if: +DSAs and pathological evidence +/- clinical evidence

## Basic review of transplant immunology (Review)

**Adaptive immunity:** B and T cells.

**Innate immunity:** Inflammatory cells (neutrophils, monocytes, macrophages, and dendritic cells among others) and soluble mediators (the complement system being a prime example). First line firing, phagocytosis, launch adaptive. (Ischemia reperfusion)

**Antigen Presenting Cell** of DONOR (short lived) & RECIPIENT (cross-dressing) activate nT (naive T cells) in lymphoid organ (eg T-cell zones (peri-arteriolar lymphoid sheaths of the splenic white pulp)/ tissues. Tm (T memory) activated in whole body.

### B-Lymphocyte activation/differentiation

- Bly (B lymphocyte) with help of TH (T helper), internalizes the Ag, recycles and expresses it as MHC-II with contact to TH (activated by same gene).
- **CCR7 receptor on B lymphocytes & CXCR5 receptor on T-follicular cells (TFH)** lymphocytes are essential for bringing the **two** cells together at the interface between B-cell zones (or follicles) and T-cell zones in secondary lymphoid organs.
- **Blys** that receive all the necessary stimulatory signals coalesce in the follicles to form **germinal** centers then differentiate (with transcriptional repressor B lymphocyte-induced maturation protein-1 [**BLIMP-1**]) to Plasma cells, considered the Ab factory (require **IL6** for survival), reside the BM for long time after exiting the lymphoid organ/tissue and memory B-cells, populate secondary lymphoid tissues and circulate in the blood.

### Antibody (Ab) or Immunoglobulin (Ig)

- Glycosylated protein composed of two “heavy” and two “light” linked to each other by disulfide bonds. N-terminus regions of the heavy & light chains are where the variability between one antibody molecule and another resides. Subtypes IgM, IgD, IgG, IgA, and IgE distinguished based on C-terminus of heavy chains.

### Natural Killer (NK) cells

- NK cells respond to *missing self markers of MHC and presence of activating ligands*. They have the ability to recognize stressed cells in the absence of Abs or MHC. Once activated, they secrete perforin, granzyme, and IFN $\gamma$  and differentiate to memory cells. Great value in virus infected cells.

**Direct Allorecognition** T Cell Receptors (TCRs) of recipient - Intact donor HLA proteins.

**Indirect Allorecognition** TCRs of recipient - Processed donor HLA proteins (and expressed by recipients APCs).

## Lymphocyte activation in transplant

**Signaling in Lymphocyte activation:**

**Signal 1**, TCR signaling

TCRs (CD3) on T lymphocytes bind to HLA-peptide complexes on APCs.

- **Tyrosine kinases** - recruitment and activation of the enzyme phospholipase C-g (PLC-g).
- **PLC-g** catalyzes the breakdown of the membrane lipid phosphatidylinositol biphosphate (PIP<sub>2</sub>) to generate two second messengers:
  1. Diacylglycerol (DAG) activates the protein kinase C (PKC) and mitogen-activated protein (MAP) kinase pathways
  2. Inositol 1,4,5-triphosphate (IP<sub>3</sub>) triggers the *calcineurin* pathway by increasing intracellular calcium concentration.
- IL1 + IP3 + PKC + MAP activate transcription factors NFkB, NFAT, AP-1.
- OKT3 (Anti-CD3), removed from the market.
- TK – ↑PLC-g – PIP<sub>2</sub> → 1.DAG (↑PKC & MAP) & 2.IP3 (↑calcineurin [CN] via Ca thru cyclophilins in cyclosporin or FK binding ptn in Tacrolimus) together with IL1 ultimately all activate transcription factors NFkB, NFAT, AP-1.

