UW Medicine

UNIVERSITY OF WASHINGTON
MEDICAL CENTER

Heart Transplant Medication Guidelines

Handbook

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(for staff use only)

Disclaimer: The following Handbook is a summary of some UWMC Division of Transplantation protocols excerpted from the official Cardiac Transplantation Protocol. It is provided as a general guide and not the ultimate source of information or standard of care upon which to base clinical decisions. Transplant is a rapidly changing area of medicine. These protocols/ guidelines may undergo frequent modification post-publication as dictated by changing clinical thought.

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I. Heart Transplant Induction Immunosuppression Guideline

Standard Immunosuppression

Induction: ATG (Thymoglobulin®) (polyclonal antibody) induction will be used with a target of receiving 4.5mg/kg/course. EBV mismatch patients (Donor +/Recipient -) may not receive any induction depending on the decision of the Cardiology attending due to increased risk of PTLD. Potential benefits with induction therapy include possibly delaying acute rejection, prolonging graft survival, delaying initiation of calcineurin inhibitors, and possible prevention of coronary allograft vasculopathy.

Maintenance immunosuppression: Tacrolimus (Prograf®) is the preferred calcineurin inhibitor for maintenance immunosuppression. Because of potential nephrotixicity, it is initiated between POD 2-4 depending on Scr. The usual starting dose is 0.5-1mg PO q12h with a target level goal of 12-15 ng/ml. Since **mycophenolate** is not renal toxic, it is immediately started post-op as **Mycophenolate Mofetil (Cellcept®)** 1000mg PO/IV bid unless the patient develops severe neutropenia or GI disturbances. A mycophenolic acid (MPA) level is available but is used primarily to assess toxicity and extent of absorption in long-term follow-up patients. An alternative to **Mycophenolate Mofetil (Cellcept®)** is **Mycophenolic acid (Myfortic®)** which is used in the event the patient has intolerable nausea/vomiting/diarrhea (Cellcept 1000mg = Myfortic 720mg).

I. Heart Transplant Induction Immunosuppression Guideline

Day Post-Op	Steroid Taper	**ATG (Thymoglobulin®)	Mycophenolate Mofetil (Cellcept®)	Tacrolimus (Prograf®, FK506)
Intraop Day 0	Methylpred-nisolone 500mg IV (before crossclamp removal)	**Dose #1: Start 1.5mg/kg IV (round to nearest 25mg) infused over 6 hours (before crossclamp removal). May be given by peripheral vein	1000mg IV (at skin incision)	
Postop (ICU) Day 0	MP 125mg IVq12hrs x 3 doses	None	1000mg IV/PO bid	
Day 1	same	**Dose #2: 1 mg/kg IV infused over 6 hours at 21:00	same	
Day 2	Prednisone 0.15mg/kg/dose po BID (started 12 hours after last MP dose). Weaned outpatient per attending.*	None	same	**ATG induction:** Check with attending for start time &dose. Typically 0.5mg po Q12hrs. Start when Scr is ≤ 2. ALC should be <100 if tacrolimus is delayed. Target: 10-15 ng/ml
Day 3	same	**Dose #3: 1 mg/kg IV infused over 6 hours at 21:00	same	same
Day 4	same	None	same	same
Day 5	same	**Dose #4: 1mg/kg IV infused over 6 hours at 21:00	same	same

Note: POD # is based upon REPERFUSION time, not time patient arrived in the ICU. This can be confirmed in the operative record, or be obtained from the surgical fellow or attending.

Note: MUST check Plt count prior to giving ATG. Hold ATG if Plt < 70,000. Also check with surgical fellow or attending to ensure that ATG is okay to give.

