UNIVERSITY OF NORTH CAROLINA MEDICAL CENTER
ABDOMINAL TRANSPLANT GUIDELINE (SCUT MONKEY)
Revised 2017

IMMUNOSUPPRESSION AND PROPHYLAXIS GUIDELINES PAGE

REJECTION GUIDELINES

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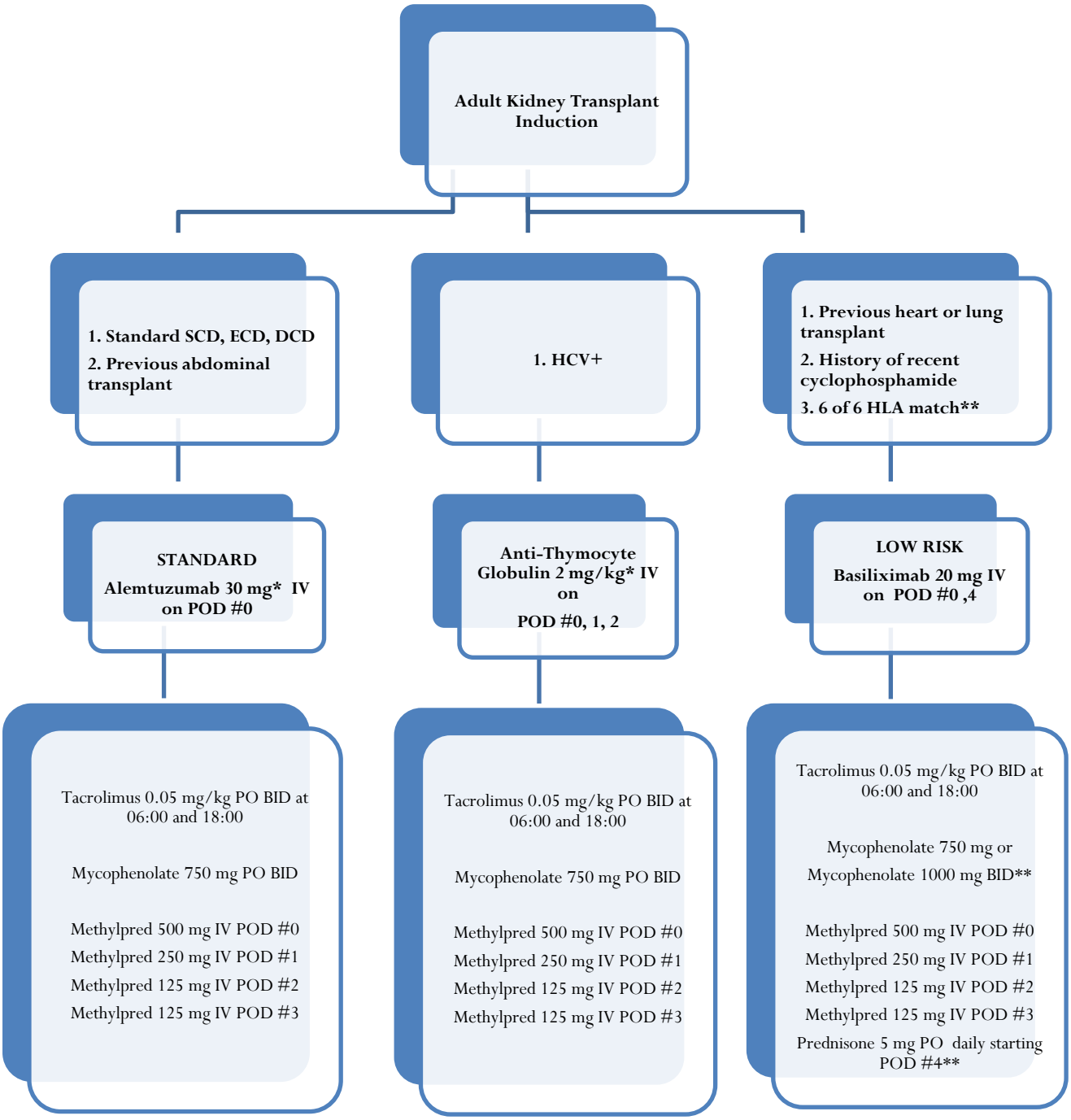
APPENDIX

ADULT KIDNEY TRANSPLANT - INDUCTION AND MAINTENANCE REGIMEN



¥ **HIV+ Recipients & ABO incompatible living donor pairs: See separate guideline**

* Requires premedication with methylprednisolone 500 mg, APAP 650 mg, diphenhydramine 50 mg intra-op

** Adult HLA 6 of 6 match kidney transplant should continue on mycophenolate 750 mg BID and stop prednisone on POD #4.

If receiving basiliximab for other indication, mycophenolate 1000 mg BID and prednisone should continue on POD #4.

ADULT KIDNEY TRANSPLANT

Patients enrolled in a drug study should be EXCLUDED from standard guideline
- Consult study coordinators for further instructions

Induction Therapy

Corticosteroids

- Pre-operative (POD #0): Order methylprednisolone 500 mg IV on-call to the OR. Please write in the order comments section that dose is to be administered intra-operatively to prevent administration on the floor.
- Post-operative: Patients receiving alemtuzumab and anti-thymocyte globulin will follow the steroid discontinuation guideline. If it is decided post-operatively to continue steroids, please refer to steroid continuation taper in the low-risk guideline. For anti-thymocyte globulin, ensure post-operative steroid taper is administered prior to anti-thymocyte globulin. For patients receiving alemtuzumab and anti-thymocyte globulin, the post-operative steroid taper is as follows:

POD #0: methylprednisolone 500 mg IVPB
POD #1: methylprednisolone 250 mg IVPB
POD #2: methylprednisolone 125 mg IV
POD #3: methylprednisolone 125 mg IV

Monoclonal Antibody: Alemtuzumab, Campath® (Standard)

- Pre-operative: Order alemtuzumab 30 mg IV on-call to the OR. Please write in the order comments section that the dose is to be given intra-operatively to prevent administration on the floor. This product is stable for 8 hours and should be protected from light. Please do not order this until you are 100% certain the case will move forward (kidney at UNC, crossmatch (XM) completed, OR seems to be running "on-time").
- Pre-operative pre-medications (POD#0) include acetaminophen 650 mg PO or IV, diphenhydramine 50 mg PO or IV, and methylprednisolone 500 mg IV all on-call to OR
- Post-operative: Patients are not to receive any additional alemtuzumab

Polyclonal Antibody: Anti-Thymocyte Globulin, rATG, Thymoglobulin®

- Pre-operative (POD #0): Order rabbit anti-thymocyte globulin 2mg/kg using actual body weight, unless weight is ≥120% of ideal body weight, then use adjusted body weight. Use admission body weight for calculations. Round dose to the nearest 25 mg and order for on-call to OR. This product is stable for 24 hours at room temperature. Please do not order this until you are 100% certain the case will move forward (kidney at UNC, XM completed, OR seems to be running "on-time").
  - How to calculate **IDEAL BODY WEIGHT (**for patients >120% of ideal body weight, calculate and use adjusted body weight to dose rATG):
    - MALES: 50 kg + (inches over 60 x 2.3)
    - FEMALES: 45.5 kg + (inches over 60 x 2.3)
  - How to calculate **ADJUSTED BODY WEIGHT**: Ideal body weight + [0.4 (total body weight – ideal body weight)]
- Pre-operative pre-medications (POD #0) include acetaminophen 650 mg PO or IV, diphenhydramine 50 mg PO or IV and methylprednisolone 500 mg IV all on-call to OR
- Post-operative (POD #1,2): Total goal dose of anti-thymocyte globulin is 6 mg/kg given over 3 days at 2mg/kg/day. However, dosing is subject to change according to WBC, platelet count, anaphylaxis/tolerability of medication, and infectious signs and symptoms. Do not order subsequent doses of anti-thymocyte globulin until after rounds on POD #1 and 2. Doses may be held/reduced at the discretion of the attending on service based upon WBC, PLT and other ADR. Consider dose reductions or discontinuation based on platelet count <75,000 cells/mm^3 and/or WBC <3,000 cells/mm^3.

- Please order the appropriate anti-thymocyte globulin preparation based upon administration - central versus peripheral and make sure morning dose of steroids is given prior to administration
- CD3 count should not be ordered unless directed by the physician. CBC with diff and Chem7 should be ordered daily on POD #1 and 2.
- When ordering POD#1 and 2 anti-thymocyte globulin, the emergency orders (Adult Chemotherapy, Biotherapy, and Iron Infusion Hypersensitivity and Anaphylaxis Reactions protocol for infusion reaction (HSR order set)) should be ordered with the removal of the NaCl infusion and NaCl bolus prn orders. This ensures there are rescue medications available if patient has an adverse drug reaction to anti-thymocyte globulin.
- Continue premedication with acetaminophen, diphenhydramine, and methylprednisolone 30 minutes prior to each anti-thymocyte globulin infusion. Methylprednisolone premedication dosing should be as follows:

  POD #1: methylprednisolone 250 mg IVPB
  POD #2: methylprednisolone 125 mg IV
  POD #3: methylprednisolone 125 mg IV

Monoclonal Antibody: Basiliximab, Simulect®

- Pre-operative (POD #0): Order basiliximab 20 mg IV on-call to the OR. Please write in the order comments section that the dose is to be given intra-operatively to prevent administration on the floor. This product is stable for 4 hours at room temperature. Please do not order this until you are 100% certain the case will move forward (kidney at UNC, XM completed, OR seems to be running "on-time").
- Post-operative (POD #4): Order basiliximab 20 mg IVPB x 1. Can be given on POD #3 at physician discretion.

<u>Maintenance Immunosuppression</u>

Calcineurin Inhibitor (Drug of choice: tacrolimus)

- Pre-operative: Patients are not to receive any doses
- Post-operative: Patients are to receive tacrolimus dosed per algorithm above based on induction agent used. Time to initiation is per the attending/fellow on service, but will ideally commence within the first 24h post-transplant. Doses may be initiated at a higher or lower dose depending upon concern for allograft function, concomitant medication interactions, pharmacogenetic profile. Doses are to be adjusted based upon trough levels as follows:

  0 - 3 months: 8-10 ng/mL
  4 - 12 months: 6-8 ng/mL
  >12 months: 5-7 ng/mL (based upon patient-specific parameters)

Antiproliferative (Drug of choice: mycophenolate mofetil in the peri-operative period)

- Pre-operative: Patients are not to receive any doses
- Post-operative: Patients are to receive mycophenolate mofetil PO BID starting the evening or morning post-op, dosed per algorithm above based on induction agent used

Corticosteroid taper for patients on chronic steroid therapy

POD #1: methylprednisolone 500 mg IVPB x 1 dose (if >50 kg) and 250 mg IVPB (if <50 kg)
POD #2: methylprednisolone 50 mg IV BID
POD #3: methylprednisolone 40 mg IV BID
POD #4: methylprednisolone 30 mg IV BID
POD #5: methylprednisolone 20 mg IV BID
POD #6-10: prednisone 10 mg PO daily
POD #11-365: prednisone 5 mg PO daily
>Month 12: discuss with provider

ADULT ABO INCOMPATIBLE (ABOi) KIDNEY TRANSPLANT GUIDELINE

Titer Technique

The schedule for the ABOi treatment guideline is based on the initial ABO antibody (Ab) isohemagglutinin titer, which will aid the physician in determining the number of therapeutic plasma exchange (TPE) treatments needed to decrease the ABO Ab titer. These titers will be performed using the Anti-Human Globulin (AHG) phase methodology for greater sensitivity (IgG antibody). Order test antibody titer and choose option AHG from drop down menu in comments. When ordering the titer, on the comment line, specify "Isohemagglutinin titer, A1, A2, and B". All ABO antibody levels will be checked so all potential donor blood type antibodies are identified. All titers will be done at UNCH to maintain standardization of testing and result reporting.

Note: Sensitivity of titers using AHG phase is increased by approximately x1 dilution on average as compared to the test tube method, e.g. 1:8 test tube method would result as 1:16 AHG method. The Ab titer is defined by the reciprocal of the highest dilution producing 1+ agglutination on 0-4 scale.

ABO Antibody Titers

Pre Transplant: First titer should be drawn 1 month prior to transplant

POD #0: Order ABO ab titers prior to each TPE session and on the day of surgery. Labs can be drawn in the plasmapheresis unit pretreatment. Acceptable ABO titers for transplant are 1:4 to 1:8 based on pre-transplant titer levels.

The schedule below identifies the potential schedule need based on the initial titer. This schedule assumes a Tuesday surgery and will eliminate elective preoperative TPE over the weekend. (See calendar below for sample schedule.)

Pre-transplant titer levels will determine the overall course of treatment; an initial titer below 1:8 may not require preoperative TPE; the treatment plan will be individually determined by the patient's transplant nephrologist.

IVIG: If more than 4 TPE sessions are needed, IVIG 0.5 g/kg will be administered following the **fifth** TPE session only. Never give IVIG before or during TPE treatment as TPE will remove the IVIG.

How to schedule TPE prior to transplant: Ideally, TPE will be scheduled early in the morning to accommodate multiple visits on the same day (e.g. dialysis, etc.).

Post-Transplant ABO ab Titer Schedule:

- POD #1 (Wednesday) and POD #3 (Friday)
- Twice weekly x 4 weeks
- Monthly x 2, at scheduled with Month 2 and 3 post-transplant visit
- With each kidney biopsy (indefinitely)

THERAPEUTIC PLASMA EXCHANGE (TPE)

Initial AHG Titer	**# Pre-op TPE**	**Pre-Op Days before surgery**
<1:8	TBD	To be determined by MD
1:8 or 1:16	2	1, 4 [Mon. & Fri. pre transplant]
1:32	3	1, 4, 6
1:64	4	1, 4, 6, 8
1:128	5	1, 4, 6, 8, 11 (IVIG after 5th TPE treatment*)
1:256	6	1, 4, 6, 8, 11, 13 (IVIG after 5th TPE treatment*)
Post-Transplant **(if initial titer is ≤1:4)**		No Post-Tx TPE is planned if initial titer ≤1:4
Post-Transplant **(if initial titer is >1:4)**		2 TPE Post-Tx on POD #1 and #3. A need for further post-transplant TPE will be determined individually.*
* An increase in ABO ab titer post-transplant of ≥1:64 or a two dilution increase (e.g., 1:8→1:16→1:32) should prompt a kidney biopsy. Based on results of kidney biopsy, TPE may be ordered. If unable to biopsy, physician will determine if TPE needed.		

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
		Day -14 START MYCOPHENOLATE Dialysis	Pre-op day -13 Labs Ab Titer #5340 TPE	Dialysis	Pre-op Day -11 Labs (incl. Ab Titer #5340) TPE	Dialysis
	Pre-op Day -8 Labs Ab Titer #5340 TPE	Dialysis	Pre-op Day -6 Labs (incl. Ab Titer #5340) TPE	Dialysis	Pre-op Day -4 Labs Ab Titer #5340 TPE +/- IVIG (Ask MD)	Dialysis
START TACROLIMUS	Pre-op Day -1 Labs Ab Titer #5340 PM fibrinogen level TPE with FFP Dialysis x 2 hr +/- IVIG (Ask MD) Bowel Prep HS	SURGERY DAY Day = 0 Labs Ab Titer #5340	Post – Op Day +1 Labs Ab Titer #5340 Tacrolimus trough TPE		Post-OP Day +3 Labs Ab Titer #5340 TPE	

Therapeutic plasma exchange is done to decrease the circulating ABO antibodies, by exchanging the patient's plasma with a colloidal substitute (e.g. albumin, or Fresh Frozen Plasma (FFP)).

Plasma is replaced volume for volume with 5% albumin; the estimated volume exchange per TPE session is 1x plasma volume (~3-4L). [Estimated plasma volume (in liters) = 0.07 x weight (kg) x (1 - hematocrit)]. (Note: these are typical TPE orders, which will be written by Transfusion Medicine MD)

If TPE procedure occurs <48 hrs before surgery the patient will typically receive FFP (matched to donor blood type) as part or all of the volume for volume replacement to correct TPE induced coagulopathy. Orders for replacement will be written by Transfusion Medicine MD

Important points regarding TPE: Ensure IVIG is given after TPE, discontinue ACE-inhibitor prior to start of TPE, and make sure medications are timed appropriately and dosed appropriately with TPE

Note: any time the patient has an invasive procedure, e.g. kidney biopsy, and TPE within the same 48 hour period, FFP will be given as above to reverse potential coagulopathy/bleeding complications

Vascular Access for TPE

Patient's current fistula or temporary dialysis catheter should be used for access. If the patient does not have a dialysis access, please send the patient to have a vascular access assessment. Insertion of two large bore IV's are required for each treatment, and if the patient does not have adequate venous access for this, it may be recommended that they have a temporary dialysis catheter placed in VIR before starting TPE.