### Signal 2, TCR Co-stimulation to prevent T-cell deletion/anergy.

1. **Integrins LFA-1 & CD2 (LFA-3)** on T lymphocytes bind to ICAM-1&2 and CD58, respectively, on Dendritic cells.
  - Anti-LFA-1 (efalizumab) and anti-CD2 antibodies (Alefacept) with side effects of: PML by JC virus
2. **CD28 on T Lymphocytes bind to B7.1 (CD80) and B7.2 (CD86) on mature APCs.**
  - CTLA4-Ig (Belatacept), binds with high affinity to B7 (CD80/86) molecules and prevents them from engaging CD28.
3. **CD154 or CD40 ligand (CD40L)**, on activated CD4+ T cells bind on CD40 on APC. CD154 has a role in Ab switching IgM to IgG.
  - Anti-CD154 caused serious thromboembolic side effects owing to CD154 expression on platelets

### Signal 3, Cytokines: Interleukins Proliferation/Differentiation

- **IL-2** produced by T cells and they express IL2R (auto/paracrine). If produced, CD25 expressed increases IL2 to IL2R affinity.
- **Anti-CD25** (basiliximab) inhibit T cell proliferation modestly, by blocking α chain (expressed upon activation), likely due to
  - Presence of several other ILs and β & γ-chains (via JAK3 kinase)
  - T regulatory cells express high levels of IL-2Rα
- Cytokines cause CD4+ to diff/proliferate to → (Th1, Th2, Th17, TFH) & 1reg (Treg) From APC: IL2 & 4 activate CD4-H1/2 while IL2 & 12 activate CD8 then TH1 → IFN γ (also has



reg functions), TNF, IL-2, IL-6, IL-12 (from APC) → activate Macrophages and some differentiate to T-memory.

- Anti IL-12 (ustekinumab) approved for the treatment of Psoriasis
- **TH2** → IL4, IL10, IL13 → activate Bly to secrete Ab
- **OTHER**: TH17 (dependent on TGFb, IL-6, and IL-21, IL-23-for stabilizing) → IL-17 (fungal). secukinumab, anti-IL17 for psoriasis & RA. TH1FH → IL-21. TH9 → IL-9
- Treg → IL-10
- Cytokines cause **CD8+** to diff/proliferate to Cytotoxic T cells (w/ help of IF  $\gamma$ ), which secrete perforin and granzymes → Target cell killing.
- **De-sensitization- getting rid of antibodies**: Plasmapheresis/IVIG, Proteasome inhibitors (bortezomib), rituximab, complement inhibitors (eculizumab), anti-IL-6 receptor blockers and immunoglobulin-G-degrading enzyme of Streptococcus pyogenes (IdeS).

## Immunosuppression

### Immunosuppression (Review)

#### Induction (ideally given prior to allograft reperfusion)

**Thymoglobulin**: Common, first dose in O.R. and 3-5 more doses in the early post-op, with about 250mg-500mg of Solumedrol given in O.R. (Check Op Note to calculate remaining dose). Expect platelets and WBC to drop. Lymphocyte depleting

**Alemtuzumab**: Anti-CD52 (mature lymphocyte marker), single dose given in the O.R. Lymphocyte depleting.

**Simulect** (basiliximab): Anti-IL-2, non-lymphocyte depleting, reserved for patients who don't require high immunosuppression, with first dose in O.R. and 2<sup>nd</sup> dose given on post op day #4

Antibody	Brand	Class	Lymphocyte depleting	Antigenic targets and cells	Typical prescription	Side effects
<b>Basiliximab</b>	Simulect (Novartis)	Chimeric Monoclonal	No	IL2 receptor (CD25)  Activated T cells	20 mg x2 doses 2 doses: POD# 0 and 4. U\$4,254	Hypersensitivity reaction (rare)
<b>Rabbit antithymocyte globulin</b>	Thymoglobulin (Genzyme); ATG (Fresenius)	Polyclonal	Yes (mainly complement-mediated cell lysis followed by Fc removal by RES)	Multiple antigens (CD2, CD3, CD4, CD5, CD7, CD8, CD11a, CD25, CD28, CD38, CD45, CD50, CD98, CD107, CD147)  Mainly T cells, to a lesser extent B and NK cells	1.5 mg/kg daily 4 doses: POD #0, 1, 2 and 3.  U\$7,824-18,256 (First dose prior to reperfusion)  Premedicate with steroids and acetaminophen Decrease dose by half if WBC<3K/ $\mu$ L or Platelets<75K/ $\mu$ L	Myelosuppression and cytokine release syndrome (fever, chills, dyspnea, hypotension, pulmonary edema). Less common: serum sickness due to development of antirabbit antibody)  Increased risk of melanoma, lymphoma and genitourinary cancer
<b>Alemtuzumab</b>	Campath 1H (Berlex Laboratories)	Monoclonal	Yes (more prolonged)	CD52  T, B and NK cells, monocytes, macrophages, dendritic cells, eosinophils, mast cells	30 mg x1 dose intraoperative U\$2,065	Myelosuppression; Infusion-related (nausea, diarrhea, headache). ? increased risk of humoral rejection  Increased risk of lymphoma, thyroid cancer and colon cancer