I. Heart Transplant Induction Immunosuppression Guideline

Biopsy Schedule Guidelines

Time Post Transplant	Biopsy Frequency
0-4 weeks	Qweek (no biopsy #3)
2-3 months	Q2 weeks (no biopsy #7)
4-6 months	Q1 month
6-12 months	Q1-1.5 months (every other month)
12-24 months	Q3 months
2-5 years	Q6 months
5-10 years	Annually
>10 years	None unless indicated

*Routine Prednisone Taper After Transplant

- Prednisone is maintained at the same dose (0.15mg/kg po BID) throughout the 1st post-transplant month.
- After the 1st month, the following management is suggested **if all recent biopsies are 0R/1R AND hemodynamically stable:**

Weight	Starting Dose (mg)	Wean (mg)*
> 120kg	20/15	
90-120kg	15/15	15/15
70-90kg	15/10	15/10
<70kg	10/10	10/10
		10/5
		12.5
		10
		5
		2.5
		OFF

*Starting at 4 weeks post-transplant. Institute each change 2 weeks prior to next biopsy.

II. Heart Transplant Non-Induction Immunosuppression Guideline

Day Post-Op	Steroid Taper	Mycophenolate Mofetil (Cellcept®)	Tacrolimus (Prograf®, FK506)
Intraop Day 0	Methylpred-nisolone 500mg IV (before crossclamp removal)	1000mg IV (before incision). Consider 1500mg if know beforehand pt will receive no induction*	
Postop (ICU) Day 0	MP 125mg IVq6hrs x 4 doses (start 6 hrs post op)	1500mg IV/PO bid	Tacrolimus 1mg po Q12 hrs (start 6 hrs post op). Check with attending if Scr elevated.
Day 1	same	same	same
Day 2	Prednisone 0.5mg/kg/dose po BID (started 12 hours after last MP dose). Taper by total of 5mg/day until 20mg po BID, then taper per normal biopsy wean schedule.	same	same
Day 3	same	same	same
Day 4	same	same	same
Day 5	same	same	same

* Patients are often switched to non-induction protocol after transplant due to intolerance of ATG, ie thrombocytopenia, severe infusion reactions, etc. However, if providers know before transplant, that pt will receive no ATG, ie due to allergies, please consult transplant attending whether they want a higher dose of intraop Mycophenolate mofetil.

III. Infectious Disease Prophylaxis Guidelines

	Timing of Initiation	Agent/Dose	Duration
Peri-Operative			
Standard	Preop and Intraop	**Preop/Intraop:** Cefazolin 2g (or 3g if pt is >120kg) IV preop then intraop (Redose every 3 hrs) **and** Vancomycin IV preop dosed by wt as follows then intraop (Redose after 8 hrs) : -50-70kg = 1g vanco (over 60 min) -71-100kg = 1.5g vanco (over 90 min) -at least 101kg = 2g vanco (over 2 hr) **Postop:** Cefazolin 1gm IV q8h x 48h postop **and** Vancomycin dosed by wt (see above) IV q12h x 48h postop and Mupirocin 2% nasal ointment q12h x 6 doses	48 hours postop
PCN allergy (anaphylaxis)	Preop and Intraop	**Preop/Intraop:** Vancomycin IV preop dosed by wt (see above) then intraop (Redose after 8 hrs) **and** Levofloxacin 750mg IV preop x 1 dose **Postop:** Vancomycin dosed by wt (see above) IV q12h x 48h postop **and** Levofloxacin 750mg IV q24h x 48h **and** Mupirocin 2% nasal ointment q12h x 6 doses	48 hours postop
Pneumocystis jirovecii (PCP)			
Standard	POD 14 or discharge (whichever is sooner)	1. Trim/Sulfa 80mg/400mg (ss) po qhs or 2. Trim/Sulfa 160mg/800mg (ds) po tiw	Indefinite
Sulfa allergy or Neutropenia	POD 14 or discharge (whichever is sooner)	***Consider consulting allergy for sulfa allergy as Trim/Sulfa is preferred.** 1. Dapsone 100mg po qd - check G6PD or 2. Pentamidine 300mg inhaled qmonth	Indefinite
CMV / HSV			
CMV: **D(+)R(-)** **D(+) R(+)** **D(-) R(+)**	POD 1	Ganciclovir 5mg/kg IV q24h while NPO, then Valganciclovir 900mg po qd	3 months
CMV: D(-) R(-)	POD 1	Acyclovir 400mg po bid	3 months

