UCSF Kidney Transplant Service Guidelines 2015

Inpatient Transplant Team	
Medical	**Surgical**
Transplant Nephrology Attending Transplant Nephrology Fellow General Nephrology Fellow Nurse Practitioner	Transplant Surgery Attending Transplant Surgery Fellow Surgical Residents Surgical Interns
Ancillary Services	**Other**
Pharmacist Social worker Dietitian Nurse	Medical student Pharmacy resident/ student NP fellow/ student Nursing student Visitors (e.g., visiting doctors)

KTU Intern Daily Schedule:
6:30 AM- Get sign out from night float get pager and spectra-link phone.
7-10 AM- Go see the patients on list. Get orders for the day ready (ex. POD 1 orders, thymoglobulin, etc.), discharge summaries, review patient list with fellow who will typically call you. Touch base with the NP when she arrives to split up the am work.
9:30-9:45 AM- print out lists and cover page. Make 12 copies.
10:00 AM- Multi-disciplinary rounds typically run by fellow. Discuss non-medical issues
10:15-12:00- Medical rounds. Surgical interns and NP present patients. When you're not presenting enter orders in Apex and take notes on your sign-out as you need to update the list after rounds.
1:30-2:00 PM- Get drug levels for each patient; have numbers ready to review with the fellow in the afternoon. You must review levels prior to 5 pm so the pharmacy has time to make changes in PM doses.
2:00-6 PM- Update list with any dose changes in meds and plans for the day, culture results, ultrasounds, new admissions, etc.
6:00 PM- Sign out to the night float

Foley Removal:
1. Check with surgeon if he/ she prefers Foley catheter to be removed on POD 2 or 3
2. Enter order in Apex to check for post-void residual (PRV) every hour x3
3. Notify physician if PVR >100ml for new transplants and >50ml for old transplants

Steroids:

Corticosteroids have been an integral part of the immunosuppressive regimen since the early days of transplant. However, chronic steroid use has been associated with significant complications such as HTN, glaucoma, cataracts, PUD, osteoporosis, obesity, and DM. Steroid withdrawal is associated with fewer metabolic complications but a higher risk of early acute rejection so it is preferably avoided in high immunologic risk patients such as those with a history of prior transplantation, high PRA or DSA, and African Americans. We also tend to keep patients with ESRD secondary to GN and those with DGF on steroids.

Induction therapy:

1. Refers to administration of an intensive immunosuppressive regimen during perioperative period
2. Has shown to reduce the frequency of acute rejection

Causes of Sensitization:

1. Exposure results from
    a. Blood transfusions
    b. A previous transplant
    c. Pregnancy, the mother is exposed to the father's antigens, which expressed on the cells of the developing baby
    d. Viral/bacterial infection – relatively rare
    e. Vaccines?

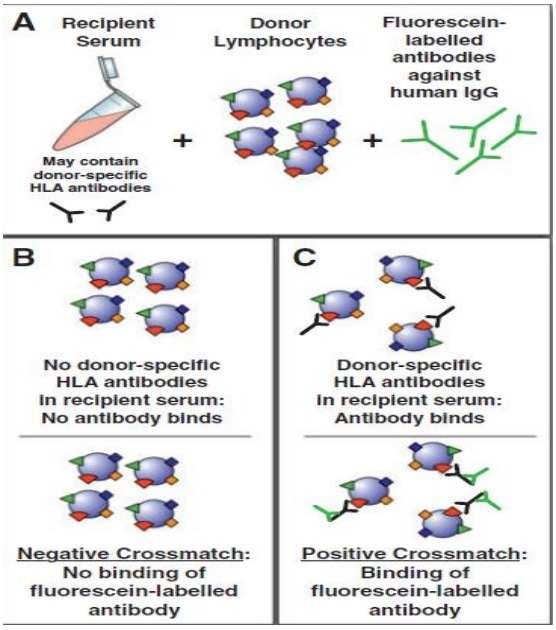
Panel Reactive Antibody (PRA):

1. Assesses the level and range of anti-HLA antibodies in the blood using a cytotoxicity test (recipient's serum is mixed with a panel of lymphocytes from random people)
2. Score is based on % of wells with positive cytotoxic readout and can be 0-100%
3. Roughly represents the percentage of US population to which the potential recipient would react.