Induction agent- Basiliximab

- Pre-operative (POD #0): Order basiliximab 20mg IVPB on-call to the OR. Please write in the order comments section that the dose is to be given intra-operatively to prevent administration on the floor. This product is stable for 4 hours at room temperature.
- Post-operative (POD #4): Order basiliximab 20 mg IVPB x 1 dose. Can be given on POD #3 by physician discretion.

Methylprednisolone

- POD #0 (day of surgery): 500 mg IV intra-operatively
- POD #1: methylprednisolone 250 mg IVPB
- POD #2: methylprednisolone 125 mg IV
- POD #3: methylprednisolone 125 mg IV

Maintenance Immunosuppression (start pre-transplant)

Patient should take mycophenolate mofetil and tacrolimus on the morning of surgery.

Tacrolimus: 0.05 mg/kg PO BID initiated 48 hrs **pre-transplant – Start on POD #-2 prior to day of surgery**. Order tacrolimus trough the morning before surgery for baseline trough level.

Tacrolimus 12hr trough goals:

0 - 3 months: 8-10 ng/mL
4 - 12 months: 6-8 ng/mL
> 12 months: 5-7 ng/mL (based upon patient-specific parameters)

Mycophenolate mofetil 1000 mg PO BID starting two weeks **prior to transplant** (if using mycophenolate sodium, dose is 720 mg BID)

Post-transplant corticosteroid taper (prednisone):

- POD #4: prednisone 30 mg PO daily (decrease prednisone dose to 20 mg daily once tacrolimus level is at goal range (8-10 ng/mL)
- POD #30: prednisone 15 mg PO daily
- POD #60: prednisone 10 mg PO daily
- POD #90: prednisone 5 mg PO daily (final daily dose, do not withdraw prednisone)

An increase in ABO ab titer post-transplant of $\geq$ 1:64 or a two dilution increase (e.g., 1:8→1:16→1:32) should prompt a kidney biopsy. Based on results of kidney biopsy, TPE may be ordered. If unable to biopsy, physician will determine if TPE needed.

ID Prophylaxis Guideline

Refer to standard ID prophylaxis guideline on page 16

ADULT HIV POSITIVE KIDNEY TRANSPLANT GUIDELINE

Eligibility for Transplant

Patients must satisfy requirements prior to listing:

- Stable on current anti-retroviral therapy (ART) x 6 months
- HIV RNA below quantifiable limit for ≥1 years
    - A single plasma HIV-1 RNA ≥ limit of quantification but <1000 copies/mL within the prior year is allowed if followed by HIV-1 RNA below quantifiable limits
- CD4 ≥ 200 x 6 months
- No active infections
- No active hepatitis C infection
- Cleared by UNC Transplant infectious disease physician based on individual's history of infections and/or malignancy

Pre-transplant Evaluation

Standard

- Assign patient to an enhanced care nurse
- Follow current UNC renal transplant work-up with transplant surgery, nephrology and pharmacy
- Notify patients of additional risks and possible difficulties of HIV+ transplantation
- Recommendations for immunization requirements
- Obtain immigration and travel history for special exposures
- Perform screening serologies and tests for opportunistic infections
- Review infectious disease and/or malignancy history

HIV-Specific

- All HIV-infected candidates for renal transplant need to be evaluated by a designated Transplant ID/HIV physician as part of pre-transplant work-up
- For patients on Tu/Th/Sat dialysis, the pre-transplant coordinator should contact the ID clinic requesting HIV+ pre-transplant evaluation with a designated Transplant ID/HIV physician (Dr. Cindy Gay)
- For patients on M/W/F dialysis, the Pre-transplant coordinator should contact Transplant ID/HIV physician to schedule an appointment
- Patients may continue HIV care with their present HIV provider whether at UNC or with an outside provider, but they must complete the pre-transplant evaluation with a designated Transplant ID/HIV physician
- Confirm and review importance of adherence to ART
- Obtain HIV viral tropism, HLA B57, G6PD levels in anticipation of future options
- Any special prophylaxis requirements will be established, including for tuberculosis
- Discuss and evaluate additional risks associated with further immunosuppression

Antiretroviral Therapy (ART)

Pre-transplant evaluation will include an assessment of the need or recommendation to change ART. Integrase-based regimens are preferred if appropriate per history of prior ARVs, accumulated mutations and co-morbidities.

Pre-transplant pharmacokinetic/pharmacodynamic studies of ARTs or immunosuppressants will be considered

Alternative ART should be considered for the following:

- Regimens including a ritonavir-boosted protease inhibitor (PI) ± non-nucleoside reverse transcriptase inhibitor (NNRTI) (due to unpredictable drug interactions)
- Regimens including cobicistat (due to unpredictable drug interactions)
- Regimen contains zidovudine (due to potential for antagonism with MMF)
- Regimen contains tenofovir disoproxil fumarate (due to nephrotoxicity with tacrolimus or cyclosporine)
    - Note: tenofovir alafenamide fumarate (TAF) permitted

Transplant Admission

Transplant nephrology and the transplant infectious disease service are to be notified immediately after the patient has agreed to come in for transplant.

If transplant surgeon on service has concerns regarding the patient, these services may be consulted prior to contacting the patient.

These services will follow the patient throughout his/her hospital admission, though SRF will remain as the primary service.

- Admission orders to follow current guidelines (labs, physical exam, OR scheduling, etc)
- Medication orders to follow HIV transplant guideline
    - **All** ARV medications should be restarted as soon as transplant recipients are taking oral medications
    - At no time should patients be administered partial ART regimens (holding of 1 or more, but not all ARVs)
- Anticipated transition from transplant surgery to nephrology/ID care will occur around 1 month post-transplant

Post-Transplant Care

- Nephrology and HIV care to continue at UNC
- Close follow-up with transplant pharmacist in transplant clinic
- The patient's post-transplant coordinator will have primary responsibility for management and coordination of care
- The patient's HIV enhanced care nurse will work with their post-transplant coordinator to maintain communication between the two services. It will be their responsibility to work with the appropriate attending physicians for patient care.
- Labs to follow current UNC guidelines. The transplant coordinator is responsible for contacting appropriate nephrologist/ID attending/pharmacist with abnormal values and any actions taken. These events are to be recorded in Phoenix/EPIC.
- Adjust dose of ART therapy, if needed, based on improved renal function

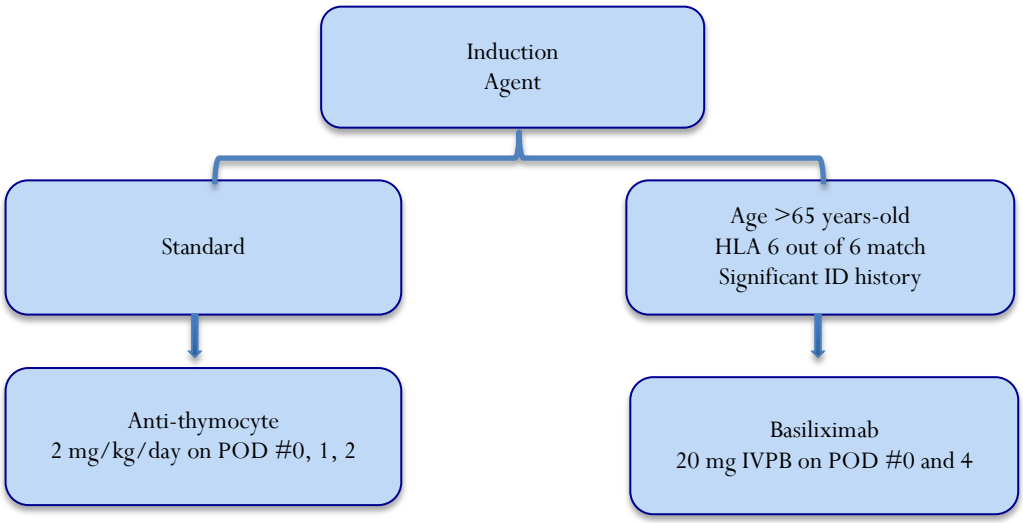
The ID attending/enhanced care nurse may request additional labs/tests as necessary.

CD4 count/HIV viral load testing to be followed by ID as follows:

- Within 30 days prior to transplant (pre-transplant – to be ordered with admission labs if >30 days since last check
- At first post-hospital visit (~4 weeks)
- Within 30 days of any med changes expected to alter ART levels
- With any major change in health status (i.e. hospitalizations)
- At 60-90 day intervals for 12 months after transplant
- At 90-120 day intervals afterwards if fully suppressed and transplant condition is stable (per HIV guidelines)
- Additional considerations that require the transplant coordinator to notify the enhanced care nurse:
    - Medication changes that may alter ART concentrations

- Medication changes that may alter immunosuppressant concentrations
- Changes to immunosuppression
- Changes to prophylactic medications
- Ordering any non-guideline labs/tests (in the event the ID service has additional requests/considerations)

Induction Therapy



Standard Induction Agent: Anti-thymocyte globulin

- Pre-operative (POD #0): Order rabbit anti-thymocyte globulin 2mg/kg using actual body weight, unless weight is >120% of ideal body weight, then use adjusted body weight. Use admission body weight for calculations. Round dose to the nearest 25 mg and order for on-call to OR. This product is stable for 24 hours at room temperature. Please do not order this until you are 100% certain the case will move forward (kidney at UNC, XM completed, OR seems to be running "on-time").
  - How to calculate **IDEAL BODY WEIGHT** (for patients >120% of ideal body weight, calculate and use adjusted body weight to dose rATG):
    - MALES: 50 kg + (inches over 60 x 2.3)
    - FEMALES: 45.5 kg + (inches over 60 x 2.3)
  - How to calculate **ADJUSTED BODY WEIGHT**: Ideal body weight + [0.4 (total body weight – ideal body weight)]
- Pre-operative pre-medications (POD #0) include acetaminophen 650 mg PO or IV, diphenhydramine 50 mg PO or IV and methylprednisolone 500 mg IV all on-call to OR
- Post-operative (POD #1,2): Total goal dose of anti-thymocyte globulin is 6 mg/kg given over 3 days at 2mg/kg/day. However, dosing is subject to change according to WBC, platelet count, anaphylaxis/tolerability of medication, and infectious signs and symptoms. Do not order subsequent doses of anti-thymocyte globulin until after rounds on POD #1 and 2. Doses may be held/reduced at the discretion of the attending on service based upon WBC, PLT and other ADR. See page 3 for dose adjustments due to WBC and platelet counts.
- Please order the appropriate anti-thymocyte globulin preparation based upon administration - central versus peripheral and make sure morning dose of steroids is given prior to administration
- CD3 count should not be ordered unless directed by the physician. CBC with diff and Chem7 should be ordered daily on POD #1 and 2.
- When ordering POD#1 and 2 anti-thymocyte globulin, the emergency orders (Adult Chemotherapy, Biotherapy, and Iron Infusion Hypersensitivity and Anaphylaxis Reactions protocol for infusion reaction (HSR order set)) should be ordered with the

removal of the NaCl infusion and NaCl bolus prn orders. This ensures there are rescue medications available if patient has an ADR to anti-thymocyte globulin.

- Continue premedication with acetaminophen, diphenhydramine, and methylprednisolone 30 minutes prior to each anti-thymocyte globulin infusion. Methylprednisolone premedication dosing should be as follows:

  POD #1: methylprednisolone 250 mg IVPB
  POD #2: methylprednisolone 125 mg IV
  POD #3: methylprednisolone 125 mg IV

Alternative Induction Agent (due to patient's risk factors, ID recommendation, recipients >65 years old, HLA 6 out of 6 match, and transplant team's preference): Basiliximab

- Pre-operative (POD #0): Order basiliximab 20 mg IV on-call to the OR. Please write in the order comments section that the dose is to be given intra-operatively to prevent administration on the floor. This product is stable for 4 hours at room temperature. Please do not order this until you are 100% certain the case will move forward (kidney at UNC, XM completed, OR seems to be running "on-time").
- Post-operative (POD #4): Order basiliximab 20 mg IVPB x 1. This can be given on POD #3 at physician discretion.

Maintenance Immunosuppression

Calcineurin inhibitor (CNI):

Patient to receive CNI starting on POD #1 (preference is tacrolimus unless otherwise stated or changed by attending on service). Initiation may be delayed at the discretion of the attending on service.

Tacrolimus (TAC)

- For patients receiving ART containing a PI ± NNRTI, the starting dose will be 1 mg PO once. TAC typically NOT dosed over two times per week on this regimen
- TAC trough levels should be drawn daily starting on morning of POD #2
- For patients on an integrase inhibitor (No PI), the starting dose of TAC should be 0.05 mg/kg PO BID

Goal TAC trough concentrations as follows (based upon patient specific parameters):

- Months 0-3: 8-11 ng/mL
- Months 4-12: 6-8 ng/mL
- Months >12: 5-7 ng/mL

Cyclosporine (CsA)

For patients who require conversion to CsA, use the following dosing considerations. May adjust up or down based upon clinical situation, however the correlation between TAC and CsA dosing is not as clear as for patients not on ARTs.

- For patients receiving ARTs containing a PI ± NNRTI, the starting dose of CsA will be 25-50 mg PO twice daily
- For patients on an integrase inhibitor (No PI), the starting dose will be CsA 4 mg/kg PO BID
  - Start CsA 250 mg PO BID if the patient is on efavirenz
  - Start CsA 200 mg PO BID if the patient is on nevirapine

Goal CsA trough concentrations as follows (based upon patient specific parameters):

- Months 0-3: 200-250 ng/mL

- Months 4-12: 150-200 ng/mL
- Months >12: 100-150 ng/mL

Antiproliferative:

If anti-thymocyte globulin induction was given, patient should receive mycophenolate mofetil 750 mg PO BID starting POD #0. If basiliximab induction was given, mycophenolate mofetil dose should be 1000 mg PO BID starting on POD #0. Doses may be adjusted based upon tolerability and clinical judgment.

Antimicrobial Prophylaxis

Standard Post-transplant Prophylaxis:

1. Peri-operative Antimicrobials

****Please refer to ID note regarding any specific recommendations for peri-op or post-op antimicrobials****

Standard: cefazolin 2 g IV x 1 dose ordered on-call to the OR and one dose should be given 6-8 hours post-operatively

Penicillin allergy: clindamycin 900 mg IVPB may be used in place of cefazolin

2. PJP

- Sulfamethoxazole/trimethoprim (SMZ/TMP) 800/160 mg PO QMWF or SMZ/TMP SS 1 tablet PO daily
- For sulfa allergy, may use dapsone 100 mg daily if not G6PD deficient.
- If sulfa allergy & G6PD deficiency, consider aerosolized pentamidine 300 mg monthly or atovaquone 1500 mg PO daily.
- ID clinic phone number for pentamidine administration (ask for Jonah Pierce at 984-974-0163 or leave a message at 984-974-0164)
- All transplant recipients should receive a minimum of:
    - 6 months of prophylaxis following transplant
    - 6 months following treatment for rejection
    - Thereafter, PJP prophylaxis should continue if CD4 count is <200 or CD4% is <14

See daily dosing of SMZ/TMP for toxoplasmosis (see toxoplasmosis section below).