III. Infectious Disease Prophylaxis Guidelines

	Timing of Initiation	Agent/Dose	Duration
Fungal			
Standard	POD 1	Nystatin 500,000 units swish and swallow Q6hours while intubated, then Clotrimazole 10mg mucosal QID after meals OR Fluconazole 200mg po qweek	Until Prednisone is <10mg/day. Check Tacrolimus level within 5-7 days after discontinuation of azole antifungal.
Toxoplasma gondii (donor or recipient seropositive)			
Standard	POD 1	1. Trim/Sulfa 160/800mg (ds) po qhs or 2. Trim/Sulfa 80/400mg (ss) po qhs	Indefinite
Sulfa allergy	POD 1	Dapsone 50mg po qd and Pyrimethamine 50mg qweek and Leucovorin 25mg po qweek	Indefinite

IV. Prophylactic Medication Guidelines

	Timing of Initiation	Agent	Duration
Vitamins	POD 1	Multivitamin (PNV) po qd	Indefinite
Ulcer/GERD	POD 1	Famotidine 20mg po qd or Omeprazole 20mg po qd	Indefinite
Thrombosis	After 1st biopsy	ASA-EC 81mg po qd	Indefinite
Anemia	After transfer to floor	Ferrous sulfate 325mg po qd	3 months
Lipid management	After transfer to floor	Pravastatin 20mg po qd	Indefinite
Osteoporosis	After transfer to floor; Bisphosphonate at time of discharge	Cholecalciferol 1000u po qd **and** Calcium carbonate 1gm po bid Ca2+ intake to = 1200-1500mg/day total intake **and** Alendronate 70mg po qwk if CrCl > 35 ml/min	1 year unless pt remains on steroids or develops osteoporosis
Bowel Program	POD 1	Senna 17.2mg po qhs (3 mo) Bisacodyl 10mg PR PRN Use of MOM, Mag citrate-check Mg	while taking opiate pain meds
Magnesium Supplement	PRN	Magnesium oxide 400mg po qday-tid (PRN) or Magnesium plus protein 133mg po qday-tid (PRN)	PRN
Phosphate Supplement	PRN	Sodium phosphate 250mg-500mg po qday-tid (PRN)	PRN

V. Immunosuppression Target Blood Level Guideline Table*

Heart Transplant: Target Trough Blood Levels*

Time post-transplant	Immuno	0-2 mo	2-3 mo	3-6 mo	6-12 mo	> 12 mo
FK506 (Tacrolimus) (whole blood LCMSMS)	**FK - MMF or AZA - Pred**	10-15 ng/ml	8-12	8-12	5-10	4-8
CSA (Cyclosporine) (whole blood LCMSMS)	**CSA-MMF or AZA-Pred**	250-350 ng/ml	200-325	150-250	125-225	75-150
Rapa (Sirolimus) **(LCMSMS)**	**Rapa – FK**	Sirolimus level : 4-6 ng/ml with combined FK +Siro level = original FK target level				

*** Target levels may vary depending upon function of organ, biopsy, presence of infection, rejection, and/or combination of immunosuppressive drugs used for maintenance therapy.**