Table from [Kidney Transplant eBook](#) from Leonardo Riella, MD, PhD.

### Maintenance Immunosuppression:

- [The ABCs of immunosuppression](#): A primer for primary care physicians.
- Immunosuppressive medications

**Calcineurin inhibitor (CNI):** Most commonly use Tacrolimus (Prograf), alternative is Cyclosporine (Gengraf)

- Aim for tacrolimus trough around 8-10 ng/mL in early post-transplant; After one year, aim for levels around 5-7 ng/mL. **All drug levels can be patient and program specific so ask your attending for target levels**
- Always confirm 12 hour trough or if not how long the level was drawn from the time the CNI was taken
- Aim for cyclosporine trough around 250-300 ng/mL for 1<sup>st</sup> 3 months, 150-200 ng/mL for first year, and around 100 ng/mL for greater than 1 year (this varies by institution)

**Anti-metabolites:** Most commonly use Cellcept (Mycophenolate Mofetil abbreviated MMF) or Myfortic (Mycophenolic Acid abbreviated MPA), less commonly use Azathioprine (Imuran), check thiopurine methyltransferase (TPMT) before starting Azathioprine because if low increased risk of bone marrow toxicity

- Higher doses of MMF required with cyclosporine because it enhances the metabolism of MMF. Usual dose of MMF is 500 mg BID to 1 g BID with tacrolimus and 1000 mg BID with cyclosporine. If patient cannot tolerate CellCept or Myfortic usually due to GI intolerance including developing colitis then can consider azathioprine (Imuran)
- No allopurinol/febuxostat with azathioprine! - can cause profound leukopenia.

**Steroids:** Steroid free and steroid using centers

- Prednisone is weaned down to 20 mg in the first week, then down to 5 mg by the end of first month but depends on your program's protocol, avoid late steroid withdrawal .

**Other agents:** Belatacept and m-tor inhibitors (Sirolimus, Everolimus)

- Belatacept is a once a month infusion levels are not checked, patient must be EBV+

**Combinations:** Most popular is Tacrolimus with Cellcept or Myfortic +/- Prednisone, otherwise can see Tacrolimus replaced by Belatacept or mTOR inhibitor, sometimes combo of Tacrolimus and mTOR inhibitor

Side Effects	CsA	Tacrolimus	mTOR inhibitor	Prednisone	MMF
Hypertension	++	+		++ (high dose)	
Nephrotoxicity	+++	++	+		
Dyslipidemia	++	+	+++	+	
Hyperglycemia	+	++	+	++	
Hyperkalemia	+++	+++			
GI side effects		+	+		+++
Tremor	+	++			
Malignancy	+	+			
Osteoporosis	+	+		+++	
Anemia			+		+
HUS/TTP	+	+			
Leukopenia		+(neutropenia)	+		++

Table taken from [Kidney Transplant eBook](#) by Leonardo Riella, MD, PhD.