3. CMV

Risk Status	Agent/Max Dose/Regimen	Duration
High-risk (Donor +/Recipient -)	valganciclovir 900 mg PO daily x 3 months, then 450 mg PO daily x 3 months	6 months
Moderate-risk (Donor +/Recipient +) (Donor -/Recipient +)	valganciclovir 450 mg PO daily	3 months
Low-risk (Donor -/Recipient -)	acyclovir 400 mg PO BID	3 months

Renal Dosing for Valganciclovir based on 900 mg daily dose: use Cockcroft-Gault Equation for eCrCl
eCrCl ≥60 ml/min: 900 mg once daily for high-risk and keep at 450 mg daily for moderate-risk

eCrCl 40-59 mL/minute: 450 mg once daily
eCrCl 25-39 mL/minute: 450 mg every 2 days
eCrCl 10-24 mL/minute: 450 mg twice weekly

4. EBV

- High-risk EBV (donor +/recipient -) are to receive ganciclovir 5 mg/kg IV daily (renally dose adjust) while in the hospital
- Transition to valganciclovir 900 mg PO daily (renally dose adjust) x 1 year from day of discharge
- This takes the place of CMV prophylaxis in these patients

5. Candidiasis:

- Nystatin 10 mL (1,000,000 units) PO TID while on steroids
- CD4 <200, start fluconazole 100 mg PO daily instead of nystatin

HIV-specific Prophylaxis:

1. MAC

- CD4 <50, patients are to receive azithromycin 1200 mg PO every week until 6 months after CD4 count is >100
- With history of MAC infection, patients are to receive azithromycin 600 mg PO daily + ethambutol 15 mg/kg/day x 1 month post-transplant or post-treatment of rejection. The use of rifabutin may also be utilized by the infectious diseases service.

2. Toxoplasmosis

- CD4 count <100, prophylaxis continues until six months after CD4 count recovers to >200. These patients do not need additional PJP coverage.
- Toxo IgG+ and CD4 count <100, patients are to receive sulfamethoxazole/trimethoprim (SMZ/TMP) 800/160 mg PO daily until six months after CD4 count recovers to >200. Patients do not need additional PJP coverage.
- With history of clinical toxoplasmosis infection, patients are to receive 25 mg PO daily + sulfadiazine 100 mg/kg PO daily + leucovorin 25 mg PO daily x 1 month post-transplant or post-treatment of rejection
- With a past infection and a sulfa allergy, patients are to receive pyrimethamine 25 mg PO daily + clindamycin 600 mg PO TID. These patients need additional medication for PJP prophylaxis.

3. Cryptococcosis, extrapulmonary

- CD4 count <200, patients are to receive prophylaxis until 6 months after CD4 count recovers to >200
- With history of cryptococcosis, patients are to receive fluconazole 200 mg PO daily x 1 month post-transplant or post-treatment of rejection.

4. Histoplasmosis

- With history of histoplasmosis, patients are to receive itraconazole 200 mg PO BID (take with food) or fluconazole 400 mg PO daily (renally dose adjust) lifelong

5. Coccidiodioides

- With a history of prior infection or prior residence in a Cocciodioides immitis-endemic area and a CD4 count <250, patients should be considered for prophylaxis with itraconazole or fluconazole

6. Specific vaccinations

- Streptococcus pneumoniae immunization should be given every 3-5 years

Drug Interactions

Refer to Appendix C and D

Acute Rejection

All patients should receive ID prophylaxis similar to post-transplant HIV specific antimicrobial recommendations as well as the standard antimicrobial prophylaxis recommended post-rejection treatment. See adult kidney transplant rejection guidelines for treatment of rejection.

- Rituximab recipients positive for Hepatitis B core antibody should have ID consult for start of hepatitis B prophylaxis depending on patient's ART regimen
- Prophylaxis will continue for 6-12 months post-rituximab administration

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ADULT KIDNEY TRANSPLANT PROPHYLAXIS

Perioperative Antibiotics:

- Pre-operative: Cefazolin 2 grams IVPB (<120 kg), 3 grams (>120 kg) ordered on-call to OR
- Pre-operative (**PCN allergy**): Clindamycin 900 mg IVPB on call to the OR
- Refer to ID note, if applicable, for alternative perioperative antibiotics based on infection history and risk factors

CMV:

Risk Status	**Agent/Max Dose/Regimen**	**Duration**
High-risk (Donor +/Recipient -)	valganciclovir 900 mg PO daily x 3 months, then 450 mg PO daily x 3 months	6 months
Moderate-risk (Donor +/Recipient +) (Donor -/Recipient +)	valganciclovir 450 mg PO daily	3 months
Low-risk (Donor -/Recipient -)	acyclovir 400 mg PO BID	3 months

Renal Dosing for Valganciclovir based on 900 mg daily dose: use Cockcroft-Gault Equation for eCrCl
eCrCl ≥60 ml/min: 900 mg once daily for high-risk and keep at 450 mg daily for moderate-risk
eCrCl 40-59 mL/minute: 450 mg once daily
eCrCl 25-39 mL/minute: 450 mg every 2 days
eCrCl 10-24 mL/minute: 450 mg twice weekly

PJP:

- Sulfamethoxazole/trimethoprim (SMZ/TMP) 400/80 mg PO every Mon, Wed, Fri x 6 months
- Sulfa allergy: Dapsone 100 mg PO daily x 6 months. Check G6PD prior to initiation.
- Sulfa allergy + G6PD deficiency: Pentamidine 300 mg inhalation monthly x 6 months or atovaquone 1500 mg PO daily x 6 months
    - ID clinic phone number for pentamidine administration (ask for Jonah Pierce at 984-974-0163 or leave a message at 984-974-0164)

Thrush:

- Nystatin 10 mL PO TID while inpatient

Hepatitis B: See page 37 for Adult Hepatitis B Guideline

Stress ulcer:

- Famotidine 20 mg PO twice daily (renally dose adjust)
    - If patient is on an H2-blocker or proton-pump inhibitor at home, continue home medication or formulary equivalent
    - If acid reflux/heartburn is uncontrolled with famotidine, transition patient to a proton-pump inhibitor
    - If patient has indication for stress ulcer prophylaxis*, start a proton-pump inhibitor
        - *Indications:
            - Transplant recipient in ICU peri-operatively (can transition to H2-blocker once clinical status has improved and patient is on the floor)

- Coagulopathy (platelets <50K, INR >1.5 (if not on warfarin), or aPTT >2xULN)
- Mechanical ventilation for more than 48 hours
- History of GI ulceration or bleeding within 12 months
- Head injury or multiple trauma
- Burn >35% BSA
- At least two of the following: sepsis, ICU stay of >1 week, occult or overt bleeding for >6 days, corticosteroid therapy (>250 mg hydrocortisone or equivalent daily dose)

Cardiovascular:

- Aspirin 81 mg PO daily

Bowel Regimen:

- Docusate 100 mg PO BID
- Senna 8.6 mg PO QHS
- Miralax 17 gm PO daily

DVT Prophylaxis:

Heparin 5,000 units SQ Q8H or 7,500 units SQ Q8H if patient's weight is ≥100 kg

ADULT KIDNEY TRANSPLANT – DONOR ORDERS

- **Admit to SRF**
- **Vitals:** Q4H x 24 hours, then Q8H
- **Activity:**
  - OOB to chair evening of surgery
  - Ambulate POD1 w/assistance TID
- **I/Os:** Strict Q4H
- **Nursing**
  - D/C foley at 6 am on POD #1, unless clinically indication by surgical team
    - Check PVR/bladder scan if no void within 4 hours
    - If >150 cc, notify HO
  - Call HO:
    - Temp >38.5
    - Pulse >110 or <50
    - RR >30 or <10
    - SBP >160 or <90
    - DBP >100 or <50
    - O_2 <92%
    - UOP <50 cc/hr x 2 hours
    - UOP volume decreases suddenly
  - Incentive spirometry x 10 Q1H
  - Wean O_2 to sats >90%
  - SCDs continuous
- **Diet**
  - NPO except meds/ice chips, then diet when bowel function returns
  - IVF: $D_5$1/2NS

- **Post-operative Medications – Enhanced Recovery Orders**
    - Hydromorphone 0.5 mg IV Q6H as needed for severe pain
    - Acetaminophen 1000 mg PO TID (if LFTs are not elevated above clinical ranges and continue as long as patient is taking tramadol or opioids)
    - Gabapentin 300 mg PO TID (renally dose adjust)
    - Tramadol 50 mg PO Q6H as needed for moderate pain or 100 mg PO Q6H as needed for severe pain
        - If unable to tolerate tramadol or have contraindication/allergy, order oxycodone 5-10 mg Q6H as needed for moderate pain
    - Ondansetron 4 mg IV Q8H as needed
    - Bisacodyl suppository on POD #1, then daily thereafter until flatus/BM
    - Miralax 17gm PO daily
    - Docusate 100 mg PO BID
    - Senna 8.6 mg PO qHS
    - Famotidine 20 mg PO twice daily (renally dose adjust)
        - If patient is on an H2-blocker or proton-pump inhibitor at home, continue home medication or formulary equivalent
        - If acid reflux/heartburn is uncontrolled with famotidine, transition patient to a proton-pump inhibitor
    - Heparin 5,000 units SQ Q8H or 7,500 units SQ Q8H for patients $\geq$100 kg (start per attending discretion)
    - Rectus muscle spasm: lorazepam 2 mg PO (per attending discretion)

- **Post-op Labs**
    - Chem 7 and CBC in PACU and CBC that evening
    - CBC POD #1 <u>ONLY</u> unless otherwise directed by physician

ADULT SIMULTANEOUS PANCREAS-KIDNEY or PANCREAS ALONE TRANSPLANT

Corticosteroids

- Pre-operative (POD #0): Order methylprednisolone 500 mg IV on-call to the OR. Please write in the order comments section that dose is to be administered intra-operatively to prevent administration on the floor.
- Post-operative: Patients receiving alemtuzumab will follow the steroid discontinuation guideline. If it is decided post-operatively to continue steroids, please refer to steroid continuation taper in the low-risk guideline. For patients receiving alemtuzumab, the post-operative steroid taper is as follows:

POD #1: methylprednisolone 250 mg IVPB
POD #2: methylprednisolone 125 mg IV
POD #3: methylprednisolone 125 mg IV

Monoclonal Antibody

- Pre-operative: Order alemtuzumab 30 mg IV on-call to the OR. Please write in the order comments section that the dose is to be given intra-operatively to prevent administration on the floor. This product is only good for 8 hours, so please do not order this until you are 100% certain the case will move forward (kidney/pancreas at UNC, XM completed, OR seems to be running "on-time").

Calcineurin Inhibitor (Most patients will receive tacrolimus)

- Pre-operative: Patients are not to receive any doses of tacrolimus

- Post-operative: Patients are to receive tacrolimus 0.025 mg/kg PO BID. (Lower dose due to peri-operative fluconazole). Initiation to be decided per the attending/fellow on service, but will ideally commence within the first 24h after transplant. Doses may be initiated at a higher or lower dose depending upon concern for ATN or concomitant medication interactions. Doses are to be adjusted based upon trough levels as follows:

  0 - 3 months: 10-12 ng/mL
  4 - 12 months: 7-9 ng/mL
  >12 months: 6-8 ng/mL - barring mycophenolate dose is $\geq$500 mg BID

Antiproliferative (most patients will receive mycophenolate mofetil in the peri-operative period)

Post-operative: Patients are to receive mycophenolate mofetil 1000 mg PO BID starting on POD #0

ADULT PANCREAS AFTER KIDNEY TRANSPLANT

Corticosteroids

- Pre-operative (POD #0): Order methylprednisolone 500 mg IV on-call to the OR. Please write in the order comments section that dose is to be administered intra-operatively to prevent administration on the floor.
- Post-operative: Patients will follow the steroid discontinuation guideline. If it is decided post-operatively to continue steroids, please refer to steroid continuation taper in the low-risk kidney guideline. The post-operative steroid taper is as follows:

  POD #1: methylprednisolone 250 mg IVPB
  POD #2: methylprednisolone 125 mg IV
  POD #3: methylprednisolone 125 mg IV

Monoclonal Antibody

- Pre-operative: Order alemtuzumab 30 mg IV on-call to the OR. Please write in the order comments section that the dose is to be given intra-operatively to prevent administration on the floor. This product is only good for 8 hours, so please do not order this until you are 100% certain case will move forward (pancreas at UNC, OR seems to be running "on-time").

Calcineurin Inhibitor (most patients will receive tacrolimus)

- Pre-operative: Patients are not to receive any doses of tacrolimus
- Post-operative: Patients are to receive tacrolimus 0.025 mg/kg PO BID. (Lower dose due to peri-operative fluconazole). Initiation to be decided per the attending/fellow on service, but will ideally commence within the first 24h after transplant. Doses may be initiated at a higher or lower dose depending upon concern for ATN or concomitant medication interactions. Doses are to be adjusted based upon trough levels as follows:

  0 - 3 months: 10-12 ng/mL
  4 - 12 months: 7-9 ng/mL
  >12 months: 6-8 ng/mL - barring mycophenolate dose is $\geq$500 mg BID

Antiproliferative (most patients will receive mycophenolate mofetil in the peri-operative period)

- Post-operative: Patients are to receive mycophenolate mofetil 1000 mg PO BID starting on POD #0

ADULT KIDNEY-PANCREAS & PANCREAS TRANSPLANT PROPHYLAXIS

Perioperative Antibiotics:

- **Pre-operative**: Ampicillin/Sulbactam 3 grams ordered on-call to OR
- **Pre-operative (PCN allergy):** Clindamycin 900 mg IVPB and levofloxacin 500 mg IVPB on call to the OR.

- **Post-operative**: Ampicillin/Sulbactam 1.5 grams IVPB q8h x 3 doses
- **Post-operative (PCN allergy):** Clindamycin 900 mg IVPB q8h x 2 doses and levofloxacin 500 mg IVPB x 1 dose on POD #1 (24 hours after levofloxacin dose given in OR)

- Refer to ID note, if applicable, for alternative pre- and post-operative antibiotics based on infection history and risk factors

CMV:

Risk Status	Agent/Max Dose/Regimen	Duration
High-risk (Donor +/Recipient -)	valganciclovir 900 mg PO daily x 3 months, then 450 mg PO daily x 3 months	6 months
Moderate-risk (Donor +/Recipient +) (Donor -/Recipient +)	valganciclovir 450 mg PO daily	3 months
Low-risk* (Donor -/Recipient -)	acyclovir 400 mg PO BID	3 months

Renal Dosing for Valganciclovir based on 900 mg daily dose: use Cockcroft-Gault Equation for eCrCl
eCrCl ≥60 ml/min: 900 mg once daily for high-risk and keep at 450 mg daily for moderate-risk
eCrCl 40-59 mL/minute: 450 mg once daily
eCrCl 25-39 mL/minute: 450 mg every 2 days
eCrCl 10-24 mL/minute: 450 mg twice weekly

PJP:

- Sulfamethoxazole/trimethoprim (SMZ/TMP) 400/80 mg PO every Mon, Wed, Fri x 6 months
  Sulfa allergy: Dapsone 100 mg PO daily x 6 months. Check G6PD prior to initiation.
  Sulfa allergy + G6PD deficiency: Pentamidine 300 mg inhalation monthly x 6 months or atovaquone 1500 mg PO daily x 6 months
    - ID clinic phone number for pentamidine administration (ask for Jonah Pierce at 984-974-0163 or leave a message at 984-974-0164)

Thrush:

- Pre-operative: Fluconazole 200 mg PO x 1 dose
- Post-operative: Fluconazole 100 mg PO Daily x 7 days, then nystatin 10 mL PO TID. Discontinue at discharge.

Stress ulcer:

- Famotidine 20 mg PO twice daily (renally dose adjust)
    - If patient is on an H2-blocker or proton-pump inhibitor at home, continue home medication or formulary equivalent
    - If acid reflux/heartburn is uncontrolled with famotidine, transition patient to a proton-pump inhibitor

- If patient has indication for stress ulcer prophylaxis*, start a proton-pump inhibitor
  - *Indications:
    - Transplant recipient in ICU peri-operatively (can transition to H2-blocker once clinical status has improved and is on the floor)
    - Coagulopathy (platelets <50K, INR >1.5 (if not on warfarin), or aPTT >2xULN)
    - Mechanical ventilation for more than 48 hours
    - History of GI ulceration or bleeding within 12 months
    - Head injury or multiple trauma
    - Burn >35% BSA
    - At least two of the following: sepsis, ICU stay of >1 week, occult or overt bleeding for ≥6 days, corticosteroid therapy (>250 mg hydrocortisone or equivalent daily dose)

CV/Thrombosis:

- Pre-operative: aspirin 325 mg PO x 1 dose ordered STAT
- Post-operative: aspirin 325 mg PO daily
- Heparin 5,000 units SQ Q8H or 7,500 units SQ Q8H if weight ≥100 kg

Prevention of anastomosis leakage:

- Octreotide to be given at time of incision
- Octreotide 100 mcg SQ TID for first 7 days post-transplant

ADULT LIVER TRANSPLANT

Blood Products: Use order sets and set up (on-call to OR)
10units PRBC
10units FFP
12units Platelets

Induction Therapy
Most patients will ONLY receive steroids intra-operatively.
For adult patients with a pre-operative SCr ≥1.5 mg/dL or requiring renal replacement therapy, order basiliximab 20 mg on-call to OR once case confirmed.