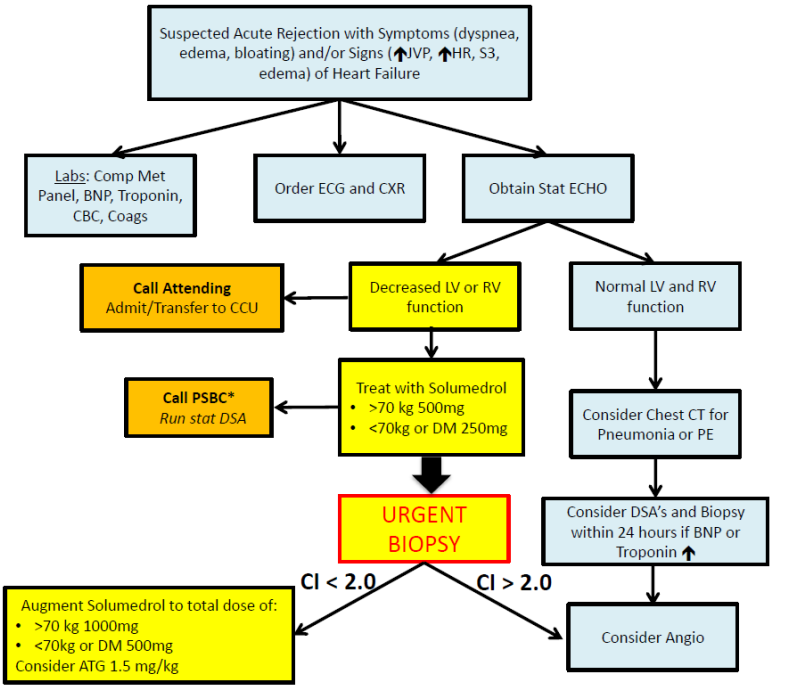
VI. Cylex Immuknow™ Assay Level of Immune Function

The **Cylex Immuknow™ assay** may be used to test the level of cell-mediated immunity, reduce the risk of toxicity, and allow a more individualized approach to managing immunosuppression. The assay will be used to monitor overall level of immune function and risk of infection and as a tool to adjust immunosuppressive drug therapy. It does not accurately predict ongoing or absence of rejection. It will be used in patients who have prolonged complicated post-op courses or patients who develop severe multiple infectious episodes or as a guide in long-term follow-up patients.

ATP Level (ng/ml)	Result
<=225	Low Immune Cell Response
226-524	Moderate Immune Cell Response
>=525	Strong Immune Cell Response

VII. Acute Rejection Guidelines: Heart Transplant

Acute Rejection Flowsheet



ask for on call HLA lab technician to be paged

VII. Acute Rejection Guidelines: Heart Transplant

Acute Cellular Rejection Drug Treatment Algorithm

Biopsy Findings (ISHLT grade-1990)	Rejection treatment	Maintenance Immunosuppression
Grade 0	None	Wean prednisone if appropriate
Grade 1 (mild)		
A-Focal	None	Wean prednisone if appropriate
B- Diffuse	None	Continue Prednisone dose. Optimize Calcineurin inhibitor levels if poor hemodynamics.
Grade 2 (moderate)	Oral steroid pulse: Prednisone 50-60mg qd x 3 days. Pulse may be followed by taper as follows: Decrease by 5mg per day until you reach home maintenance dose or 10mg a day (whichever is higher).	Escalate oral
Grade 3 (moderate)		
A-Focal B-Diffuse	Without hemodynamic compromise: -IV MP 250-1000mg qd x 3 days (Choose lower dose if uncontrolled diabetes). -ATG 1.5mg/kg/day x 3-5 doses. With hemodynamic compromise: IV MP 500-1000mg qd x 3 days (Choose lower dose if uncontrolled diabetes). -ATG 1.5mg/kg/day x 3-5 doses. After IV pulse, start Prednisone at 60mg per day. Taper per attending.	Escalate oral
Grade 4 (severe)	IV MP 1000mg qd x 3 days; ATG 1.5mg/kg/day x 3-5 doses Subsequent steroid doses per attending.	Escalate oral

VII. Acute Rejection Guidelines: Heart Transplant

Table 1. ISHLT Standardized Cardiac Biopsy Grading: Acute Cellular Rejection[b]

2004		1990	
Grade 0 R[a]	No rejection	Grade 0	No rejection
Grade 1 R, mild	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage	Grade 1, mild A—Focal	Focal perivascular and/or interstitial infiltrate without myocyte damage
		B—Diffuse	Diffuse infiltrate without myocyte damage
		Grade 2 moderate (focal)	One focus of infiltrate with associated myocyte damage
Grade 2 R, moderate	Two or more foci of infiltrate with associated myocyte damage	Grade 3, moderate A—Focal	Multifocal infiltrate with myocyte damage
Grade 3 R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage ± vasculitis	B—Diffuse	Diffuse infiltrate with myocyte damage
		Grade 4, severe	Diffuse, polymorphous infiltrate with extensive myocyte damage ± edema, ± hemorrhage + vasculitis

[a]Where "R" denotes revised grade to avoid confusion with 1990 scheme.