Calculated Panel Reactive Antibodies (cPRA):

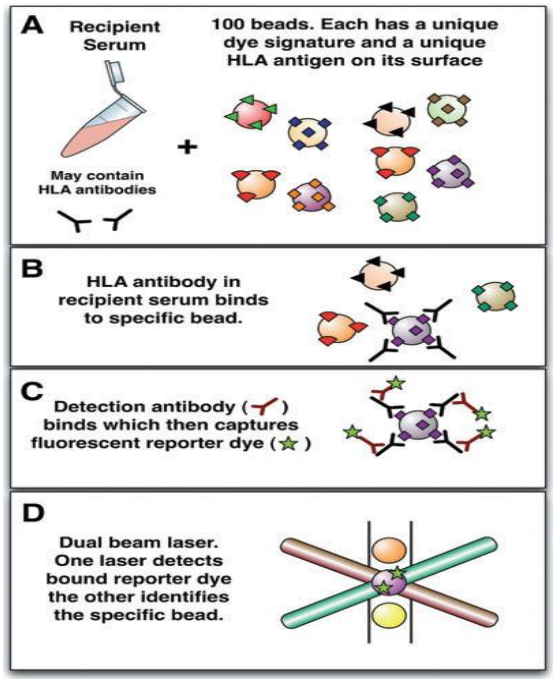
1. The specificity and strength of anti-HLA antibody in a patient's serum is measured using beads coated with single antigens
2. Transplant center-specific threshold is set to define which HLA antigens will be deemed unacceptable (Antibodies below the threshold are often reported with the confusing designation of "CPRA: pos" rather than 0%)
3. Any HLA antibody with a value above the set threshold is entered into UNet. The UNet calculator calculates a value for the PRA based on the unacceptable antigens entered and the known frequency of those HLA antigens in 10,000 recently added deceased donors.
4. The cPRA therefore gives a measure of the chances of a patient finding a compatible donor in the donor pool

Flow Crossmatch:



Recipient serum potentially containing donor specific anti-HLA antibodies is added to donor T or B lymphocytes, along with fluorescein-labeled antibodies against human IgG (A). If donor-specific antibodies are not present, no binding occurs and the result is deemed negative (B). If donor-specific anti-HLA antibodies bind to the lymphocytes these can then bind the fluorescein-labeled antihuman IgG antibody, and this will be detectable by flow cytometry (C). The strength of the fluorescence can be measured and expressed as 'channel shifts' or MESF above the control sample

Virtual Crossmatch/Luminex



Each bead is coated with a set of antigens (screening beads) or for more precise detail, with a single antigen (single antigen beads). A unique dye signature (up to 100) specifies the identity of each bead (A). If anti-HLA antibodies are present these will bind to the appropriate bead (B) and detection antibody can subsequently bind and capture a reporter dye (C). Each unique bead can then be interrogated for the presence of the reporter dye on its surface using a dual beam laser (D). A profile of antibodies can thus be identified in the recipient and compared with the known HLA identity of any potential donor, allowing a prediction of the crossmatch result.

Immunosuppression Protocols

Immunologic Risk	
Low	**High**
1. First Transplant 2. Low cPRA	1. Repeat transplant 2. African American 3. High PRA 4. Positive DSA/ positive cross-match ± IVIG desensitization 5. ABO incompatibility

I. IL2R ANTIBODY INDUCTION

DAY	Prednisone	CNI	MMF/MPA	Basiliximab
0	500 mg		1 gm/720mg bid	20 mg
1	250 mg	Start in AM tacrolimus at ≤ 0.1 mg/kg bid	↓	
2	125 mg	↓	↓	
3	60 mg	↓	↓	20 mg
4	30 mg	↓	↓	
5	Stop or taper by 10 mg/week to 5 mg/day depending on immunologic risk	↓	↓	

Target Population

Patients with low immunological risk who are going to be on a CNI based regimen

II. THYMOGLOBULIN INDUCTION

DAY	Prednisone	CNI	MMF/MPA	Thymo (3-6 mg/kg)
0	500 mg		1gm/720mg pre-op	1.5 mg/kg
1	250 mg	Start	500 mg/360 mg bid	1-1.5 mg/kg
2	125 mg	when ΔScr by 25%		↓
3	60 mg			
4	30 mg than taper by 10 mg/week to 5 mg/day		Increase to 1 gm/720 mg bid when Thymo D/C if WBC OK	Target total dose of 3-6 mg/kg

Target Patients	
3 mg/kg	**6 mg/kg**
1. DGF 2. High immunologic risk but increased risk of complications	1. High immunologic risk 2. Pedi-en-bloc recipients

Steroid Plan:

1. Those with low immunologic risk who have DGF can be taken off steroids once graft function is established
2. Stop
    a. Patients with low immunologic risk who have immediate graft function
    b. Patients with increased cardio-metabolic risk

III. NO ANTIBODY INDUCTION

DAY	Prednisone	CNI	MMF/MPA
0	500 mg		1 gm/720 mg bid
1	250 mg	Start in AM	
2	2mg/kg	Full dose bid	
3	2 mg/kg		
4	Taper by 20 mg/day to 0.5 mg/kg then taper by 10mg/week until 5-10 mg/day		

Target Population

Rare – very low immunologic risk

IV. INDUCTION FOR BELATACEPT BASED REGIMEN

DAY	Prednisone	MMF/MPA	Thymo	Belatacept
0	500 mg	500mg/360mg bid	1.5 mg/kg	
1	250 mg		1-1.5 mg/kg	10mg/kg/dose
2	125 mg	Increase to 1 gm/720 mg bid	Target total dose of 3 mg/kg	
3	60 mg			
4	30 mg than taper by 10 mg/week to 5 mg/day			10mg/kg/dose on POD 4-7 then per infusion clinic schedule