Corticosteroids

- Pre-operative (POD #0): Order methylprednisolone 500 mg IV on-call to the OR. Please write in the order comments section that dose is to be administered intra-operatively to prevent administration on the floor.
- Post-operative: Steroid taper is as follows:

  POD #1: methylprednisolone 500 mg IVPB
  POD #2: methylprednisolone 50 mg IV BID
  POD #3: methylprednisolone 40 mg IV BID
  POD #4: methylprednisolone 30 mg IV BID
  POD #5: methylprednisolone 20 mg IV BID
  POD #6: prednisone 20 mg PO
  POD #7: prednisone 15 mg PO
  POD #8: prednisone 10 mg PO
  POD #9-14: prednisone 5 mg PO daily (leave for AIH, PBC/PSC patients and some HCV patients*)
  POD #15-30: prednisone 2.5 mg PO daily, then discontinue

Exceptions to this taper include:

- Patients admitted on steroids → Remain on steroids at a minimum of prednisone 5 mg PO daily
- Autoimmune hepatitis (AIH) and PBC/PSC patients → Remain on steroids at a minimum of prednisone 5 mg PO daily
- *HCV patients → Remain on steroids, prednisone 5 mg daily x 6 months, then discontinue. An exception is patients who have completed HCV treatment and sustained viral load at 12 weeks post therapy (SVR12) is negative, then patient can follow the standard prednisone taper.
- If cryptogenic/idiopathic etiology, consider longer than standard prednisone taper if etiology is possible AIH

Monoclonal Antibody - Basiliximab (For SCr ≥ 1.5mg/dL or on renal replacement therapy)

- Pre-operative (POD #0): Order basiliximab 20 mg IV on-call to the OR. Please write in the order comments section that the dose is to be given intra-operatively to prevent administration on the floor. This product is stable for 4 hours at room temperature. Please do not order this until you are 100% certain that the case will move forward (liver at UNC, OR seems to be running "on-time").
- Post-operative (POD #4): Order basiliximab 20 mg IV x 1

Maintenance Immunosuppression

Calcineurin Inhibitor (Drug of choice: tacrolimus)

- Pre-operative: Patients are not to receive any doses of tacrolimus
- Post-operative: Patients are to receive tacrolimus 0.05 mg/kg PO BID. Initiation is to be decided per the attending/fellow on service, but will ideally commence within the first 24h after transplant. *When basiliximab is given as*

induction therapy, tacrolimus initiation should be delayed until POD #3 or #4 (initiation date is decided per the attending). Doses may be initiated at a higher or lower dose depending upon concern for ATN or concomitant medication interactions. Doses are to be adjusted based upon trough levels as follows:

0 - 3 months: 8-10 ng/mL
4 - 12 months: 6-8 ng/mL
>12 months: 4-6 ng/mL

Antiproliferative (Drug of choice: mycophenolate mofetil in the peri-operative period)

- Post-operative: Patients are to receive mycophenolate mofetil 500 mg PO BID starting on POD #0

Corticosteroids – see above in corticosteroids for induction therapy for steroid taper

ADULT COMBINED LIVER/KIDNEY TRANSPLANT

Blood Products: Use order sets and set up (on-call to OR)
10units PRBC
10units FFP
12units Platelets

<u>Induction Therapy</u>
Standard induction therapy is methylprednisolone 500 mg IV and basiliximab 20 mg IV on call to the OR.

Corticosteroids

- Pre-operative (POD #0): Order methylprednisolone 500 mg IV on-call to the OR. Please write in the order comments section that dose is to be administered intra-operatively to prevent administration on the floor.
- Post-operative: Steroid taper is as follows:

POD #1: methylprednisolone 500 mg IVPB
POD #2: methylprednisolone 50 mg IV BID
POD #3: methylprednisolone 40 mg IV BID
POD #4: methylprednisolone 30 mg IV BID
POD #5: methylprednisolone 20 mg IV BID
POD #6: prednisone 20 mg PO
POD #7: prednisone 15 mg PO
POD #8: prednisone 10 mg PO
POD #9: prednisone 5 mg PO daily, through the first year post-transplant

Monoclonal Antibody - Basiliximab

- Pre-operative (POD #0): Order basiliximab 20 mg IV on-call to the OR. Please write in the order comments section that the dose is to be given intra-operatively to prevent administration on the floor. This product is stable for 4 hours at room temperature. Please do not order this until you are 100% certain the case will move forward (kidney and liver at UNC, XM completed, OR seems to be running "on-time").
- Post-operative (POD #4): Order basiliximab 20 mg IV x 1

<u>Maintenance Immunosuppression</u>

Calcineurin Inhibitor (Drug of choice: tacrolimus)

- Pre-operative: Patients are not to receive any doses of tacrolimus
- Post-operative: Patients are to receive tacrolimus 0.05 mg/kg PO BID. Initiation to be decided per the attending/fellow on service, but will ideally commence within the first 24h after transplant. Doses may be initiated at a

higher or lower dose depending upon concern for ATN or concomitant medication interactions. Doses are to be adjusted based upon trough levels as follows:

0 - 3 months: 8-10 ng/mL
4 - 12 months: 6-8 ng/mL
>12 months: 4-6 ng/mL

Antiproliferative (Drug of choice: mycophenolate mofetil in the peri-operative period):

- Post-operative: Patients are to receive mycophenolate mofetil 750 mg PO BID starting on POD #0

Corticosteroids – see above in corticosteroids for induction therapy for steroid taper

ADULT LIVER & COMBINED LIVER/KIDNEY TRANSPLANT PROPHYLAXIS

Perioperative Antibiotics:

- **Pre-operative**: Piperacillin/Tazobactam 3.375 grams IV x 2 doses ordered on-call to OR. Re-dose 3.375 gm after anhepatic phase
- **Pre-operative (PCN allergy):** Clindamycin 900 mg IV and levofloxacin 500 mg IV on call to the OR

- **Post-operative**: Piperacillin/Tazobactam 3.375 grams IV q8h x 2 doses
- **Post-operative (PCN allergy**): Clindamycin 900 mg IV q8h x 2 doses and levofloxacin 500 mg IV x 1 dose on POD #1 (24 hours after levofloxacin dose given in OR)

Refer to ID note, if applicable, for alternative pre- and post-operative antibiotics based on infection history and risk factors

CMV:

Risk Status	**Agent/Max Dose/Regimen**	**Duration**
High-risk (Donor +/Recipient -)	Valganciclovir 900 mg PO daily x 3 months, then 450 mg PO daily x 3 months	6 months
Moderate-risk (Donor +/Recipient +) (Donor -/Recipient +)	Valganciclovir 450 mg PO daily	3 months
Low-risk* (Donor -/Recipient -)	Acyclovir 400 mg PO BID	3 months

Renal Dosing for Valganciclovir based on 900 mg daily dose: use Cockcroft-Gault Equation for eCrCl
eCrCl ≥60 ml/min: 900 mg once daily for high-risk and keep at 450 mg daily for moderate-risk
eCrCl 40-59 mL/minute: 450 mg once daily
eCrCl 25-39 mL/minute: 450 mg every 2 days
eCrCl 10-24 mL/minute: 450 mg twice weekly

PJP:

- Sulfamethoxazole/trimethoprim (SMZ/TMP) 400/80 mg PO every Mon, Wed, Fri x 6 months
  Sulfa allergy: Dapsone 100 mg PO daily x 6 months. Check G6PD prior to initiation.
  Sulfa allergy + G6PD deficiency: Pentamidine 300 mg inhalation monthly x 6 months or atovaquone 1500 mg PO daily x 6 months

- ID clinic phone number for pentamidine administration (ask for Jonah Pierce at 984-974-0163 or leave a message at 984-974-0164)

Hepatitis B: See page 37 for Adult Hepatitis B Guideline

Stress ulcer:

- Pantoprazole 40 mg PO daily for at least the first month post-transplant

Cardiovascular:

- Aspirin 81 mg PO daily to be started per discretion of attending/fellow

DVT Prophylaxis:

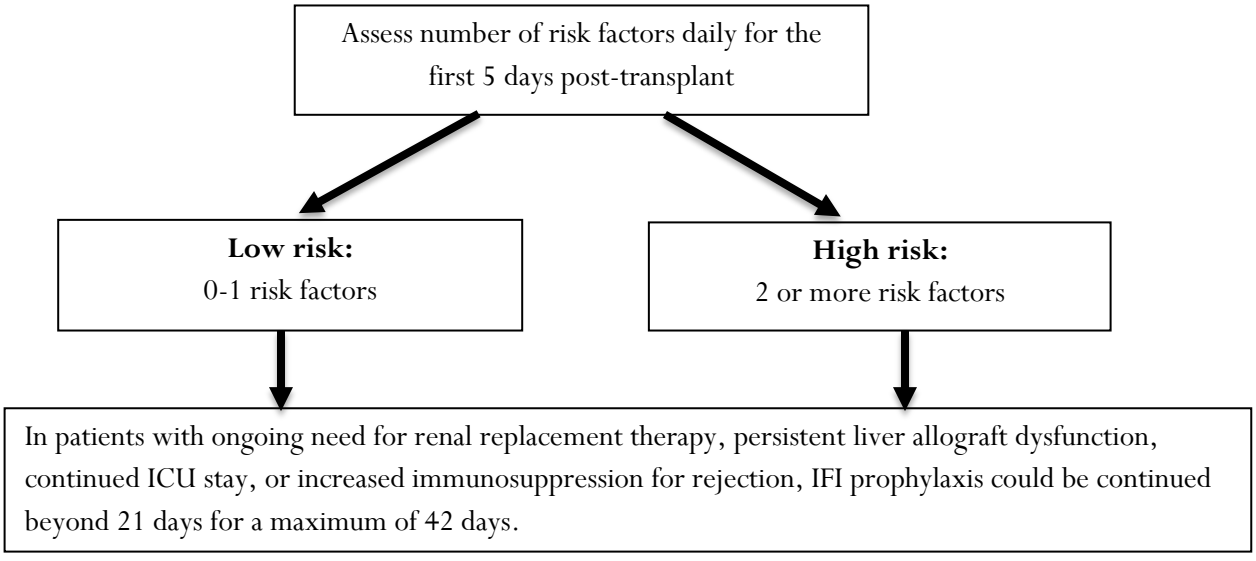
- Heparin 5,000 units SQ Q8H or 7,500 units SQ Q8H if weight ≥100 kg, only start per discretion of attending

Anti-fungal Prophylaxis:

Combined liver/kidney transplant recipients, should receive micafungin 100 mg IV daily until discharge or POD #21.
Liver transplant recipients:

Risk Factors for Invasive Fungal Infection (IFI)

- MELD ≥30 on day of transplantation
- Choledochojejunostomy anastomosis
- Re-transplantation
- Intra-operative administration of >40 units of cellular blood products (including platelets, PRBCs, cell saver/auto-transfusion blood product excluding cryoprecipitate or plasma)
- Pre-operative serum creatinine >2.0 mg/dl or need for any form of renal replacement therapy
- Candida isolation from more than 2 of the following sites between 48 hours before and after OLT: sputum, urine, wound, and bile
- Return to the operating room within 5 days of OLT for laparotomy because of bile or other anastomotic leak, intra-abdominal bleeding, vascular accident other than bleeding (hepatic artery thrombosis) or primary graft non-function



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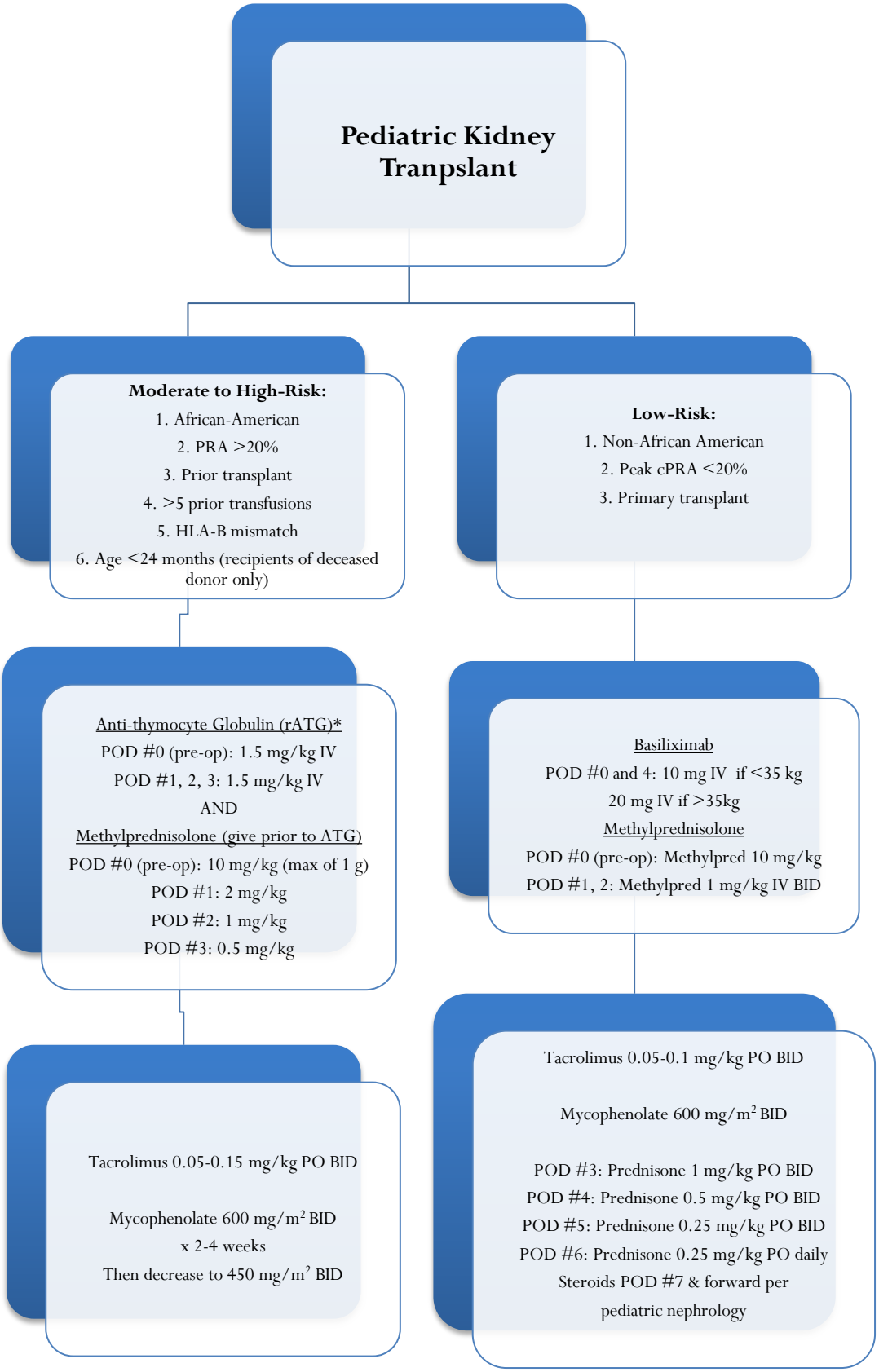
PEDIATRIC KIDNEY TRANSPLANT



*Round all anti-thymocyte globulin doses to the nearest 25 mg *Anti-thymocyte globulin requires pre-medication with methylprednisolone, acetaminophen and diphenhydramine

Induction Therapy

Low Risk Recipients (Non-African American patients receiving first transplant with a peak cPRA <20%)

- Pre-operative (POD #0): Order basiliximab 10 mg IV x 1 if patient weighs <35 kg. Order basiliximab 20 mg if patient weighs >35kg IV on-call to the OR. Please write in the order comments section that the dose is to be given intra-operatively to prevent administration on the floor. This product is stable for 4 hours, so please do not order this until you are 100% certain the case will go forward (kidney at UNC, XM completed, OR seems to be running "on-time").
- Post-operative (POD #4): Patients are to receive a second dose of basiliximab 10 mg IV x 1 dose if patient weighs <35 kg. Order basiliximab 20 mg IV x 1 dose if patient weighs >35 kg.