J Heart Lung Transplant 2005;24:1710 –20.

VII. Acute Rejection Guidelines: Heart Transplant

Acute Antibody-Mediated Rejection: Guidelines for Plasmapheresis

Plasmapheresis is an adjunctive treatment in AMR that is intended to remove circulating pathogenic antibodies and potentially other pro-inflammatory components from the circulation. While plasmapheresis does not address the primary driver of antibody production, it provides rapid removal of pathologic antibodies that can lead to both acute graft failure and late graft atherosclerosis. These conditions are fatal and can only be treated by re-transplantation. A recent survey of AMR treatment in heart transplantation reported that >50% of centers use plasmapheresis as initial treatment, as does the largest transplant center on the West Coast.

A. Diagnosis of AMR:

1. Functional: Evidence of allograft dysfunction defined as:
    a. EF <45% or a drop in EF of >25%
    b. CI <2.0

2. Histologic: Detection of antibody-mediated graft injury including antibody deposition in microvasculature, C4d present in microvasculature as evidence of antibody mediated complement activation, and in severe AMR, evidence of microvascular edema, mixed inflammatory cell infiltrates (CD68, CD3) and tissue damage. Consult cardiac pathologists regarding equivocal histological findings.

pAMR 0:	negative routine histology and immunopathology (IF or IHC)
pAMR1(H+):	routine histology positive, immunopathology (IF or IHC) negative
pAMR1(I+):	immunopathology (IF or IHC) positive, routine histology negative
pAMR2:	both immunopathology (IF or IHC) and routine histology positive
pAMR3:	severe pathologic AMR with evidence of microvascular compromise

Table 1: Current ISHLT nomenclature for reporting of histopathologic findings of AMR[1]

3. Immunologic: Detection of donor specific antibodies (DSA) on Luminex platform performed by the HLA lab. Not all antibodies are pathogenic, particularly class II at lower MFI's. Review of initial crossmatches, previous samples for DSA's, performance of retrospective crossmatches, etc may provide additional information. Consider discussion with the HLA laboratory for guidance.

VII. Acute Rejection Guidelines: Heart Transplant

B. Algorithm for Initial Treatment of AMR with Plasmapheresis:

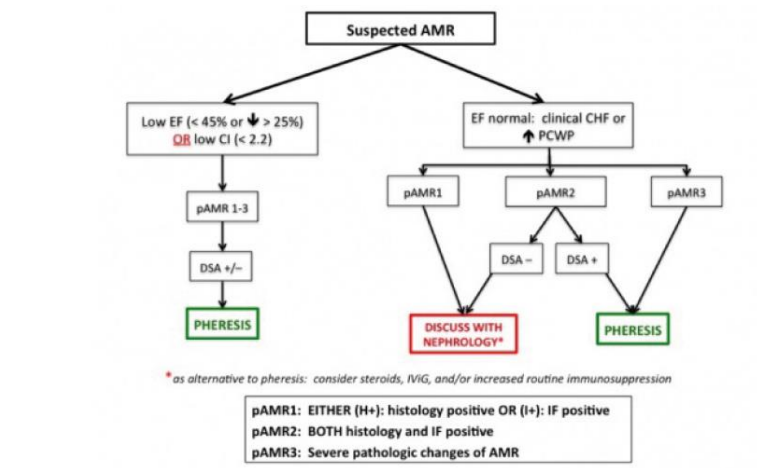
1. Right Heart Catheterization and Echocardiography are necessary to document cardiac function prior to determining need to therapy.