VI. REJECTION THERAPY

A. Borderline rejection and non-specific inflammation)

Oral Prednisone Pulse

Day 1	2 mg/kg x 3 days
Day 4	1 mg/kg x 3 days
Day 7	40 mg/day taper by 10 mg every 3 days until 5 mg/day

B. Type 1a acute cell-mediated rejection

Solumedrol Pulse

Day 1	500 mg IV
Day 2	500 mg IV
Day 3	500 mg IV
Day 4	2 mg/kg
Day 5	Taper by 20 mg every day until 5 mg/day

C. Type 1b and greater and/or steroid resistant rejection

Thymoglobulin Therapy

DAY	Thymoglobulin	Prednisone
1	1.5 mg/kg	500 mg
2	1.5 mg/kg	250 mg
3	1.5 mg/kg	125 mg
4	1.5 mg/kg	60 mg
5	STOP	30 mg taper by 10 mg/week until 5 mg/day

D. Acute antibody mediated rejection:

Day	Steroid	Plasmapheresis	IVIG	Rituxan
1	500 mg	X	0.1g/kg	–
2	250 mg	X	0.1 g/kg	–
3	125 mg	X	1g/kg (max 70g)	
4	60 mg once, then 30 mg daily taper by 10mg/week until 5mg/day		1g/kg (max 70g)	375 mg/m^2 (after IVIg)

*Rituximab 1g IV x1 after IVIG is completed. Arrange 2nd dose 2 weeks later

E. Chronic active antibody mediated rejection

Day	Steroid	IVIG	Rituxan
1	500 mg	1g/kg (max 70g)	
2	250 mg	1g/kg (max 70g)	375 mg/m^2 (after IVIg)
3	125 mg	-	
4	60mg once, then 30mg daily taper by 10mg/week until 5mg/day		

*Rituximab 1g IV x1 after IVIG is completed. Arrange 2nd dose 2 weeks later

F. <u>KTU Eculizumab (Soliris) guidelines for Antibody Mediated Rejection (AMR)</u>

Patients with biopsy proven acute AMR should receive standard therapy

Day	Steroid	Plasmapheresis	Rituximab	IVIg
1	500 mg	X		*0.1g/kg
2	500 mg	X		*0.1 g/kg
3	500mg	X		1g/kg (max 70g)
4	1 mg/kg taper by 20mg every day until 5 mg/day		375 mg/m^2 (after IVIg)	1g/kg (max 70g)

* At the discretion of treating physician

Notes:

Complete plasmapheresis treatments before giving rituximab or high dose IVIg. Arrange 2nd dose in 1 week later.

1. Treatment response
    a. Defined at 1 week post standard inpatient treatment for acute AMR
    b. Responder: Improvement in SCr to baseline or to ≤50% of peak value during episode of acute rejection
2. Treatment with Eculizumab
    a. Indication: ONLY if any one of the following is present
        i. TMA on biopsy along with acute AMR

ii. Refractory acute AMR: Defined as biopsy showing acute AMR in a patient who did not respond to standard therapy (see definition of treatment response above)
iii. Note: Presence of DSA by itself should not be used to guide the dosing or re-dosing of eculizumab

b. Vaccination
   i. Ensure that patient is current with adult vaccination schedule (particularly *Streptococcus pneumoniae* and *Neisseria meningitidis*).
   ii. If the patient has not been previously vaccinated against encapsulated organisms
      1. Vaccinate prior to first infusion of eculizumab
      2. Prophylaxis with ciprofloxacin 500 mg twice daily (adjust per renal function) for 1 month after the last dose of eculizumab

c. Dosing
   i. Recycle standard therapy of acute AMR.
      1. If plasmapheresis is needed, administer it PRIOR to giving eculizumab. AVOID plasmapheresis while on eculizumab.
   ii. Initial dose: 1200mg.
   iii. Second dose (900mg) may be used 1 week later if there is no clinical improvement
   iv. Supplemental dose of 600 mg is required post-plasmapheresis (avoid concomitant plasmapheresis if possible)

VII. Drug Dosing and Monitoring

A. CNI

Tacrolimus Maintenance

Starting dose 0.1 mg/kg bid, often started at dose 50% of targeted dose

Target level (assuming no rejection and/or toxicity)

1-3 months:	8-12 ng/mL
3-12 months:	6-10 ng/mL
>1year	4-8 ng/mL

Cyclosporine

Starting dose 2.5-5 mg/kg bid

Target trough level

1-3 months:	200-300 ng/mL
3-12 months:	150-250 ng/mL
>1 year	50-100 ng/ mL

Target peak (C2) levels

1-3 months: 1150-1550 ng/mL
3-6 months: 800-1200 ng/mL
6-12 months: 750-900 ng/ml
>1 year >600 ng/ mL