High Risk Recipients (PRA >20%, repeat transplant, African American recipients)

- Pre-operative (POD #0): Order anti-thymocyte globulin 1.5 mg/kg (rounded to the nearest 25 mg) IV on-call to the OR using actual body weight, unless weight is >120% of ideal body weight, then use adjusted body weight. Use admission body weight for calculations. Round dose to the nearest 25 mg and ordered for on-call to OR. This product is stable for 24 hours at room temperature. Please do not order this until you are 100% certain the case will go forward (kidney at UNC, XM completed, OR seems to be running "on-time").
    - How to calculate **IDEAL BODY WEIGHT** (for patients >120% of ideal body weight, calculate and use adjusted body weight to dose rATG):
        - MALES: 50 kg + (inches over 60 x 2.3)
        - FEMALES: 45.5 kg + (inches over 60 x 2.3)
    - How to calculate **ADJUSTED BODY WEIGHT**: Ideal body weight + [0.4 (total body weight – ideal body weight)]
- Pre-operative pre-medications (POD #0) include acetaminophen PO or IV, diphenhydramine PO or IV and POD #0 methylprednisolone on-call to OR
- Post-operative (POD #1,2,3): Total goal dose of anti-thymocyte globulin is 6 mg/kg given over 4 days at 1.5 mg/kg/day. However, dosing is subject to change according to WBC, platelet count, anaphylaxis/tolerability of medication, and infectious signs and symptoms. Do not order subsequent doses of anti-thymocyte globulin. Should be ordered each day after attending/fellow on service have discussed dosing. Doses may be held/reduced at the discretion of the attending fellow on service based upon WBC, PLT and other ADR. See page 3 regarding dose reductions or discontinuation based on PLT or WBC.
- Please order the appropriate anti-thymocyte globulin preparation based upon administration - central versus peripheral and make sure morning dose of steroids is given prior to administration
- CD3 count should not be ordered unless directed by the physician. CBC with diff and Chem7 should be ordered daily on POD #1 and 2.
- When ordering POD #1,2,3 anti-thymocyte globulin and the patient weight is that of adult dosing, the emergency orders (Adult Chemotherapy, Biotherapy, and Iron Infusion Hypersensitivity and Anaphylaxis Reactions protocol for infusion reaction (HSR order set)) should be ordered with the removal of the NaCl infusion and NaCl bolus prn orders. This ensures there are rescue medications available if patient has an adverse drug reaction to anti-thymocyte globulin.

Maintenance Immunosuppression

Calcineurin Inhibitor (drug of choice: tacrolimus)

- Pre-operative: Patients are not to receive any doses of tacrolimus
- Post-operative: Patients are to receive tacrolimus 0.05-0.1 mg/kg PO BID. Initiation to be decided per the attending/fellow on service, but will ideally commence within the first 24h after transplant. Doses may be initiated at a higher or lower dose depending upon concern for allograft dysfunction or concomitant medication interactions. Doses are to be adjusted based upon trough levels as follows:

    0 - 3 months: 8-10 ng/mL
    4 -12 months: 6-8 ng/mL

>12 months: per Peds Nephrology (Based upon patient-specific parameters)

Antiproliferative (Drug of choice: mycophenolate mofetil in the peri-operative period)

- Post-operative: Patients are to receive mycophenolate mofetil 600 mg/m^2 BID on POD #0
- Alternative solid dosage forms according to BSA as follows:
  - CellCept®:
    - If BSA 1.25-1.5 m^2 → 750 mg BID
    - If BSA >1.5 mg/m^2 → 1000 mg BID
  - Myfortic®:
    - If BSA 1.19-1.58 m^2 → 540 mg BID
    - If BSA >1.58 m^2 → 720 mg BID

Corticosteroids – see above for steroid taper

PEDIATRIC KIDNEY ANTIMICROBIAL PROPHYLAXIS

CMV:

Dosing valganciclovir (mg) = 7 x BSA x eCrCl (per modified Schwartz formula; cut-off at 150 mL/min/1.73 m^2); max valganciclovir dose of 900 mg PO daily for high-risk and 450 mg daily for low-risk

- D+/R- (high-risk): valganciclovir (dosed per above equation) x 6 months
- D-/R+, D+/R+, and D-/R- (moderate- and low-risk): valganciclovir (dosed per above equation) x 3 months
- See adult kidney antimicrobial prophylaxis for renal dose adjustments to valganciclovir

PJP:

- Age <12 years-old: Sulfamethoxazole/trimethoprim (SMZ/TMP) dosed based on TMP - 2.5 mg TMP/kg twice a day (max 80 mg TMP) PO every Mon, Wed, Fri x 6 months (use actual body weight); may consider once daily for UTI prevention
- Age 12-18 years-old refer to adult guideline on page 16

Thrush:

- Nystatin 500,000 units (5 mL) four times per day x 3 months (discharge dosing is 500,000 units three times per day)

PEDIATRIC LIVER TRANSPLANT

Induction Therapy

Corticosteroids

- Pre-operative (POD #0): Order methylprednisolone 10 mg/kg (maximum of 500 mg) IV on-call to the OR. Please write in the order comments section that dose is to be administered intra-operatively to prevent administration on the floor.
- Post-operative: Patients are to receive a steroid taper as follows:

POD #1:	methylprednisolone	10 mg/kg IV x 1
POD #2	methylprednisolone	2 mg/kg IV Q 12h
POD #3	methylprednisolone	1.5 mg/kg IV Q 12h
POD #4	methylprednisolone	1 mg/kg IV Q 12h
POD #5	methylprednisolone	0.9 mg/kg IV Q 12h
POD #6	prednisone	0.8 mg/kg PO Q 24h
POD #7	prednisone	0.7 mg/kg PO Q 24h

POD #8	prednisone	0.6 mg/kg PO Q 24h
POD #9-14	prednisone	0.5 mg/kg PO Q 24h
POD #15-30	prednisone	0.4 mg/kg PO Q 24h
POD #30-60	prednisone	0.3 mg/kg PO Q 24h
POD #60-90	prednisone	0.2 mg/kg PO Q 24h
POD #90-180	prednisone	0.1 mg/kg PO Q 24h

Polyclonal Antibody: **Anti-thymocyte Globulin, ATG, Thymoglobulin**

- Pre-operative (POD #0): Order anti-thymocyte globulin 1.5 mg/kg (rounded to the nearest 25 mg) IVPB on-call to the OR. Please write in the order comments section that the dose is to be given intra-operatively to prevent administration on the floor. This product is stable for 24 hours, and it may be ordered as soon as resident has seen patient and discussed them with the attending/fellow on service.
- Post-operative (POD #1,3,5): Patients are to receive anti-thymocyte globulin 1.5 mg/kg (rounded to the nearest 25 mg) IVPB daily on POD #1, 3, and 5. Total goal dose of anti-thymocyte globulin is 6 mg/kg given over 4 days at 1.5 mg/kg/day. However, dosing is subject to change according to WBC, platelet count, anaphylaxis/tolerability of medication, and infectious signs and symptoms. Do not order subsequent doses of anti-thymocyte globulin. Should be ordered each day after attending/fellow on service have discussed dosing. Doses may be held/reduced at the discretion of the attending fellow on service based upon WBC, PLT and other ADR. See page 3 for dose adjustments due to WBC and platelet counts.
- Please order the appropriate anti-thymocyte globulin based upon administration - central versus peripheral and make sure morning dose of steroids is given prior to administration
- CD3 count should not be ordered unless directed by the physician. CBC with diff and Chem7 should be ordered daily on POD #1 and 2.
- When ordering POD #1,2,3 anti-thymocyte globulin and the patient weight is that of adult dosing, the emergency orders (Adult Chemotherapy, Biotherapy, and Iron Infusion Hypersensitivity and Anaphylaxis Reactions protocol for infusion reaction (HSR order set)) should be ordered with the removal of the NaCl infusion and NaCl bolus prn orders. This ensures there are rescue medications available if patient has an adverse drug reaction to anti-thymocyte globulin.

Monoclonal Antibody: Basiliximab, Simulect (For living-related transplant patients)

- Pre-operative (POD #0): Order basiliximab 10 mg IV if <35 kg and basiliximab 20 mg IV if ≥35 kg on-call to the OR. Please write in the order comments section that the dose is to be given intra-operatively to prevent administration on the floor. This product is stable for 4 hours at room temperature. Please do not order this until you are 100% certain the case will move forward (liver at UNC, OR seems to be running "on-time").
- Post-operative (POD #4): Order basiliximab 20 mg IV x 1 dose

Maintenance Immunosuppression

Calcineurin Inhibitor (Drug of choice: tacrolimus)

- Pre-operative: Patients are not to receive any doses of tacrolimus
- Post-operative: Patients are to receive tacrolimus 0.05 mg/kg PO BID. Initiation to be decided per the attending/fellow on service, but will ideally commence within the first 24h after transplant. Doses may be initiated at a higher or lower dose depending upon concern for ATN or concomitant medication interactions.
- Doses are to be adjusted based upon trough levels as follows:

  0 - 3 months: 10-12 ng/mL
  4 - 12 months: 8-10 ng/mL
  >12 months: 6-8 ng/mL

Antiproliferative (Drug of choice: mycophenolate mofetil)

- Pre-operative: Patients do not require any doses of mycophenolate mofetil
- Post-operative: Patients are to receive mycophenolate mofetil 600 mg//m^2 PO BID (max dose of 1,000 mg BID) starting on POD #0

Corticosteroids – see above for steroid taper

PEDIATRIC LIVER ANTIMICROBIAL PROPHYLAXIS

CMV:

Dosing valganciclovir (mg) = 7 x BSA x eCrCl (per modified Schwartz formula; cut-off at 150 mL/min/1.73 m^2); max valganciclovir dose of 900 mg PO daily for high-risk and 450 mg daily for low-risk

- D+/R- (high-risk): valganciclovir (dosed per above equation) x 6 months
- D-/R+, D+/R+, and D-/R- (moderate- and low-risk): valganciclovir (dosed per above equation) x 3 months
- See adult kidney antimicrobial prophylaxis for renal dose adjustments to valganciclovir

PJP:

- Age <12 years-old: Sulfamethoxazole/trimethoprim (SMZ/TMP) dosed based on TMP - 2.5 mg TMP/kg twice a day (max 80 mg TMP) PO every Mon, Wed, Fri x 6 months (use actual body weight)
- Age 12-18 years-old refer to adult guideline on page 16

Thrush:

- Nystatin 500,000 units (5 mL) four times per day for total of 3 months (discharge dosing is 500,000 units three times per day)

ADULT KIDNEY AND/OR PANCREAS TRANSPLANT CELLULAR REJECTION

Corticosteroid Treatment

Methylprednisolone 500 mg IV Q 24h for 3 days (*Taper may vary based upon patient-specific criteria)

Prednisone Taper Following methylprednisolone IV for rejection:
Prednisone 80 mg x 2 days
Prednisone 60 mg x 2 days
Prednisone 40 mg x 2 days
Prednisone 20 mg x 2 days
Prednisone 10 mg daily - To be tapered on individual basis in clinic

Rabbit Anti-Thymocyte Globulin Guideline for Severe or Steroid-resistant Cellular Rejection

Rabbit anti-thymocyte globulin

- Used in combination with corticosteroid treatment above or started if unresponsive to steroids alone
- Order rabbit anti-thymocyte globulin 1.5 mg/kg using actual body weight, unless weight is >120% of ideal body weight, then use adjusted body weight. Use admission body weight for calculations. Round dose to the nearest 25 mg and ordered for on-call to OR. This product is stable for 24 hours at room temperature.
    - How to calculate **IDEAL BODY WEIGHT** (for patients >120% of ideal body weight, calculate and use adjusted body weight to dose rATG):
        - MALES: 50 kg + (inches over 60 x 2.3)
        - FEMALES: 45.5 kg + (inches over 60 x 2.3)
    - How to calculate **ADJUSTED BODY WEIGHT**: Ideal body weight + [0.4 (total body weight – ideal body weight)]
- **Pre-medications** include acetaminophen 650 mg PO or IV, diphenhydramine 50 mg PO or IV, and methylprednisolone or prednisone dose as per steroid taper. If patients received methylprednisolone >1000 mg IV prior to the start of anti-thymocyte globulin therapy, use methylprednisolone 125 mg IV as premedication prior to the first anti-thymocyte dose, and then continue prednisone taper.
- Ensure central versus peripheral access is known prior to placing the order (peripheral infusions are admixed with heparin and hydrocortisone to prevent phlebitis)
- Usual course of anti-thymocyte globulin therapy is 1.5 mg/kg IV q 24hours for 7 to 14 days. Each case to be individual per attending and pathologist review of biopsy, clinical status, and other laboratory information (donor specific antibody, underlying glomerular disease, etc). Dosing is subject to change according to WBC, platelet count, anaphylaxis/tolerability of medication, and infectious signs and symptoms. Do not order subsequent doses of anti-thymocyte globulin until after rounds. Doses may be held/reduced at the discretion of the attending fellow on service based upon WBC, PLT and other adverse drug reactions (hypotension, rigors, fever, and anaphylaxis). Review of patient, clinical response, and biopsy with attending should be discussed no later than 7 days into anti-thymocyte globulin therapy to determine total duration to be administered.

WBC	Platelets	rATG Dose
>3000	>50,000	100% (1.5 mg/kg or full dose)
2000 – 3000	30,000 – 50,000	Consider reduction by 50% (Reassess hold parameters daily)
<2000	<30,000	HOLD rATG x 24 hours

- Always administer rATG ***after*** dialysis and plasma exchange if applicable

- A minimum of 1000 mg of methylprednisolone should be given during treatment of rejection course (usually administered in the form of pre-medication during the first 3 doses of anti-thymocyte globulin)
- CD3 count should not be ordered unless directed by the physician. CBC with diff and Chem7 should be ordered daily.
- When ordering POD #1,2,3 anti-thymocyte globulin, the emergency orders (Adult Chemotherapy, Biotherapy, and Iron Infusion Hypersensitivity and Anaphylaxis Reactions protocol for infusion reaction (HSR order set)) should be ordered with the removal of the NaCl infusion and NaCl bolus prn orders. This ensures there are rescue medications available if patient has an adverse drug reaction to anti-thymocyte globulin.

Maintenance Immunosuppression:

Calcineurin inhibitors (tacrolimus or cyclosporine) **or mTOR inhibitors** (sirolimus or everolimus)

- Decrease dose by 50% (most tacrolimus goals will be 4-6 ng/mL while on anti-thymocyte globulin). Dose reductions should be discussed with attending or fellow and may vary based on the individual and severity of rejection.
- The dose should be increased back to full dose 72 hours prior to the end of anti-thymocyte globulin therapy.