2. Transplant Nephrology will be called as soon as AMR is suspected.

3. Therapy should be initiated within 24 hours of diagnosis.

4. Line placement will be arranged by Card B service.

5. *For patients who do not meet treatment criteria, non-pheresis based therapies such as augmentation of oral steroids, IV steroids, immunoglobulin or increasing target levels of routine immunosuppression medications can be instituted by transplant cardiologist dependent on clinical situation.



C. Initial Treatment Protocol for AMR:

1. **Steroids:** Methylprednisolone 500mg IV qd x 3 days.
   -Dose adjust to 250mg qd x 3 days if insulin requiring diabetes or weight <70kg.
2. **Plasmapheresis:** Daily x 3 days
   -Avoid ACEi during this period due to anaphylactic risk.
3. **Immunoglobulin:** Sucrose-free preparation only.
   -Give 100mg/kg after pheresis 1-4
   -Give 1gm/kg/day x 2 doses following last pheresis.
   -Max doses 140gm over 2 days.
4. If severe cardiac dysfunction or pAMR3 with high DSA, add rituximab 375mg/m^2 IV x1 following Plasmapheresis and final IVIG. Consider repeat dose of rituximab at day 22.

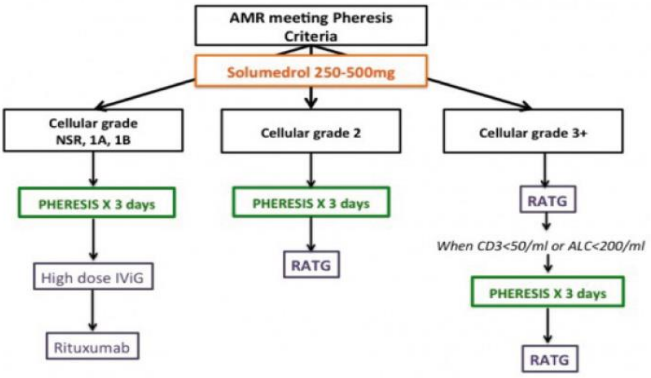
D. Follow up Evaluation and Therapies for AMR:

1. Repeat ECHO, DSA, RHC, and Biopsy 14 days after completion of therapy.
2. If persistent indication for AMR treatment per algorithm above, repeat therapeutic sequence above with addition of rituximab or ATG (1mg/kg IV x 1-2 doses) depending on clinical background of AMR (previous alloimmunization vs low immunosuppression). If persistent AMR requiring treatment after two cycles would consider initiation of bortezomib with pheresis per desensitization protocol.

VII. Acute Rejection Guidelines: Heart Transplant

E. AMR in Conjunction with Cellular Rejection:

1. **Steroids:** Methylprednisolone 500mg IV qd x 3 days
   -Dose adjust to 250mg qd x 3 days if insulin requiring diabetes or weight <70kg.
2. **Plasmapheresis:** Timing per algorithm
3. **Adjuvant Therapies:** RATG (1.5mg/kg daily until ALC <200) for grade 2 rejection and higher



Addition of Sirolimus to Calcineurin Inhibitor Based Therapy

Sirolimus and Everolimus are both mTOR inhibitors with potent antiproliferative and antimigratory effects that can either be added on as a secondary agent to a calcineurin inhibitor (CNI) or used as the primary immunosuppressant. Possible indications include preservation of kidney function by sparing the use of calcineurin inhibitors and treatment of coronary allograft vasculopathy.

The process of replacing Mycophenolate or Azathioprine with Sirolimus varies depending on the pt's risk of rejection, risk of adverse effects, and the presence of drug-drug interactions.

The following is just one possible approach to converting therapy:

1. On day of therapy change, start Sirolimus at 0.5-1mg po qd.
   1.1. Discontinue Mycophenolate/Azathioprine.
   1.2. Continue CNI at current dose; reduce CNI dose preemptively by 25% if aiming for lower target levels and risk of adverse effects outweighs risk of rejection.
   1.3. Must give Sirolimus at least 4h apart from Cyclosporine due to drug interaction.