B. MMF/MPA →target dose 1000mg/720mg bid

May increase dose to 1500 mg/1080 mg bid for African-American patients or those with CNI intolerance/low CNI levels

C. Thymoglobulin

Administer in 25 mg increments

Monitor total lymphocyte count daily (CBC with differential)

Target < 100 cells/mm^3

May consider adjusting dose (50% reduction) for:

WBC < 2,000

Platelet count < 70,000

May consider holding dose for:

WBC<1,000 and/or neutropenia

Platelet count <50,000

D. Sirolimus

Starting dose is 3 mg PO daily (no loading dose)

Trough should not be drawn until 4-5 days after initiation of medication

Target trough level:

	With MMF/MPA	With CNI
0-6 months:	8-12 ng/mL	3-6
6-12 months:	6-10 ng/mL	3-6
>1year	4-8 ng/mL	3-6

E. Everolimus

Starting dose is 0.75mg po BID

Target trough level:

With CNI	3-8 ng/mL
With MMF or belatacept	6-10 ng/mL

F. Belatacept

De Novo Belatacept	
Target Population	Exclusion Criteria
Epstein Bar Virus seropositive and 1. Low immunological risk recipients (e.g., cPRA <30% with no DSA) 2. First transplant	1. Enrolled in a clinical trial 2. History of prior transplant 3. Difficult IV access 4. Difficulty with travel 5. Insurance coverage (e.g., high co-pay or not covered) 6. Pedi-En-bloc

The DeNovo Belatacept Target Population

Initial phase:

Day	Belatacept Dose
At the time of transplantation (1st dose)	10 mg/kg
Day 4-7 post-transplant (2nd dose)	10 mg/kg
Day 14 (3rd dose)	10 mg/kg
Day 28 (4th dose)	10 mg/kg
Day 56	10 mg/kg
Day 84	10 mg/kg

Maintenance phase: given every 4 weeks (plus or minus 3 days)

Day	Belatacept Dose
Week 16	5 mg/kg

Concomitant maintenance immunosuppression with belatacept:
MMF or MPA full dose for 28 days then convert to everolimus 0.75 mg bid with 1 week of overlap provided WBC allows (urine pr/cr to be done pre-conversion).
Goal everolimus trough 6-10 ng/mL

Conversion from CNI to Belatacept:

1. Strongly consider conversion in patients with:
    a. Slow graft function/prolonged DGF (need for dialysis or SCr > 2 mg/dL >14 days after transplant) AND
    b. Kidney biopsy negative for rejection and positive for ATN

2. May consider conversion in patients with:
    a. Persistent poor allograft function with significant biopsy-proven vascular disease or IG/TA
    b. Serious adverse effects of CNI(renal toxicity, neurologic side effects, TMA)
    c. New onset diabetes mellitus after transplantation

Conversion Protocol for patients < 6 months post-transplant (except TMA):

CNI	Day	Belatacept Dose	Steroid
50%	0	10 mg/kg	Add 5 mg prednisone daily (if not already on it)
Stop	14	10 mg/kg	
Stop	28	10 mg/kg	
Stop	42	5 mg/kg	
Stop	56	5 mg/kg	
Stop	Monthly*	5 mg/kg	

Conversion Protocol for patients > 6 months post-transplant:

CNI	Day	Belatacept Dose	Steroid
Full dose	0	10 mg/kg	Add 5 mg prednisone daily (if not already on it)
50%	14	5 mg/kg	
Stop	28	5 mg/kg	
Stop	42	5 mg/kg	
Stop	56	5 mg/kg	
Stop	Monthly*	5 mg/kg	

*Note: Round down to the nearest 250 mg vial monthly

Notes on viral prophylaxis and monitoring for patients on belatacept:

1. All patients receiving *de novo* belatacept should receive CMV prophylaxis with valganciclovir (not acyclovir) as noted below in CMV section.
2. All belatacept conversion patients (both <6 months and > 6 month groups) should receive valganciclovir prophylaxis for at least 3 months from time of conversion.
3. All belatacept patients (*de novo* and conversion) should have CMV and EBV PCR check at month 3 and 6 from the start of belatacept.

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CMV Prophylaxis Protocol

CMV Antibody (IgG) Donor (D)/Recipient (R)	**Thymoglobulin**	**Simulect**
D+/R-	Valganciclovir 6 months	Valganciclovir 3 months
D+/R+	Valganciclovir 3 months	Acyclovir 3 months
D-/R+	Valganciclovir 3 months	Acyclovir 3 months
D-/R-	Valganciclovir 3 months	Acyclovir 3 months

***All *de novo* belatacept transplant recipients should receive valganciclovir for at least three months. If thymoglobulin induction is used then follow above thymoglobulin protocol to determine the duration.

Dose adjustments for renal function: Calculating the creatinine clearance is the most accurate method to dose all of these medications. Can substitute eGFR for CrCl.