### Other Common Immunosuppression Side Effects: This is not an exhaustive list!

- **CNI: Hyperkalemia**, hypomagnesemia, tremor, hair loss with Tacrolimus, hirsutism with Cyclosporine, HTN, neurotoxicity, bone marrow suppression, AKI with supratherapeutic levels (N.B particularly in the setting of volume depletion and diarrhea), new onset diabetes after transplant.  
**CNI Nephrotoxicity**
- **Anti-metabolite: Cellcept and Myfortic** - bone marrow suppression, GI intolerance Azathioprine - avoid with allopurinol, higher risk for skin cancer, bone marrow suppression
- **Steroids**: hyperglycemia, mental status change, bone loss
- **m-TOR inhibitor**: mouth ulcers, bone marrow suppression, proteinuria, dyslipidemia, poor wound healing (if patient going for major elective surgery consider transitioning to CNI off of m-tor for instance)
- **Belatacept**: Patient must be EBV +, increased incidence of CNS lymphoma in those that were EBV negative
- For leukopenia discuss with attending about holding the anti-metabolite and/or valcyte and r/o CMV viremia
- All drugs put the patient at higher risk for malignancy and infection
- Drug Interactions: ask attending to help you adjust the dose
- CNI's (tacrolimus and cyclosporine) are metabolized by cytochrome p450-3A4 system
- Azole can increase m-TOR inhibitor levels
- Dose colchicine carefully with CNI's
- Statins with CNI monitor for myalgias and elevated LFT's

Inhibit cytochrome P450-3A4 Decrease metabolism Increased CNI Levels	Induce Cytochrome P450-3A4 Increased metabolism Decrease CNI levels
"Azole" anti-fungals: Fluconazole, Itraconazole, Ketocanazole, Posaconazole, Voriconazole	Anti-convulsants: Phenytoin, Phenobarbital, Carbamazepine
Erythromycin, Clarithromycin	Anti-TB: Rifampin, INH
Verapamil, Diltiazem, Nicardipine	St. John's Wart
Amiodarone	
Protease inhibitors like Saquinavir, Indinavir, Nelfinavir, and Ritonavir	

Significant liver dysfunction	
Food: Grapefruit, Blood Oranges	
?Marijuana ?Pomegranate	

## Prophylaxis

Typically consists of Nystatin, Bactrim, Valcyte or Acyclovir

### CMV Prophylaxis

For CMV prophylaxis (with alemtuzumab induction) This is a typical protocol but follow your transplant program's protocol

- D+/R- (highest risk): Valcyte for 6 months.
- D+/R+ or D-/R+ (moderate risk): Valcyte for 3 months
- D-/R- (lowest risk): Acyclovir for 3 months for HSV prophylaxis
- Other option of pre-emptive monitoring
- Review for [CMV](#) prevention, diagnosis, treatment, and managing resistance:

For CMV ppx (with Thymo induction)

- D+/R- (highest risk): Valcyte for 3 months, then monthly CMV PCR X 3 months
- D+/R+ or D-/R+ (moderate risk): Weekly CMV PCR x 3 months
- If D-/R- (lowest risk): Monitor prn concern for CMV

### Drug dosing

Valcyte (valganciclovir) dosing:

- 900 mg daily for CrCl > 90 ml/min
- 450 mg daily for CrCl > 30 ml/min
- 450 mg 2x week (Mon/Thurs) for CrCl < 30 ml/min

Acyclovir

- 400 mg twice daily for CrCl > 30 ml/min
- 200 mg twice daily for CrCl < 30 ml/min
- 200 mg daily while on hemodialysis

### PJP (pneumocystis jirovici) prophylaxis

Bactrim first choice, atovaquone or dapsone if allergic

- Bactrim SS QD for 6 mo.
- If CrCl < 30 ml/m, give Bactrim SS qod
- If allergic, atovaquone 1500 mg QD (if not available, dapsone 100 QD but need G6PD level)
- **Thrush ppx** - Nystatin swish and swallow 5 times per day (or occasionally Mycelex)

**Review** of common infections in Kidney transplant recipients

Remember to adjust medications for improved kidney allograft function!