2. Check Sirolimus and CNI levels in 7 days (due to Sirolimus long t1/2 = 48-78 hrs).
   2.1. If Sirolimus level is very low, increase dose by an increment of 0.5mg per day.
   2.2. If Sirolimus level has reached 50% of goal, consider reducing CNI dose by 50%.
   2.3. If Sirolimus level is at goal, reduce CNI dose to achieve desired CNI target trough level.
      2.3.1. If converting to Sirolimus monotherapy, discontinue CNI.

VIII. Acute Rejection Drug Treatment Guidelines

Pulse Steroid Treatment Guideline

Action: Corticosteroids block numerous cytokine synthesis including IL-1 which activates T-cells.
When: First line agent used to treat mild-moderate cellular rejection
Dose/Administration: Doses <=125mg are given IVP; doses >125mg are diluted in 50ml of D5W and infused over 30 minutes.
Monitoring: VS, wt, BS, BG
Other immuno: Continue maintenance or escalate doses; adjust to higher target levels
Blood glucose management: Type 1 & 2 diabetics: insulin infusion guideline; non-diabetics: hospital standard low dose lispro sliding scale

Cost: 1000mg = $20

ATG (Thymoglobulin®) Treatment Guideline

Action: Polyclonal anti-thymocyte globulin derived from rabbits immunized with human thymocytes. Interacts with peripheral lymphocytes resulting in the blockade of T-cell functions and selective depletion of T-cells. Indicated for treatment of acute renal graft rejection
When: First line agentused to treat severe cellular and humoral rejection; also used as induction agent
Dose/Administration: 1-1.5mg/kg/dose IV x 5-10 doses. May be administered on alternate days if needed due to low WBC counts. Infuse over 4-12 hours. A central line is preferred for administration but may be given peripherally mixed in 500ml NS + Hydrocortisone 20mg and Heparin 1000units. Doses are stable for 24 hours stored in the refrigerator. Administer with a 0.22 micron filter separately from other drugs and IV fluids including D5W. Infuse first dose over 12 hours, then 4-6 hours thereafter. Doses are on call from inpatient pharmacy due to expense ($1000-2000). Premeds of antihistamine, acetaminophen and methyprednisolone are given 60 minutes pre-dose.
Premeds: **Tylenol®:** 650mg PO/PR 60 min pre & q4h prn fever, HA.
Benadryl®: 25-50mg PO/IV 60 min pre & q4h prn chills, itching
Methylprednisolone: First dose:250-500mg or1mg/kg IV 60 min pre (for induction: see specific guideline)
Monitoring: O2 saturation measured pre-infusion. Weight is measured daily. VS: First dose: monitored pre and every 30 minutes x 2 hours, then hourly x 4 hours. Subsequent doses: pre and at 30 minutes, then q4h. Monitor for s/s of anaphylaxis (SOB, face swelling, hives, hypotension), rash, infusion-related reactions. Notify physician for T>37.8;BP>160/95 or <90/50, respiratory distress, pain in chest or abdomen, s/s of infection. Maintain CD3 lymphocyte count <0.1; WBC > 3.0; PLTs > 50 K.
Major Adverse Effects: Infusion related 25-70% (chills, fever, dyspnea, hypertension, tachycardia); Hematologic 35-60% (neutropenia, thrombocytopenia); Other (30-40%): N/V/D, peripheral edema, infection, myalgia/arthralgia, serum sickness.
Other immuno: Continue maintenance or escalate doses; adjust to higher target levels
Blood glucose management: Hospital standard low dose lispro sliding scale