Antiproliferative (mycophenolate derivative)

- Decrease dose by 50% or discontinue the antiproliferative. Held doses or reductions should be discussed with attending or fellow and may vary based on the individual, severity of rejection, and response to anti-thymocyte globulin therapy.
- Restart full dose of mycophenolate after last dose of anti-thymocyte globulin

Corticosteroids

- Most patients remain on 5 to 10 mg of prednisone after anti-thymocyte globulin therapy

ADULT KIDNEY TRANSPLANT HUMORAL REJECTION

- IVIG, TPEs, ± rituximab
    - Selection of treatment and frequency of therapy will be discussed and determined on an individual basis with the transplant team and attending on service
- IVIG
    - Product
        - Should be selected as sucrose-free formulation and may be 5% or 10% concentration per attending request
        - Use Privigen® 10%
    - Dosing
        - Usual post-pheresis IVIG dose = 100 - 200 mg/kg (Rounded to the nearest 10 gm increment)
        - IVIG will be dosed based on ideal body weight unless the patient's weight is >30% IBW than adjusted body weight will be used
            - ABW = IBW + 40% (actual body weight – IBW)
        - Pharmacists will round the dose ordered to the nearest 5 gm for adults (within 10% of ordered dose) and defer to the dose standardization guideline for pediatric doses above 9 gm. Doses below 9 gm for pediatric use will be rounded to the nearest 1 gm (within 10% of the ordered dose).
        - Please refer to UNC Health Care Guideline for IVIG
        - To be given after TPE as IVIG is removed
    - Pre-medications
        - Adults: diphenhydramine 25 mg PO and acetaminophen 650 mg PO to be given 30 minutes prior to the start of infusion

Other treatment options:

- Therapeutic Plasma Exchange (TPE)
    - Ensure IVIG is given after TPE
    - Discontinue ACE-inhibitor prior to start of TPE
    - Make sure medications are timed appropriately and dosed appropriately with TPE
- Rituximab
    - Please refer to UNC Health Care Guideline on Rituximab for Treatment of Glomerular, Rheumatic, or Auto-Immune Conditions, and Antibody Mediated Rejection
- Bortezomib
- Eculizumab

ADULT LIVER TRANSPLANT CELLULAR REJECTION

Corticosteroid Treatment

Methylprednisolone 500 mg IV Q 24h for 3 days (*Taper based upon patient-specific criteria)

Prednisone Taper Following methylprednisolone IV for rejection:
Prednisone 80 mg x 2 days
Prednisone 60 mg x 2 days
Prednisone 40 mg x 2 days
Prednisone 20 mg x 2 days
Prednisone 10 mg daily x 2 days
Prednisone 5 mg daily - To be tapered on individual basis in clinic

Steroid-resistant Rejection/Severe Rejection (RAI 7-9)

Rabbit anti-thymocyte globulin

- Refer to anti-thymocyte globulin dosing for kidney transplant cellular rejection on page 32-33

Maintenance Immunosuppression

- Refer to maintenance immunosuppression for kidney transplant cellular rejection on page 33

PEDIATRIC KIDNEY TRANSPLANT CELLULAR REJECTION

Corticosteroid Treatment Taper

Day 1-2	Methylprednisolone	10 mg/kg IV Q 24h x 2 days (max 500 mg/dose)
Day 3	Methylprednisolone	4 mg/kg IV Q 12h
Day 4	Methylprednisolone	3 mg/kg IV Q 12h
Day 5	Methylprednisolone	2 mg/kg IV Q 12h
Day 6	Methylprednisolone	1 mg/kg IV Q 12h
Day 7	Methylprednisolone	0.5 mg/kg IV Q 12h
Day 8	Methylprednisolone	0.5 mg/kg IV Q 24h
Day 9	RETURN TO BASELINE PREDNISONE DOSE	

*If patient loses access or is to be discharged, intravenous methylprednisolone may be substituted with oral prednisone or oral prednisolone

Steroid-resistant rejection or severe cellular rejection

Rabbit anti-thymocyte globulin

- Refer to anti-thymocyte globulin dosing for kidney transplant cellular rejection on page 32-33

Maintenance Immunosuppression

- Refer to maintenance immunosuppression for kidney transplant cellular rejection on page 33

PEDIATRIC LIVER TRANSPLANT CELLULAR REJECTION

Corticosteroid Treatment

Day 1-2	Methylprednisolone	10 mg/kg IV Q 24h x 2 days
Day 3	Methylprednisolone	4 mg/kg IV Q 12h
Day 4	Methylprednisolone	3 mg/kg IV Q 12h
Day 5	Methylprednisolone	2 mg/kg IV Q 12h
Day 6	Methylprednisolone	1 mg/kg IV Q 12h
Day 7	Methylprednisolone	0.5 mg/kg IV Q 12h
Day 8	Methylprednisolone	0.5 mg/kg IV Q 24h
Day 9	RETURN TO BASELINE PREDNISONE DOSE	

*If patient loses access or is to be discharged, intravenous methylprednisolone may be substituted with oral prednisone or oral prednisolone

Steroid-resistant Rejection

Rabbit anti-thymocyte globulin therapy

- Refer to anti-thymocyte globulin therapy section of kidney transplant on page 32-33

Maintenance Immunosuppression

- Refer to maintenance immunosuppression for kidney transplant cellular rejection on page 33

ANTIMICROBIAL PROPHYLAXIS POST-REJECTION EPISODE

- **CMV**
  - If treated with:
    - IVIG and/or rituximab: recommend no prophylaxis
    - Steroids: recommend prophylaxis for one month regardless of CMV risk
      - High-risk CMV (D+/R-): valganciclovir 900 mg PO daily x 1 month (renally dose adjust)
      - Moderate-risk CMV (D-/R+, D+/R+): valganciclovir 450 mg PO daily x 1 month (renally dose adjust)
      - Low-risk CMV (D-/R-): acyclovir 400 mg BID x 1 month
    - Anti-thymocyte globulin: recommend prophylaxis for 6 months if high-risk CMV and 3 months for moderate-or low-risk CMV
      - High-risk CMV (D+/R-): valganciclovir 900 mg PO daily x 3 months, then reduce to 450 mg PO daily x 3 months (renally dose adjust)
      - Moderate-risk CMV (D-/R+, D+/R+): valganciclovir 450 mg PO daily x 3 months (renally dose adjust)
      - Low-risk CMV (D-/R-): acyclovir 400 mg BID x 3 months
- **PJP**
  - If treated with:
    - IVIG or rituximab: recommend no prophylaxis
    - Steroids or on prednisone $\geq$20 mg (or equivalent steroid dose) for 5 days or longer: recommend prophylaxis x 1 month from start of high-dose steroids
    - Anti-thymocyte globulin: recommend prophylaxis x 6 months
    - See PJP medication prophylaxis options on page 16

HEPATITIS B GUIDELINES

Kidney Transplant:

KIDNEY RECIPIENTS WITH CHRONIC OR RECOVERED HEPATITIS B INFECTION

KIDNEY RECIPIENT

Chronic Hepatitis B infection

KIDNEY RECIPIENT

Recovered Hepatitis B infection

Recipient: HBV DNA should be <100 IU/mL & liver US without evidence of cirrhosis or HCC within 6 months of transplant

Hep B immunoglobulin:
None

Anti-viral therapy:
On POD1, continue the same oral anti-viral therapy patient was taking pre-transplant. Hepatology may consider drug switch if this is not entecavir, tenofovir, or emtricitabine/tenofovir.

Monitoring:
LFTs q1mo for the 1st year, then q3mo lifelong
HBsAg and HBV DNA q3mo life-long or for rise in LFTs
Liver US q6-12mo lifelong

Hep B surface Ab positive (natural immunity)

Anti-viral prophylaxis:
None

Monitoring:
LFTs q3mo for the 1st year
HBsAg and HBV DNA q3mo for the 1st year and for any rise in LFTs

Hep B surface Ab negative (uncertain immunity)

Anti-viral prophylaxis:
Start entecavir 0.5 mg PO daily on POD#1 for 12 months.

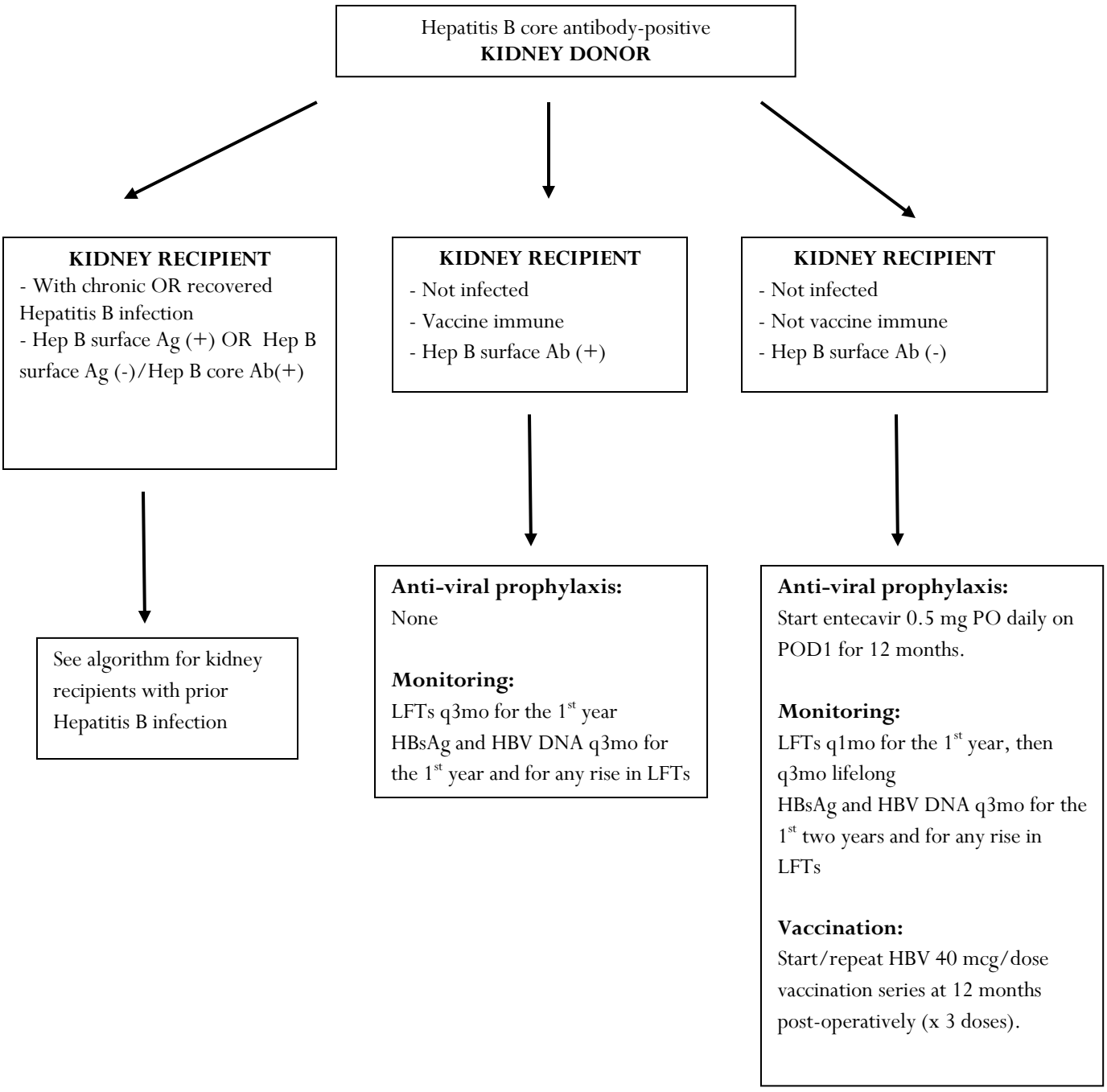
Monitoring:
LFTs q1mo for the 1st year, then q3mo lifelong
HBsAg and HBV DNA q3mo for the 1st two years and for any rise in LFTs

Vaccination:
Start/repeat HBV 40 mcg/dose vaccination series at 12 months post-operatively (x 3 doses).

Notes:

- Preferred HBV anti-viral drugs are:
  - entecavir 0.5 mg PO daily
  - tenofovir disoproxil 300mg PO daily
  - tenofovir alafenamide 25 mg PO daily
  - emtricitabine/tenofovir 200/300 mg PO daily
- **Anti-viral drug doses must be renally-adjusted**
- Consider entecavir 1mg daily for patients with a history of prior breakthrough/failure with other NRTIs.
- Lamivudine 100mg PO daily should be used only if other drugs are cost-prohibitive.

KIDNEY RECIPIENTS WITH HEPATITIS B CORE ANTIBODY POSITIVE DONORS



Liver Transplant:

LIVER RECIPIENTS WITH CHRONIC OR RECOVERED HEPATITIS B INFECTION

LIVER RECIPIENT

Chronic Hepatitis B infection

LIVER RECIPIENT

Recovered Hepatitis B infection

Recipient: Obtain HBV DNA on the day of transplant

Is the patient at high risk for HBV recurrence?

- HBV DNA >100 IU/mL at the time of transplant or HBV DNA unknown for the past 6 months
- Co-infection with Hepatitis D virus
- Co-infection with HIV
- Pre-existing multi-drug resistant HBV
- High risk for HCC recurrence (exceeding Milan with down-staging pre-transplant or vascular invasion on explant)

Anti-viral prophylaxis: None

Monitoring:

- HBV DNA q3mo for the 1st year
- HBsAg q3mo for the 1st year, then q6mo lifelong or for rise in LFTs

Vaccination:

If Hep B surface Ab (-) at the time of transplantation, start/repeat HBV 40 mcg/dose vaccination series at 12 months post-operatively (x 3 doses).

Yes

No

Hep B immunoglobulin

Intra-operatively: HBIG 10,000 units IV

Post-operatively: HBIG 10,000 units IV q24h for 6 days post-transplant (total of 7 doses)

After discharge: Redose 1560 IU (5mL) IM for Hep B surface Ab titer < 100 indefinitely.

HBIg may be discontinued after 1 year by the hepatologist based on risk assessment or for HBV recurrence.

Anti-viral therapy:

On POD1, continue the same oral anti-viral therapy patient was taking pre-transplant. Hepatology may consider a drug switch if this is not entecavir, tenofovir, or emtricitabine/tenofovir.

Monitoring:

- HBV DNA, HBsAg, & HBsAb q1mo for the 1st year, then q1-3mo (prior to each HBIg dose) lifelong or for rise in LFTs

Hep B immunoglobulin

Intra-operatively: HBIG 10,000 units IV

Post-operatively: HBIG 10,000 units IV q24h for 6 days post-transplant (total of 7 doses during transplant admission)

After discharge: none

Anti-viral therapy:

On POD1, continue the same oral anti-viral therapy patient was taking pre-transplant. Hepatology may consider a drug switch if this is not entecavir, tenofovir, or emtricitabine/tenofovir.

Monitoring:

- HBV DNA q1mo for the 1st year, then q3mo lifelong or for rise in LFTs
- HBsAg q1mo for the 1st two years, then q3mo lifelong or for rise in LFTs

LIVER RECIPIENTS WITH HEPATITIS B CORE ANTIBODY POSITIVE DONORS

Hepatitis B core antibody-positive
LIVER DONOR

LIVER RECIPIENT
- With chronic Hepatitis B infection
- Hep B surface Ag+

See algorithm for liver recipients with chronic Hepatitis B infection

LIVER RECIPIENT
- With recovered Hepatitis B infection OR no prior evidence of Hepatitis B infection regardless of immunity
- Hep B surface Ag-/Hep B core Ab+)
OR Hep B core Ab-/Hep B surface Ab+ OR Hep B core Ab-/Hep B surface Ab-

Anti-viral prophylaxis:
Start lifelong entecavir 0.5 mg PO daily on POD1.

Monitoring:
HBV DNA and HBsAg q3mo for the 1st year, then q6mo lifelong or for rise in LFTs

Vaccination:
If Hep B surface Ag negative and Hep B surface Ab negative at the time of transplantation, start/repeat HBV 40 mcg/dose vaccination series at 12 months post-operatively (x 3 doses).

Notes:
- Pre-med for IV HBIG 30 minutes prior to infusion with acetaminophen 650 mg PO & diphenhydramine 25 mg PO
- Avoid HBIG IM if INR >1.5 or platelets <50K
- Preferred HBV anti-viral drugs are:
  - entecavir 0.5 mg PO daily
  - tenofovir disoproxil 300 mg PO daily
  - tenofovir alafenamide 25 mg PO daily
  - emtricitabine/tenofovir 200/300 mg PO daily

- Anti-viral drug doses must be renally dose adjusted
- Consider entecavir 1 mg daily for patients with a history of prior breakthrough/ failure with other NRTIs.
- Lamivudine 100 mg PO daily should be used only if other drugs are cost-prohibitive.

References:
1. Huprikar S et al. Solid organ transplantation from Hepatitis B virus-positive Donors: consensus guidelines for recipient management. Am J Transplant 2015; 15: 1162-1172.
2. Levitsky J et al. Viral hepatitis in solid organ transplantation. Am J Transplant 2013; 13: 147-168.
3. Manne V et al. Strategies for the prevention of recurrent hepatitis B virus infection after liver transplantation. Gastroenterol Hepatol 2014; 10:175-179.
4. John S et al. Prophylaxis of hepatitis B infection in solid organ transplant recipients. Therap Adv Gastroenterol 2013; 6: 309-319.