### **CV (Cardiovascular) prophylaxis**

- BP meds (**no ACE/ARB, of course**; can give calcium channel blocker) (remember to avoid non-Dihydropyridines due to major drug to drug interaction with CNI/calcineurin inhibitors)
- HTN in pediatric kidney transplant
- HTN in **adult kidney** transplant
- BP goal initially after transplant for first 48-72 hours is < 160/90
- Restart home BP medications as needed, be careful holding clonidine for rebound HTN
- Start statin, e.g. usually pravachol 20 mg qhs
- Aspirin if indicated

**Review** of electrolyte disturbances in patient with a kidney transplant.

**Dialysis Access:** consider pulling HD catheter if allograft working, **usually after transplant if peritoneal dialysis patient needs dialysis will switch to HD and will need catheter**

## **AKI in after kidney transplantation**

**AKI Post Transplantation** - always know baseline serum creatinine, time from transplant, and medications compliance

Overview is to understand the differential can be split by time from transplant and assessing risk for rejection; see these reviews:

- Acute and allograft dysfunction in Kidney Transplantation
- AKI in the Transplant Setting
- AKI causes specific to the allograft - **SCRI**: **S**tructural, **C**NI toxicity, **R**ejection, **I**nfection

	Immediate -1month	Greater than 1 month & < 1 year
<b>PreRenal</b>	Severe hypovolemia/hypotension kidney vessel thrombosis	Hypovolemia
<b>Renal</b>	Ischemic ATN Hyperacute rejection Acute or accelerated rejection with ATN Acute tac/cyclosporine toxicity with ATN	ATN BK Viremia Acute tac/cyclosporine toxicity CMV
<b>PostRenal</b>	Urinary tract obstruction/leakage	UTI/Pyelonephritis Obstruction

- **IT'S NOT ALWAYS REJECTION** check for risk factors for rejection such as non-compliance (e.g. confirm patient has been physically taking medications if N/V) or low drug levels
- Think of the usual possibilities – prerenal, renal, and post-renal. Think about urodynamics and bladder. Prerenal and urodynamic are very common
- Can be as simple as dehydration: mycophenolate can cause diarrhea, patients are not used to drinking because they have been restricted on dialysis
- Acute allograft dysfunction can occur with tacrolimus toxicity (causes kidney vasoconstriction)
- Rule out obstruction. Look for patients who have a ureteral stent in the first **6 wks** of post-transplant.
- Other differential include—ureteral edema, blood clots, imperfect surgical anastomosis, ischemia of ureter due to rejection, extrinsic compression due to hematoma or lymphocele(very common), or urinary leak with urinoma
- Check transplant ultrasound, will see hydronephrosis/hydroureter or enlarged boggy kidney. Check also post-void residual if not immediately available and worry about urinary retention
- Since pts on dialysis have had a shrunken bladder or may have enlarged prostate, they might not empty properly and therefore check for postvoid residual with **bladder scanner**.
- May need CT scan for lymphocele or urinary leak(urinoma)(consider I.R guided drain –send fluid for BUN and creatinine to check for urinary leak and triglyceride, cell count with diff to check for lymphocele)
- **BK Virus Uropathy /Nephropathy** – check for BK virus in urine/blood
- **Rule out UTI.** Urinary tract infection and or asymptomatic bacteriuria frequently cause acute pyelonephritis and AKI. Cystitis may be asymptomatic as the bladder is denervated.
- Make sure to get urine cultures even if microscopy bland (write “Transplant patient, do cultures even if microscopy is negative”)

- Frequently UTIs cause acute pyelonephritis with allograft dysfunction

## Acute Rejection Diagnosis

Obtain transplant biopsy if serum creatinine rising with no clear etiology or significant proteinuria, check BK PCR blood and donor specific Ab (DSA)

- Review of histological findings in rejection based on see [Banff Criteria](#)

- All graded 0-3 (see Banff Criteria Review for further details)
- i - interstitial inflammation
- t - tubulitis
- v - arteritis
- g - glomerulitis
- ptc - peritubular capillaritis
- C4d - antibody staining on endothelial cells of PTCs and vasa recta
- ci- interstitial fibrosis
- ct - tubular atrophy
- cv - vascular narrowing
- cg - glomerular basement membrane double contours
- mm - mesangial matrix expansion
- ah - arteriolar hyalinosis (see in CNI toxicity)
- aah - hyaline arteriolar thickening
- ti- total inflammation

- **Acute Cell Mediated Rejection (ACR):** Can occur first few days until years after, even after graft stops working
- Optimization of maintenance immunosuppression: do you need to increase the basal goal levels and doses, do you need to add prednisone
- Can use prednisone taper after rejection defer to your attending.
- Regardless of the degree of rejection defer to your attending to finally decide if and how to treat.