Acyclovir:

Creatinine Clearance	Dosing
>25 mL/min/1.73 m(2)	800mg PO QID
10-25 mL/min/1.73 m(2)	800mg PO TID
<10 mL/min/1.73 m(2)	800mg PO BID
Intermittent dialysis	800mg PO daily

Valcyte (Valganciclovir):

Creatinine Clearance	Prophylaxis	Treatment
≥60 mL/min	900mg PO daily	900mg PO BID
40-59 mL/min	450mg PO daily	450mg PO BID
25-39 mL/min	450mg PO Q alternate day	450mg PO daily
10-24 mL/min	450mg PO 2/week	450mg PO Q alternate day
Intermittent dialysis	Not indicated 450mg PO 2/week after dialysis	Not indicated 450mg PO after dialysis
CRRT	450mg PO Q alternate day	450mg PO daily

IV Ganciclovir:

Creatinine Clearance	Prophylaxis	Treatment
≥ 70ml/min	5mg/kg Q24H	5mg/kg Q12H
50-60 mL/min	2.5mg/kg Q24H	2.5mg/kg Q12H
25-49 mL/min	1.25mg/kg Q24H	2.5mg/kg Q24H
10-24 mL/min	0.625mg/kg Q24H	1.25mg/kg Q24H
<10 mL/min or HD	0.625mg/kg TIW or Post HD	1.25mg/kg TIW Post HD
CRRT	1.25-2.5mg/kg Q24H	2.5-5mg/kg Q24H

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Pneumocystis jirovecii Pneumonia (PCP) Prophylaxis

Target population:

1. All new transplant recipients
2. Patients receiving prednisone, Solu-medrol pulse or Thymoglobulin for rejection therapy

Duration of Prophylaxis: 6 months

Preferred Agent: **Sulfamethaxazole and trimethoprim (Septra)** DS 800/160mg

a. Dosage for new transplants: Septra DS 1 tab PO daily for 1 month followed by 1 tablet PO QMWF x5 months
b. Dosage for patients receiving Thymoglobulin for rejection: Septra DS 1 tab PO QMWF for 6 months
c. Dosage for other patients: Septra DS 1 tab PO QMWF for 3 months

Alternative agents for those with sulfa allergy:

1. **Dapsone** 100 mg PO daily

G6PD level must be checked before starting dapsone due to risk of hemolytic anemia in patients who are G6D deficient

2. **Atovaquone** 1500 mg PO daily

3. **Pentamidine** 300 mg inhalation monthly

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UTI Prophylaxis

Target population: All new transplant recipients
Duration: 1 months
Preferred Agent: Sulfamethaxazole and trimethoprim (Septra) DS 800/160mg
Dosage: Septra DS 1 tab po PO daily for 1 month followed by 1 tablet po PO QMWF x5 months

Alternative agents for sulfa allergic patients:

1. Ciprofloxacin 250mg PO BID
3. Cephalexin PO 250mg QID

Adult Kidney Transplant Service Guidelines

Prophylactic Therapy against Candidiasis

Target population:

1. All new transplant recipients
2. Patients receiving prednisone, Solu-medrol pulse or Thymoglobulin for rejection therapy

Duration of Prophylaxis: 1 month
Preferred agent: Fluconazole 100mg po weekly
Alternative agents (e.g., if patient is enrolled in a study and study protocol prohibits the use of fluconazole)

1. Nystatin suspension 5ml PO QID swish and swallow
2. Clotrimazole Troches 10mg PO QID

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Prophylaxis for HBc positive Donor

Recipient Serology	Lamivudine duration	Labs
HBs Ab-/HBc-	1 year	6 months & 1year: HBsAg, anti-HBc, anti-HBs
HBs Ab+/HBc -	6 months	6 months: HBsAg, anti-HBc, anti-HBs
HBc+ (Regardless of donor serology)	6 months	6 months: HBsAg, HBV DNA PCR
Chronic HBV	Lifelong **Continue current HBV treatment or Consider switching to entecavir	Every 6 months HBV DNA PCR, liver US

Lamivudine dose adjustment for renal function:

Creatinine clearance	Dose
≥ 50 mL/min	100mg PO daily
30-49 mL/min	100mg PO x1, then 50mg PO daily
15-29 mL/min	100mg PO x1, then 25mg PO daily
5-14 mL/min	35mg PO x1, then 15mg PO daily
<5ml/min or HD	35mg PO x1, then 10mg PO daily

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Latent TB Infection (LTBI)

Screening:

1. PPD (regardless of history of BCG)
2. Symptom review (fever, weight loss, night sweats, cough)
3. Base line chest X-ray
    a. If abnormal consider CT scan
    b. Patients with chest X-ray findings consistent with old or active TB (granulomatous disease or calcifications) should have the following:
        1. 3 sputum samples for AFB smear and culture
        2. Comparison of CXR/CT to prior studies
        3. Consult TB control

Treatment

1. INH 300mg po daily for 9 months with Pyridoxine 50mg PO daily OR
2. Rifampin 600mg daily for 4 to 6 months (for patients with severe liver dysfunction)

Notes:

1. Longer regimens should be considered for immunocompromised patients (9 months treatment decrease risk by 70%; 12 months treatment decreases risk by 90%)
2. Baseline LFT's should be obtained with following up testing at intervals determined by the severity of the baseline abnormality.