RECIPIENTS OF PHS SOCIAL HIGH-RISK DONOR ORGANS POST-TRANSPLANT

Recipient testing at some time between 1-3 months post-transplant should include:

HIV antigen/antibody combination assay
Hepatitis B surface antigen
Hepatitis B virus DNA
Hepatitis C virus RNA

Recipient testing at 12 months post-transplant should include:

Hepatitis B surface antigen
Hepatitis B surface antibody
Hepatitis B core antibody

Reference:
1. Seem DL, et al. Excerpt From PHS Guideline for Reducing HIV, HBV and HCV Transmission Through Organ Transplantation. AJT 2013;13:1953-1962.

CMV TREATMENT GUIDELINES

CMV Viremia/Infection (as defined by one of the following):

- Asymptomatic patient with CMV PCR >1000
- Positive symptoms (leukopenia, thrombocytopenia, diarrhea, malaise, fatigue, fever) with detectable blood CMV PCR
- Induction therapy: valganciclovir 900 mg PO BID x two consecutive negative CMV PCR one week apart (minimum duration of 14 days)
- Maintenance therapy: Valganciclovir 900 mg PO daily (adjust for renal function) x 2-4 additional weeks depending on clinical status of patient or determined by physician and refer to secondary prophylaxis
- Monitor CMV PCR weekly until negative, then biweekly x 2, then monthly x 2 months

CMV Disease: As defined by tissue invasive disease or cannot tolerate PO

- Induction therapy: Ganciclovir 5 mg/kg IV BID x 2 negative consecutive CMV PCRs one week apart for a minimum of 21 days; switch to oral when clinically improved (declining PCR or clinical improvement)
- Maintenance therapy: Ganciclovir 5 mg/kg IV daily OR valganciclovir 900 mg PO daily (adjust dose for renal function) x 2-4 additional weeks depending on clinical status of patient or determined by physician and refer to secondary prophylaxis. determined by physician)
- CMV-IGIV (Cytogam®) should NOT be administered unless the following:
    - Clinical symptoms do not improve or worsen despite adequate anti-viral therapy
    - Viral load continues to rise despite adequate anti-viral therapy
    - Severe or suspected life threatening illness or severe pneumonia

- Biopsy proven tissue invasive disease
- Recommended dose: 100-150 mg/kg IV x 3 doses every 4 days at the discretion of physician

Supportive Care:

- Decrease or hold mycophenolate until viral load <1000 and symptoms have resolved if at all possible
- Valganciclovir or ganciclovir dose should not be reduced for bone marrow suppression
- Reduction of mycophenolate, azathioprine, sulfamethoxazole/trimethoprim, mTOR inhibitor
- Refer to neutropenia guideline on page 46 for ANC <1000 cell/mm^3

CMV Resistance:

- Suspect resistance when increasing or high level CMV viremia or progressive clinical drug resistance is observed during prolonged therapy (>2 weeks). Increases in viral loads in the first week of treatment are not reliable for drug resistance.
- Genotype assay testing should be sent and ID team should be consulted if resistance is detected.
- The following therapies should be considered if resistance occurs:
  - High dose IV ganciclovir, foscarnet, CMV IGIV, cidofovir; See Appendix C for suggested resistance testing

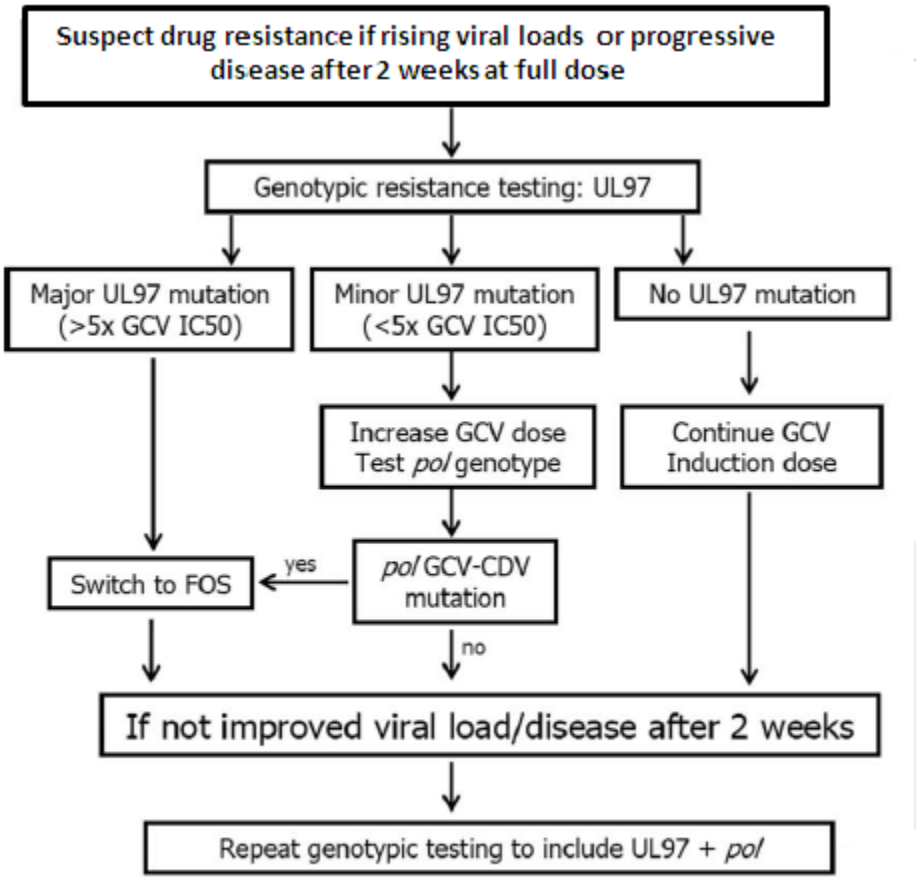
Secondary Prophylaxis: To prevent recurrent infection after successful treatment of CMV disease:

- Low to moderate-Risk (D-/R-, D-/R+, D+/R+): valganciclovir 450 mg PO daily x 1-3 months
- High-Risk (D+/R-): valganciclovir 900 mg PO daily x 3-6 months

Pediatric CMV Treatment:

- Do not reduce ganciclovir dose for leukopenia
- Consider reduction or holding mycophenolate if at all possible
- IV ganciclovir 5mg/kg/BID x 14-21 days
- Consider CMV IGIV (Cytogam) for tissue invasive disease
- Secondary prophylaxis: valganciclovir PO (dosing per above equation) x 1-6 months

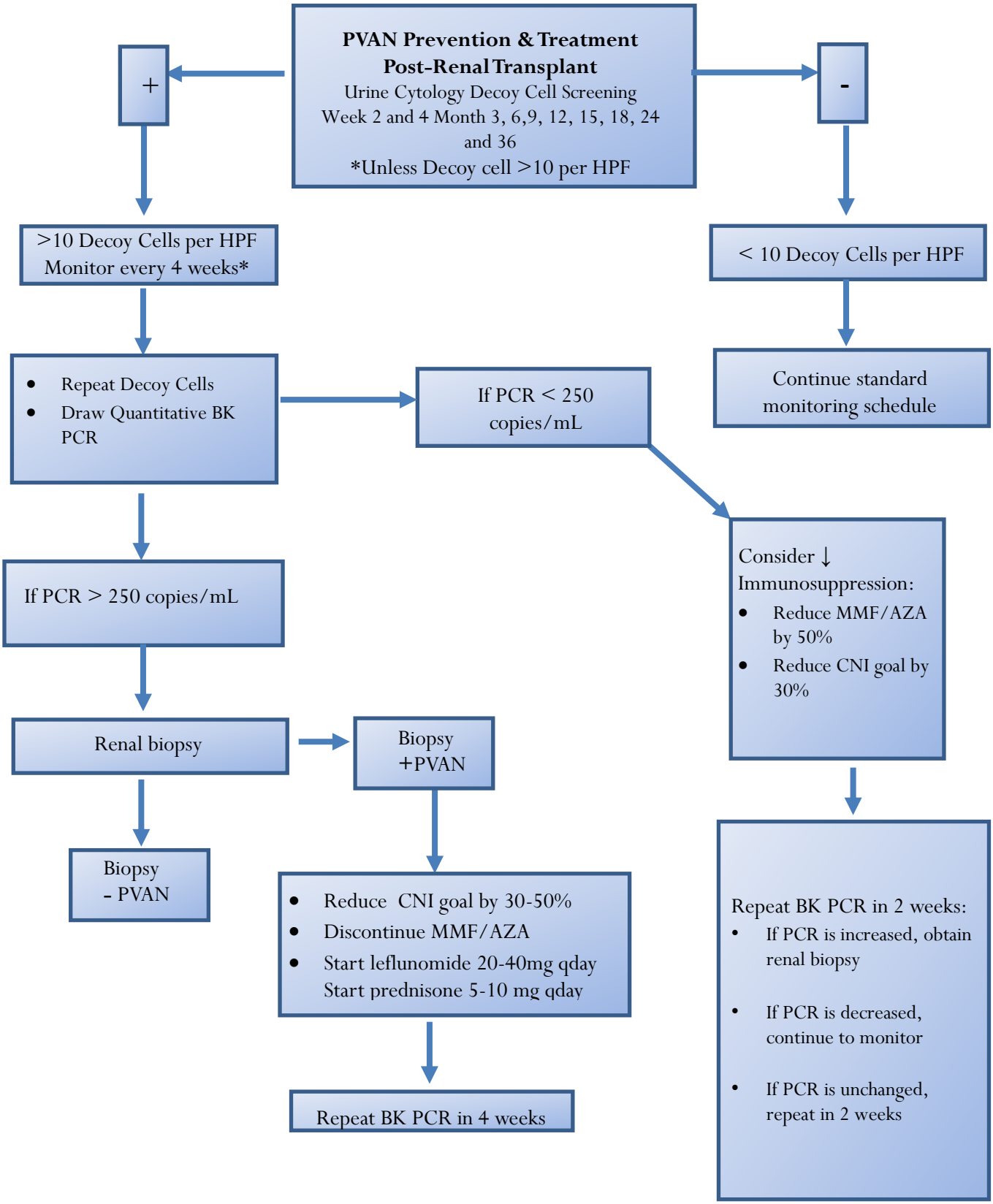
CMV Drug Resistance Algorithm



Kotton CN. International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation Transplantation. April 2010; 89: 779-795

PVAN (BKV) TREATMENT GUIDELINES FOR ADULTS

Kuypers, D. R .Management of polyomavirus-associated nephropathy in renal transplant recipients *Nat. Rev. Nephrol* April 2012. doi:10.1038/nrneph.2012.64



EBV REACTIVATION/PTLD MANAGEMENT

- Reactivation as defined by: UNC laboratory cut off for EBV PCR >250 copies/mL
    - If EBV PCR >250 copies/mL, serial EBV PCRs should be conducted every two weeks until two consecutive PCRs <250copies/mL
- EBV monitoring:
    - All EBV D+/R- recipients will be monitored with EBV viral load (blood, PCR) every 2 weeks for 3 months, then monthly for remainder of first year.
    - If an EBV D+/R- recipient receives a lymphocyte-depleting agent for treatment of rejection, then EBV viral load monitoring should be restarted every 2 weeks for 3 months, then monthly for additional 3-9 months (depending on treating provider preference).
    - If the EBV viral load is positive, obtain a transplant ID consult.

*Routine EBV monitoring is not warranted on asymptomatic patients who are R+ or D-/R- and should not be done routinely.

- Due to heightened risk of PTLD in the setting of EBV reactivation patients should be closely monitored for new onset malaise, weight loss, abdominal pain, fever, headaches and/or lymphadenopathy
    - Imaging and oncology consult are recommended in the event of increasing EBV PCRs with or without the above symptoms
- General principles for PTLD management:
    - Reduction of immunosuppression
        - Common modifications of regimens in the setting of PTLD:
            - CNI monotherapy
            - Consider replacing current agent(s) with sirolimus
            - Complete cessation of immunosuppression during active chemotherapy cycles
    - Chemotherapy/radiation
        - Most Common Chemotherapy Regimen: R-CHOP
    - Surgical intervention

PHARMACOGENETIC INFORMATION

If pharmacogenomics profile available, the following will take place:

Single Nucleotide Polymorphism	Enzyme activity: drug affected	Alteration of therapy
CYP3A5 *3/*3	Normal enzyme activity: standard of care Nonexpressors	Initiate tacrolimus at 0.1 mg/kg/day in 2 divided dose
CYP3A5*1/*1 or CYP3A5 *1/*3	Increased enzyme activity: calcineurin inhibitor Expressors	Initiate tacrolimus 0.2 mg/kg/day in 2 divided doses; max total daily dose of 20 mg/day

NEUTROPENIA GUIDELINE

Grade 1 or 2 (ANC <2000/mm^3 or <1500/mm^3)

- Consider 50% mycophenolate acid (MPA) derivative dose reduction
- Verify valganciclovir is dose adjusted for renal function
  Consider stopping SMZ/TMP if within 1 month of planned stop date

Grade 3 or 4 (ANC <1000/mm^3 or <500/mm^3)

- Hold MPA. Restart 50% dose at day 5 or when ANC >2000
- Verify valganciclovir is dose adjusted for renal function
- Consider stopping SMZ/TMP if within 1 month of planned stop date
- Give G-CSF (Granix® (tbo-filgrastim))
    - Dosing: 300 mcg for pt <70 kg and 480 mcg for pt >70 kg; dose as needed or daily until ANC >2000, maximum of 3 consecutive daily doses
- Monitor ANC daily before doses 2 and 3, then every other day until ANC >2000. Recheck ANC 1-2 weeks after last G-CSF dose.

APPENDIX A:

I: Tacrolimus Formulations and Conversions

Formulations

- Astagraf XL®
  - Capsules: 0.5 mg, 1 mg, 5 mg
- Prograf®
  - Oral
    - Capsules: 0.5 mg, 1 mg, 5 mg
    - Liquid suspension: 1 mg/mL
  - Sublingual
    - Use immediate release capsules
  - Intravenous: 5 mg/mL
- Envarsus XR®
  - Tablets: 0.75 mg, 1 mg, 4 mg

Conversions

- Sublingual tacrolimus
  - 50% of the oral dose given sublingually
    - Example: 8 mg PO BID = 4 mg SL BID
- Oral liquid tacrolimus
  - 100% of the oral dose given per tube
    - Example: 8 mg PO BID = 8 mg per NG tube BID
- Intravenous tacrolimus (**Contact Transplant Pharmacist prior to ordering or converting to IV tacrolimus**)
  - For an established patient, convert 1/5 of total daily tacrolimus immediate release dose to IV continuous infusion (CI), to be infused over 24 hours
  - For a new patient, dose at 0.03-0.05 mg/kg/day or dose as 1 mg IV CI over 24 hours
  - Transitioning to oral from CI, the first dose of oral therapy should be given 8-12 hours after discontinuation of IV infusion
  - Tacrolimus levels should be drawn through a separate line than the line running the tacrolimus infusion or the infusion will need to be stopped and flushed prior to drawing a level
- Prograf® to Astagraf XL®
  - Recommended conversion per package insert labeling is 1:1
    - Example: Prograf® 8 mg PO BID = Astagraf XL® 16 mg PO daily
- Prograf® to Envarsus XR®
  - Recommended conversion per package insert labeling:
    - 80% of the pre-conversion daily dose of tacrolimus immediate release formulation
  - Based on studies, the conversion is as follows:
    - 70% of the pre-conversion daily dose of tacrolimus immediate release formulation for non-African American recipients
    - 85% of the pre-conversion daily dose of tacrolimus immediate release formulation for African American recipients
- Astagraf XL® to Envarsus XR®
  - Requires lowering total daily dose by at least 20%

NOTE: Envarsus XR® and Astagraf XL® are <u>not</u> interchangeable

Administration

- Prograf® may be consistently given with or without food

- Astagraf XL® should be given on an empty stomach in the morning only

- Envarsus XR® should be given on an empty stomach in the morning only

Administering sublingual tacrolimus:

Tacrolimus capsules should be utilized for sublingual administration.