Type of ACR	Histopathology	Rx	Infectious Prophylaxis
Borderline	Suspicious changes with < 25% of interstitial inflammation( i1) with only mild tubulitis ( t1)	May treated with Solumedrol 500 mg IV daily x 3 doses  Optimization of maintenance immunosuppression	Ask your attending if only solumedrol was used
1A	Interstitial inflammation > 25% of parenchyma affected ( i2 or i3) and foci of <i>moderate</i> tubulitis (t2)	Discuss with attending about: Only Solumedrol 500 mg IV daily x 3 doses only with or without Thymoglobulin (1.5 mg/ kg x 4-6 doses)  Optimization of maintenance immunosuppression	Ask your attending if only solumedrol was used
1B	Cases with significant interstitial inflammation > 25% of parenchyma affected ( i2 or i3) and foci of <i>severe</i> tubulitis (t3)	Solumedrol 500 mg IV daily x 3 doses And Thymoglobulin 1.5 mg/kg in 500 mL of saline infused over 4-6 hours for 4-6 doses (duration per attending discretion)  Optimization of maintenance immunosuppression	If Thymoglobulin used, full prophylaxis with thrush (nystatin or clotrimazole), CMV (valcyte or acyclovir depending on CMV serostatus), and PCP/UTI (Bactrim) prophylaxis, duration should be same as at time of induction

2A	<b>Vessel wall</b> involvement once in 2A and beyond mild-to-moderate intimal arteritis (v1)	Solumedrol 500 mg IV daily x 3 doses And Thymoglobulin 1.5 mg/kg in 500 mL of saline infused over 4-6 hours for 4-6 doses (duration per attending discretion)  Optimization of maintenance immunosuppression	If Thymoglobulin used, full prophylaxis with thrush (nystatin or clotrimazole), CMV (valcyte or acyclovir depending on CMV serostatus), and PCP/UTI (Bactrim) prophylaxis, duration should be same as at time of induction
2B	Severe intimal arteritis compromising > 25% of luminal area (v2)	Solumedrol 500 mg IV daily x 3 doses And Thymoglobulin 1.5 mg/kg in 500 mL of saline infused over 4-6 hours for 4-6 doses (duration per attending discretion)  Optimization of maintenance immunosuppression	If Thymoglobulin used, full prophylaxis with thrush (nystatin or clotrimazole), CMV (valcyte or acyclovir depending on CMV serostatus), and PCP/UTI (Bactrim) prophylaxis, duration should be same as at time of induction
3	<b>Transmural</b> arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)	Attending decision to treat or not	If Thymoglobulin used, full prophylaxis with thrush (nystatin or clotrimazole), CMV (valcyte or acyclovir depending on CMV serostatus), and PCP/UTI (Bactrim) prophylaxis, duration should be same as at time of induction

### Antibody-mediated or Humoral rejection (AMR):

- *Hyperacute rejection* (pre-formed antibodies destroy graft within minutes to hours; rare due to cross match); *accelerated acute rejection* (pre-formed alloantigen B cell becomes primed to generate antibody against graft; takes hours to days); *late humoral rejection* can occur

- Check these reviews ([1](#) and [2](#)) on antibody mediated rejection from diagnosis to treatment.

Histologic evidence of humoral rejection include:

1. Histologic evidence of acute tissue injury defined by the presence of one or more of the following:
  - Glomerulitis (g >0) or peritubular capillaritis (ptc >0)
  - Intimal or transmural arteritis (v >0)
  - Acute thrombotic microangiopathy (TMA) with no other obvious cause
  - Acute tubular injury of no other obvious cause
2. Histologic evidence of antibody interaction with vascular endothelium with one of the following:
  - Linear C4d staining in the peritubular capillaries
  - At least moderate microvascular inflammation (g + ptc >2)
  - Increased expression of tissue gene transcripts indicative of endothelial injury
3. Detection of Donor Specific Antibodies (DSAs) in the serum
  - Can have [C4D negative AMR](#) (microvascular injury, positive DSA, high clinical suspicion)