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GI Prophylaxis

1. Daily PPI for 6 months then off unless patient has underline GI issues prior to transplant then continue patient's prior regimen.
2. For patients on medication with drug interactions with PPI then can use H2 blocker such as famotidine or ranitidine daily to BID for 6 months then off.

Statin Dosage Adjustment

Background:

The use of cyclosporine has been shown to increase drug levels of most statins, with increases in area under the curve (AUC) concentrations ranging from 2- to 20- fold, depending on the statin tested. The exact mechanism is unknown but it is thought to be related to competition for CYP450 3A4 enzyme metabolism. This results in increased statin drug levels potentially enhancing their toxicity (myopathy, elevated CPK, rhabdomyolysis). Several statins are not metabolized via this pathway (ex. fluvastatin and pravastatin) and may be less likely to have elevated drug levels when used in conjunction with cyclosporine.

The issues associated with tacrolimus and statins may be different. The affinity of tacrolimus for CYP3A enzymes in the liver and small intestine is similar to those of lovastatin and simvastatin and molar concentrations at the drug interaction sites can be expected to be similar. Tacrolimus therefore seems to affect lovastatin and simvastatin pharmacokinetics to a significantly lesser extent than cyclosporine.

Statin	**Dose Adjustment on CSA**	**Dose Adjustment on Tac**
Pravastatin	No dose adjustment	No dose adjustment
Fluvastatin	No dose adjustment	No dose adjustment
Simvastatin	Contraindication	Reduce dose by 50%
Lovastatin	50% reduction from baseline dose	Reduce dose by 50%
Atorvastatin	50% reduction for doses >40mg/day with a max dose of 40mg/day	Reduce dose by 50%
Pitavastatin	Contraindication- change to a different statin	Contraindication- change to a different statin
Rosuvastatin	Reduce to a max daily dose of 5mg/day	Reduce to a max daily dose of 5mg/day

No dose adjustments required for the lowest tablet size.
Once stable and 6 months post-transplant may increase statin if needed while on Tac

References:

Christians U, et al. Mechanisms of Clinically Relevant Drug Interactions Associated with Tacrolimus. Clin Pharmacokinet 2002; 41:813-851.

Neuvonen PJ, et al. Drug Interactions with Lipid-lowering Drugs: Mechanisms and Clinical Relevance. Clin Pharmacol Ther 2006; 80:565-581.

Hurst FP, et al. Incidence, predictors and associated outcomes of rhabdomyolysis after kidney transplantation. Nephrol Dial Transplant 2009; 24:3861-3866.

Adult Kidney Transplant Service Guidelines

Protocol for ABO Incompatible Kidney Transplantation at UCSF

- All donor recipient combinations
- **For sensitized patients: DSA neg (MFI 500) and neg T and B cell Flow Cross Match**
- Room temp titers = IgM, Indirect Coombs titers = IgG (AHG, these are more important to follow)
- baseline IgG ABO titers ≤ **1:512**, titers at time of transplant **< 1:16**

Table 1: Schedule of Events

Day	-16	-14	-12	-10	-8	-6	-4	-2	-1	Txp	1	2	3	4	5	6	7	8	9	10
	Tu	Th	Sa	M	W	F	Su	Tu	W	Th	F	Sa	Su	M	Tu	W	Th	F	Sa	Su
PP	X*	X*	X*	X*	X*	X*	X	X				X		X		X*		X*		
Rituxan									X											
Thymo										X	X	X	X							
Steriods											→	→	→	→	→	→	→	→	→	→
Prograf				→	→	→	→	→	→	Hold	→	→	→	→	→	→	→	→	→	→
MMF				→	→	→	→	→	→		→	→	→	→	→	→	→	→	→	→

*As needed according to Table 2

PP = Plasmapheresis MMF = mycophenolate mofetil

Table 2. Pre- and Post-Transplant PP Schedules According to Initial ABO Titers (IgG)

	Number of Treatments	
Initial ABO Titer (IgG)	**Before Transplant**	**After Transplant**
< 1:16	**2**	**2**
1:16	**2**	**2**
1:32	**3**	**3**
1:64	**4**	**3**
1:128	**5-6**	**3**
1:264	**7-8**	**4**
1:512	**9-10**	**4**

Pre-transplant:

- **MMF start 10d before txp at 2g/day**
- **FK start 10 d before txp at 2mg PO bid. hold dose morning of surgery**
- ABO titers at baseline, before and after each PP. **Aim for IgG titers <1:16 prior to txp.**
- PP (1-1.5 plasma vol or 40-60ml/kg exchange/session) on above days – this may be shortened in pts with lower titers (see table 2). Replace with 5% albumin after each PP, give low titer AB FFP for d-1 PP. **We may substitute IVIG 100mg/kg for post-PP replacement.**
- PP will be performed on 11M on an outpt. basis on non-dialysis days
- **Rituximab 375mg/m2 on d-1**

Day of Surgery -> Post-op:

- Check INR and fibrinogen preop. If INR> 1.6-1.7 or fibrinogen low, TF 2U **low titer AB** type FFP – orders for the lab tests and T&C for FFP will need to be included in prepare order sets
- Thymoglobulin (total of 5-6mg/kg) start intraop
- Solumedrol 500 intraop, 250, 2mg/kg, 0.5mg/kg while on thymo, then standard taper
- MMF 1g/d while on thymo, then 2g/d
- FK (0.1mg/kg/d) start on d 1-2

Post Transplant PP and Monitoring:

- Routine post txp PP is performed according to starting titers (see table 2) and up to 4 times after txp on alternating days
- ABO titers at time of txp, before and after each PP, 72h after last PP, weekly thereafter for 4wks, then at 2, 3, 6, and 12 months
- Check titers with each rejection episode
- Biopsies will be performed as clinically indicated
- Biopsies will need to be processed for immunofluorescence (C4d) and H&E and evaluated by pathologist for presence of AMR using criteria such as peritubular capillary C4d deposition, **neutrophil infiltrate**, **glomerular and arterial thrombi**, etc. Presence of significant AMR on biopsy should trigger treatment, even in the face of nl function/AB levels (see Fidler, et al. AJT 4:101-107, 2004)

- **Decision to use additional PP should be made based on:**
    1. Creatinine levels
    2. Biopsy results
    3. ABO titers

Treatment of AMR in ABOI kidney recipients

- Mild: every other day PP/IVIG and pulse steroids until decreasing titers and Cr are observed.
- Moderate/Severe: consider daily PP/IVIG, pulse steroids and Rituximab until decreasing titers and Cr are observed.

Adult Kidney Transplant Service Guidelines

Low Level Anti-HLA or Donor Specific Antibody 10-Day Protocol
Cytotoxic Crossmatch Negative (T and B) and Flow Crossmatch Positive (T and / or B)

PREMISE:

- ❑ Cytotoxic crossmatch negativity with flow crossmatch positivity implies low levels of antibody.
    - o Typical channel shifts are < 60.
- ❑ Low levels of antibody can be "reliably" treated with a short course of IVIG during the week preceding transplantation without need for verification that the IVIG "worked."

INCLUSION / EXCLUSION CRITERIA:

A.

- ❑ Age 18 – 70
- ❑ No cardiac Ischemia
- ❑ **NEGATIVE** cytotoxic T and B cell crossmatch
- ❑ **POSITIVE** flow T and / or B cell crossmatch
- ❑ Evidence of Anti-HLA antibody

For any **POSITIVE** flow crossmatch an **AUTO** crossmatch will be performed.

- ❑ If the autocrossmatch is **POSITIVE** and there is **NO** evidence of HLA antibody (does not meets the last three criteria in A), then candidate does not need to be treated with this protocol.
- ❑ If the autocrossmatch is **POSITIVE** and the **IS** evidence of HLA antibody (meets the last three criteria in A) < then candidate can be treated with this protocol. Ideally, the specificity of the anti-HLA antibody will be determined by the laboratory.

OR, alternatively:

B.