1. Personnel handing the capsules should use proper personal protective equipment (minimum of gloves and mask) normally used to handle biohazardous medications (if contact occurs, the skin should be washed thoroughly)
2. Have patient drink water to make mouth moist or swab mouth
3. Capsule should be open at the bedside
4. Hold capsule vertically with the smaller end down (you should be able to read the strength)
5. Tap capsule gently, forcing powder contents to bottom of capsule
6. Pinch off the top (larger) part of the capsule (all powder should be in the small end of capsule at this point)
7. Pour powder under the patient's tongue and allow to absorb (at least 15 minutes)
8. Instruct patient not to swallow during drug administration
9. Administer only one capsule at a time, allowing powder to completely dissolve before administering the next capsule
10. Wait at least 30 minutes before administering other medications, food, or drink
11. Empty capsule can be discarded in the medical waste bin

References:

1. Prograf®. 2013; Available at: https://www.astellas.us/docs/prograf.pdf. Accessed June 10, 2016
2. Envarsus® XR 2015; Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206406s000lbl.pdf Accessed June 10, 2016
3. Gaber AO, Alloway RR, Bodziak K, Kaplan B, Bunnapradist S. Conversion from twice-daily tacrolimus capsules to once-daily extended release tacrolimus (LCPT): A phase 2 trial of stable renal transplant recipients. Transplantation. 2013. 96: 191-7
4. Bunnapradist S, Ciechanowski K, West-Thielke P, et al. Conversion from twice-daily tacrolimus to once-daily extended release tacrolimus (LCPT): the phase III randomized MELT trial. Am J Transplant. 2013. 13: 760-9.
5. Budde K, Bunnapradist S, Grinyo JM, Ciechanowski K, Denny JE, Silva HT, Rostaing L; Envarsus study group. Novel once-daily extended-release tacrolimus (LCPT) versus twice-daily tacrolimus in de novo kidney transplants: one-year results of Phase III, double-blind, randomized trial. Am J Transplant. 2014;14:2796-806
6. Langone A, Steinberg SM, Gedaly R, Chan LK, Shah T, Sethi KD, Nigro V, Morgan JC; STRATO Investigators. Switching study of kidney transplant patients with tremor to LCP-Tacro (STRATO): an open-label, multicenter, prospective phase 3b study. Clin Transplant. 2015;29:796-805
7. Astagraf® XL 20; Available at https://www.astellas.us/docs/AstagrafXL.pdf. Accessed June 10, 2016

II: Conversions from Tacrolimus, Cyclosporine, Sirolimus, and Everolimus

Contact transplant pharmacist prior to converting from one immunosuppression to another

A. Tacrolimus to/from Cyclosporine (CNI change)
    a. No tapering or overlap is required when converting from one CNI to the other CNI
    b. Start new CNI dose 12 hours after last CNI dose (e.g. tacrolimus given at 6 AM and then start cyclosporine at 6 PM)
    c. Inpatient: CNI trough level should be drawn prior to 3rd-4th dose of new CNI agent; will not need CNI levels of old agent; CNI levels of the new agent can be drawn daily or every other day
B. CNI to Sirolimus
    a. Reduce CNI to 50% of the dose and start sirolimus 1 to 2 mg PO daily
    b. Keep sirolimus as the default dose time of noon to avoid DDI with CNI; can start sirolimus on day of decision regardless if reduced the dose of CNI that morning
    c. Once sirolimus reaches >50% of trough goal or at trough goal, discontinue the CNI
    d. Inpatient: sirolimus trough levels should be drawn every 3 days and the first level should be drawn prior to the 3rd dose and then every 3 days
C. Sirolimus to CNI
    a. Start CNI and change dosing time of sirolimus to noon (if not already administered at that time)
    b. Discontinue sirolimus and start CNI the next day

c. Inpatient: CNI trough level should be drawn prior to 4th-5th dose, then daily or every other day levels; check one sirolimus level three days after conversion

D. Everolimus to/from CNI
   a. No tapering or overlap is required when converting from everolimus to a CNI
   b. Start CNI or everolimus dose 12 hours after last CNI or everolimus dose
   c. Inpatient: Everolimus or CNI trough level should be drawn prior to 3rd or 4th dose of new agent; will not need levels from old agent; levels of new agent can be drawn daily or every other day

III. Conversion to Belatacept (not dosing for *de novo* use)

A. Criteria for conversion
   a. Epstein Barr Virus recipient seropositivity
   b. Greater than 6 months post-transplant
   c. Adequate long term IV access
   d. Reliable transportation to and from facility or successful establishment of home IV infusion services
   e. Financial clearance

B. Belatacept conversion dosing
   a. Belatacept (Nulojix™) 5mg/kg (total body weight, rounded to the nearest 50 mg) on days 1, 15, 29, 43, 57, then every 28 days
   b. CNI or m-TOR dosing for conversion from CNI or m-TOR to belatacept
      i. Dose adjusted to therapeutic goal
      ii. Continue 100% of dose on Day 1 of conversion
      iii. Reduce to 40-60% of dose on Day 15
      iv. Reduce to 20-30% of dose on Day 23
      v. Discontinue on Day 29 and thereafter
   c. Belatacept to CNI or m-TOR
      i. Start CNI two weeks after last infusion of belatacept

C. Other maintenance therapy
   a. Mycophenolate mofetil (CellCept®) and mycophenolic sodium (Myfortic®)
      i. CellCept®: 750 mg BID
      ii. Myfortic®: 540 mg BID
   b. Prednisone
      i. Start prednisone 5 mg PO daily

References:
1. Rostaing L, Massari P, Garcia VD, et al. Switching from Calcineurin Inhibitor-based Regimens to a Belatacept-based Regimen in Renal Transplant Recipients: A Randomized Phase II Study. Clin J Am Soc Nephrol. 2011;6:430-439.
2. Nulojix®. 2014; Available at: http://packageinserts.bms.com/pi/pi_nulojix.pdf. Accessed June 23, 2016.

III. Mycophenolate mofetil (CellCept®) and Mycophenolic Sodium (Myfortic®) Dosage Equivalents

Mycophenolic Acid Derivative Formulation	Standard	High Dose	Low Dose
MMF (CellCept®)	750 mg BID	1000 mg BID	500 mg BID
MPS (Myfortic®)	540 mg BID	720 mg BID	360 mg BID

IV: Equivalent goal levels of cyclosporine, tacrolimus, sirolimus:

Organ	Agent	Goal Month 0-3	Goal Month 4-12	Goal Month >12
KIDNEY	Tacrolimus	8-10 ng/mL	6-8 ng/mL	5-7 ng/mL
	Cyclosporine	200-250ng/mL	150-200 ng/mL	100-150 ng/mL

	Sirolimus*	8-10 ng/mL	6-8 ng/mL	4-6 ng/mL
	Sirolimus +Tac¥	Tac 4-6 ng/mL Sirolimus 4-6 ng/mL	Tac 3-5 ng/mL Sirolimus 3-5 ng/mL	Tac 2-4 ng/mL Sirolimus 2-4 ng/mL
KIDNEY PANCREAS/ PANCREAS ALONE	Tacrolimus	10-12 ng/mL	7-9 ng/mL	6-8 ng/mL – barring mycophenolate is >500 mg BID
	Cyclosporine	250-300 ng/mL	150-250 ng/mL	125-175 ng/mL
	Sirolimus*	10-12 ng/mL	7-9 ng/mL	6-8 ng/mL – barring mycophenolate is >500 mg BID
	Sirolimus +Tac¥	Tac 4-6 ng/mL Sirolimus 4-6 ng/mL	Tac 3-5n g/mL Sirolimus 3-5 ng/mL	Tac 2-4 ng/mL Sirolimus 2-4 ng/mL
LIVER	Tacrolimus	8-10 ng/mL	6-8 ng/mL	4-6 ng/mL
	Cyclosporine	200-250 ng/mL	150-200 ng/mL	100-150 ng/mL
	Sirolimus*	8-10 ng/mL	6-8 ng/mL	4-6 ng/mL
	Sirolimus +Tac¥	SUM= 8-10 ng/mL	SUM= 6-8 ng/mL	SUM= 4-6 ng/mL

*Sirolimus dosing above not intended for patients with malignancy or concomitant CNI use. For malignancy goal of sirolimus should not exceed 6-8 in combination with reduced overall immunosuppression

¥Sirolimus + Tac: Combination is synergistically nephrotoxic, reserve for patients with severe toxicities to monotherapy with either agent

APPENDIX B: Common Drug Interactions with Immunosuppression

CYP3A4 Inhibitors	**CYP3A4 Inducers**
Cardiac: Diltiazem, Verapamil**,** Amiodarone, Dronedarone, Erythromycin, Azithromycin, Clarithromycin, Boceprevir, Telaprevir, Ritonavir	**Anti-Epileptics**: Carbamazepine, Phenobarbital, Phenytoin
AntiFungal: Fluconazole, Itraconazole, Voriconazole, Ketoconazole, Posaconazole, Isavuconazole	**Antibiotics**: Rifampin, Rifabutin
Dietary: Grapefruit	**Herbal**: St. John's Wort

APPENDIX C: Common Drug Interaction with Anti-retroviral and Immunosuppression

ART	Interacting Transplant Medications	Monitoring Considerations	Additional Care Measures
NRTIs (Nucleoside reverse transcriptase inhibitor)			
Zidovudine (ZDV) (also Combivir and Trizivir)	Mycophenolate	Potential for antagonism	Try to avoid use of ZDV with MMF. Monitor for reduced effects of MMF
NNRTIs (Non-nucleoside reverse transcriptase inhibitor)			
Efavirenz (EFV)	CsA, TAC, mTORs, steroids	EFV induces P450 so will decrease CsA, TAC, mTORs, and steroids	Monitor for rejection
Etravirine (ETV)	CsA, TAC, mTORs, steroids	ETV inhibits P450 3A and induces 2C9 and 2C19; may decrease CsA, TAC, mTORs, and steroids	Monitor for rejection
Rilpivirine (RPV)	CsA, TAC, mTORs, steroids	RPV is a CYP 3A4 substrate, but is not an inhibitor or inducer	
PK Enhancers			
Cobicistat (COBI)	CsA, TAC, mTORs, steroids	CYP 3A inhibitor, so may increase CsA, TAC, mTORs, and steroids	Monitor for increased toxicity of CsA, TAC, mTORs, steroids
PIs (Protease Inhibitor)			
Atazanavir (ATV) Atazanavir/ritonavir (ATV/RTV) Atazanavir/cobicistat (ATV/COBI)	- CsA, TAC, mTORs, steroids - Mycophenolate (?)	ATV inhibits P450 so may increase CsA, TAC, mTORs, and steroids; also inhibits UGT 1A1 so may (but not likely) increase MMF (UGT 1A9 substrate)	Monitor for increased toxicity of CsA, TAC, mTORs, steroids, and MMF
Darunavir/ritonavir (DRV/RTV)	CsA, TAC, mTORs, steroids	DRV/RTV inhibits P450 so may increase CsA, TAC, mTORs, and steroids	Monitor for increased toxicity of CsA, TAC, mTORs, and steroids

Darunavir/cobicistat (DRV/COBI)			
Lopinavir/ritonavir (LPV/RTV)	CsA, TAC, mTORs, steroids	LPV/RTV inhibits P450 3A and induces 1A2, 2C9, and 2C19	Monitor for increased toxicity of CsA, TAC, mTORs, and steroids
Ritonavir (RTV)	CsA, TAC, mTORs, steroids	Low doses of RTV (100-200mg QD-BID) potently inhibits P450 so will increase CsA, TAC, mTORs, and steroids	Monitor for increased toxicity of CsA, TAC, mTORs, and steroids

APPENDIX D: Common Drug Interaction with Antiretroviral and Common Medications Used Post-transplantation

Other Therapies	**Interacting ART**	**Monitoring Considerations**	**Additional Care Measures**
		Antiepileptics	
Phenytoin, Phenobarbital, carbamazepine, oxcarbazepine	NNRTIs and PIs CsA, TAC, mTORs	- These antiepileptics greatly decrease rx concentrations - Monitor trough values of anti-rejection meds closely	Avoid concomitant use with ARTs
		Antifungals	
Ketoconazole, itraconazole	NNRTIs and PIs CsA, TAC, mTORs	- Keto and itra may increase ART concentrations and vice versa - Will increase levels of anti-rejection meds	- Monitor for toxicity of both azole and ARTs - Monitor CSA, TAC, & mTORs troughs closely; reduce TAC/CsA/mTOR by 50% for itraconazole

Voriconazole, posaconazole, *isavuconazole	NNRTIs and PIs CsA, TAC, mTORs	- These agents may increase ARTs and anti-rejection meds - NNRTIs may decrease these agents - PIs may increase these agents	- If concomitant use is required consult with ID - Avoid use with mTORs, if possible. If not, reduce mTORs to 80% of starting dose - Decrease CSA or TAC initially to 50% of starting dose - *For isavuconazole, reduce CsA or TAC dose by ~25%
Fluconazole	CsA, TAC, mTORs	Fluc will increase antirejection meds	- Decrease doses of CsA, TAC, or mTORs to 50% of starting doses if on ≥400 mg (or renally dosed equivalent) - For doses <200 mg, can monitor trough levels closely or empirically decrease doses by <50%
<u>Antihypertensives</u>			
Calcium channel blockers (CCBs)	ATV	ATV can prolong QT interval.	If used concomitantly with CCB, baseline EKG is suggested
Non-dihydropyridine CCBs	CsA, TAC, mTORs	Diltiazem and verapamil can increase levels	Monitor trough levels closely
Beta-blockers (e.g. metoprolol, propranolol)	PIs (especially RTV)	PIs may increase some beta-blockers	Atenolol is OK to use

Antituberculosis Meds			
Rifampin (RIF)	NNRTIs and PIs CsA, TAC, mTORs	RIF will decrease these meds	- If use is required, consult with ID - Monitor anti-rejection trough levels closely - Increase dose of raltegravir to 800 mg BID
Rifabutin (RBT)	NNRTIs and PIs CsA, TAC, mTORs	- RBT usually has little effect on ARTs - NNRTIs decrease RBT - PIs increase RBT - May decrease levels of anti-rejection meds	- Dose adjustments for RBT are needed for concomitant use with NNRTIs and PIs - Consult ID - Monitor trough levels closely with anti-rejection meds
Asthma Therapies			
Inhaled or nasal steroids	PIs (especially RTV), COBI	PIs can greatly increase inhaled steroid concentrations systemically (most data with fluticasone)	If inhaled steroid needed, consider beclomethasone or budesonide (no data for this). If fluticasone required, monitor cortisol regularly.
Long acting beta blockers (LABA) (e.g. salmeterol, formoterol)	PIs (especially RTV)	PIs may increase LABAs	Monitor for toxicity of LABA or avoid concomitant use
Benzodiazepines (BDZ)			
Midazolam, triazolam	PIs (especially RTV)	PIs are contraindicated with these BDZs	Avoid concomitant use
Erectile Dysfunction (ED) Meds			

Sildenfafil, Tadalafil, Vardenafil	PIs (especially RTV) CsA, TAC, mTORs	All of these medications will increase concentrations of ED medications	Dose modifications for ED meds are required. Do not start at more than 25 mg of sildenafil (or its equivalent)
<u>HMG CoA reductase inhibitors</u>			
Simvastatin, lovastatin, fluvastatin, pravastatin, atorvastatin	Efavirenz, , and etravirine (NNRTIs)	EFV and ETR may decrease exposure to statins (except rosuvastatin).	Higher doses of statins will likely be needed
Simvastatin, lovastatin, fluvastatin, atorvastatin	PIs (especially RTV)	PIs greatly increase these particular statins	See package insert and contact pharmacist for appropriate and max doses of specific statin with PIs
Rosuvastatin	PIs	PIs greatly increase statins	- 5 mg/day and not exceeding 10 mg/day when combined with atazanavir/ritonavir or lopinavir/ritonavir - US labeling for the fixed-dose atazanavir/cobicistat product also recommends a maximum rosuvastatin dose of 10 mg/day during combined therapy
Simvastatin, lovastatin, fluvastatin, atorvastatin	CsA, TAC, mTORs	These medications may increase exposure to statins.	- Do not use more than 40 mg of any of these - Okay to use atorvastatin 40 mg unless on PI (see above) - Simvastatin is contraindicated with CsA