### **AMR Treatment:**

\***Plasmapheresis** or plasma exchange usually over 4-6 sessions every other day, also can be daily depending on attending's plan

- **check AM fibrinogen levels and if to hold ACE/ARB**
- Confirm access: can be catheter or fistula/graft
- 1-1.5 Plasma volume exchange
- Can use albumin or FFP, remember if done immediately after biopsy consider FFP ([usual dose is 10-15 mg/kg and the rest albumin but discuss with attending](#)), with recent biopsy and doing this procedure always monitor for bleed, **monitor closely for Transfusion Related Acute Lung Injury (TRALI)**
- Give IVIg after each session, if giving thymo discuss with attending when to give.

\***Rituximab 375 mg/m<sup>2</sup>** may be used after completion of plasmapheresis sessions per attending discretion

\***Bortezomib 1.3 mg/m<sup>2</sup>** may be used on DAYS 1, 4, 7, 11 during treatment per attending discretion

## **Transplant Infections**

## Infection in organ transplantation

- Patient specific reduction of immunosuppressive medications
- **BK Virus**: routinely screened via blood PCR and if found decrease immunosuppression
- Rule out CMV viremia and syndrome
  - Risk factors include 1 – 6 months following transplantation or rejection therapy with lymphocyte depleting medications, patient presents with flu-like symptom
  - CMV viremia and syndrome should be verified with CMV PCR

## Transplant Core Curriculum and Review Articles:

Transplant immunology and immunosuppression including rejection.

Infectious Disease Following Kidney Transplant

Evaluation of the Potential Living Kidney Donor

Evaluation of Adult Kidney Transplant Candidates

Surgical Complications of Kidney Transplantation

Post-transplant Infection Complications

## Miscellaneous

### Medical eligibility criteria for Liver-Kidney (SLK) transplant

1. **CKD** with  $eGFR \leq 60$  mL/min for  $> 90$  consecutive days. AND one of the following:
  - Declared ESKD and on RRT in a hospital based, independent non-hospital based, or home setting
  - $GFR < 30$  mL/min at date of registration (or most recent GFR) on the kidney waiting list.
2. Sustained AKI:
  - Has been on *RRT OR  $GFR < 25$  mL/min  $> 1$  q 1 w for  $> 6$  w.* OTHERWISE candidate not eligible to receive a liver and a kidney from the same donor.
3. diagnosis of  $> 1$  of the following metabolic disorders:
  - Hyperoxaluria
  - Atypical hemolytic uremic syndrome (HUS) from mutations in factor H or factor I
  - Familial non-neuropathic systemic amyloidosis
  - Methylmalonic aciduria

**\*\*Indication for Heart/kidney transplant remains controversial**

Most common cancer is skin cancer in particular squamous cell cancer, dermatology yearly screening and if multiple cancers consider decreasing immunosuppression

[Post transplant lymphoproliferative disease](#)

Risk of developing new onset diabetes after transplant ([NODAT](#))

Management of failed kidney allograft:

- Indications, risks and impact of failed allograft nephrectomy.
- Nephrology quiz and questionnaire: transplantation.

[CKD in non-kidney transplantation](#)

[Kidney Complications after heart and lung transplant](#)

[AKI after Liver and Heart Transplantation](#)

[Pulmonary HTN and kidney transplantation](#)

[Pregnancy after transplant](#)

## **Simultaneous organ transplantation**

Look for CKD, ultrasound of kidney, urine protein: creatinine ratio, establish baseline serum creatinine if consulted in-house particularly when deciding on simultaneous liver or heart and kidney transplant

[Simultaneous Pancreas Kidney Transplant](#)

Simultaneous Liver Kidney Transplant (SLK)

[Safety Net and New indications](#)

[Review Article](#)

Simultaneous Heart Kidney Transplant (SHK)

[Review](#)

[Review of outcomes with a risk calculator](#)

Primary care and kidney transplantation:

[Review](#)