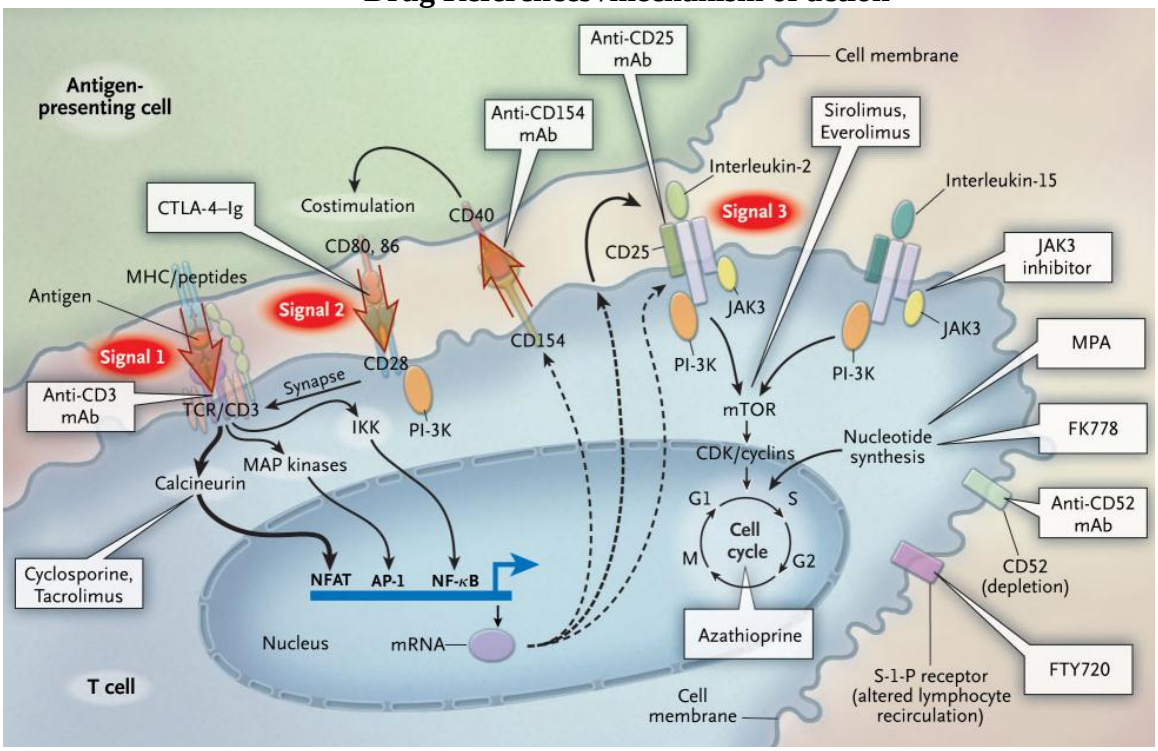
- ❑ **NEGATIVE** cytotoxic T and B cell crossmatch
- ❑ **NEGATIVE** flow T and / or B cell crossmatch
- ❑ Evidence of **DONOR SPECIFIC** anti-HLA antibody

These criteria apply for people who have a pre-defined **DONOR SPECIFIC** antibody but currently have negative cytotoixic and flow crossmatch. There may or may not have been a historically positive crossmatch.

10-Day IVIG protocol

Day	Event	Dose	Comments
-10	Crossmatch		Check Protocol Eligibility
-7	Start Cellcept	500mg BID	Also start PPI at max dose BID
-4	IVIG	1 gm/kg	not to exceed 70 grams
-2	IVIG	1 gm/kg	not to exceed 70 grams
1	IVIG	1 gm/kg	not to exceed 70 grams
0	TRANSPLANT		Thymoglobulin induction
3 - 5	Discharge		
7 - 14	DSA Screening		First Clinic Visit
28 - 32	DSA Screening		1 month
56 - 64	DSA Screening		2 months
84 - 96	DSA Screening		3 months
170 - 190	DSA Screening		6 months
350 - 375	DSA Screening		12 months

Drug References /mechanism of action



Thymoglobulin - Polyclonal antibody which appears to cause immunosuppression by acting on T-cell surface antigens and depleting CD4 lymphocytes

Simulect (basilixamb) – Chimeric (murine/human) immunosuppressant monoclonal antibody which blocks the alpha-chain of the interleukin-2 (IL-2) receptor complex; this receptor is expressed on activated T lymphocytes and is a critical pathway for activating cell-mediated allograft rejection

Campath (alemtuzumab) binds to CD52, a nonmodulating antigen present on the surface of B and T lymphocytes, a majority of monocytes, macrophages, NK cells, and a subpopulation of granulocytes. After binding to $CD52^{+}$ cells, an antibody-dependent lysis of leukemic cells occurs.

Tacrolimus - Suppresses cellular immunity (inhibits T-lymphocyte activation), by binding to an intracellular protein, FKBP-12 and complexes with calcineurin dependent proteins to inhibit calcineurin phosphatase activity

Cyclosporine - Inhibition of production and release of interleukin II and inhibits interleukin II-induced activation of resting T-lymphocytes.

Mycophenolate – MPA exhibits a cytostatic effect on T and B lymphocytes. It is an inhibitor of inosine monophosphate dehydrogenase (IMPDH) which inhibits *de novo* guanosine nucleotide synthesis. T and B lymphocytes are dependent on this pathway for proliferation.

Sirolimus - binds to FKBP-12, an intracellular protein, to form an immunosuppressive complex which inhibits the regulatory kinase, mTOR (mammalian target of rapamycin). This inhibition suppresses cytokine mediated T-cell proliferation, halting progression from the G1 to the S phase of the cell cycle.

Everolimus – same as Sirolimus but also reduces angiogenesis by inhibiting vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF-1) expression.

Belatacept – Fusion protein which acts as a selective T-cell (lymphocyte) costimulation blocker by binding to CD80 and CD86 receptors on antigen presenting cells (APC), blocking the required CD28 mediated interaction between APCs and T cells needed to activate T lymphocytes. T-cell stimulation results in cytokine production and proliferation, mediators in immunologic rejection associated with kidney transplantation.

Eculizumab – humanized monoclonal IgG antibody that binds to complement protein C5, preventing cleavage into C5a and C5b. Blocking the formation of C5b inhibits the subsequent formation of terminal complex C5b-9 or MAC.