Cost: 100 mg = $2000

IVIG (Immune globulin) Treatment Guideline

Action: Immune modulator. Polyclonal antibodies derived from human plasma. Has been shown to inhibit anti-HLA alloantibodies and has been used to treat rejection in antibody mediated rejection and reduce PRA in highly sensitized patients.
When: First or second or rescue rejection; especially antibody mediated rejection; bx results should be available; plasmapheresis may be required if post-transplant flow crossmatch is positive.
Dose/Administration: Polyimmune globulin, preferred non-sucrose containing (Gamunex®) (10%): To treat rejection: 2gm/kg IV x 1 (may be divided 1gm/kg IV qd x 2 or 500mg/kg IV qd x 4) or 100mg/kg post plasmapheresis; dose may be repeated in 1 month; typical volume is 400-1500ml infused over 4-12hours.
Alternate: **Flebogamma®** 2gm/kg IV as 5% solution (150gm/3000ml) (sorbitol-based).
Premeds: Tylenol 650mg PO/PR and Benadryl 25-50mg IV/PO 30min pre-IV IgG
Monitoring: VS, hypersensitivity reactions, infusion-related reactions
Other immunosuppression: Continue maintenance or escalate doses: adjust to high target levels

Cost: Gamumex®70gm = $5,300; Flebogamma® 70gm = $4900

VIII. Acute Rejection Drug Treatment Guidelines

Bortezomib (Velcade®) Treatment Guideline

Action: Inhibits 26S proteasome and ultimately downregulates NFkB signaling which is critical for B cell and plasma cell differentiation and survival.
When: Second line agent used to treat severe antibody-mediated (humoral) rejection; also used for desensitization prior to transplantation
Dose/Administration: 1.3mg/m^2 subQ or IV given 72 hours apart x 4 doses. Decrease dose if patient has moderate hepatic impairment (consult pharmacist). Doses are on call from oncology satellite pharmacy. Administered by oncology nurse.
Premeds: **Tylenol®:** 650mg PO/PR 30 min pre
Benadryl®: 50mg PO/IV 30 min pre
Monitoring: VS, BG, CBC, LFTs, signs of neuropathy (adjust dose per below), signs of heart failure, respiratory distress

Dose reduction for neuropathy:

Severity of Neuropathy	Modification
Grade 1 (asymptomatic, loss of deep tendon reflexes or paresthesia) without loss of function or pain.	No action
Grade 1 with pain or Grade 2 (moderate, limiting instrumental activities of daily living)	Decrease to 1mg/m^2
Grade 2 with pain or Grade 3 (severe, limiting self care ADL)	Hold therapy until toxicity resolves; reinstitute at 0.7mg/m^2 once per week
Grade 4 (life-threatening consequence; urgent intervention indicated)	Discontinue bortezomib.

Major Adverse Effects: Hematologic: Leukopenia (18-48%), Neutropenia (5-87%), Thrombocytopenia (16-72%). Neurologic: headache (14-26%), paresthesia (6-19%), peripheral neuropathy (30-54%). Other: dehydration, diarrhea, hepatotoxicity, hypokalemia, hypotension (12-15%), heart failure (5%), rash.

Cost: 2.4mg = $530

Rituximab (Rituxan®) Treatment Guideline

Action: Chimeric (mouse) monoclonal antibody directed against CD20 antigen found on normal and malignant B lymphocytes. After binding, B cell lysis occurs. Indicated for CD20 (+) B-cell non-Hodgkins lymphoma. Off label solid organ transplant uses include preconditioning treatment ABO incompatible or high HLA antibody transplants, treatment of PTLD, and treatment of severe, humoral or resistant rejection.

When: Second line agent used to treat severe antibody-mediated (humoral) or resistant rejection; also used for desensitization prior to transplantation

Dose/Administration: 375mg/m2 or 1gm IV infusion x 1; may repeat in 7-14 days; infusion over 2-4 hours via central or peripheral line; subsequent doses given days-weeks apart. Often given in combination with other rejection treatments: plasmapheresis, IV immune globulin, ATG, and steroids. Diluted in 500ml (250ml if concentrated) NS and infused starting at 50mg/hr, increased by 50mg/hr every 30 minutes to maximum of 400mg/hr. Stable for 12 hours at room temp or 24 hours refrigerated. Administered separately from other drugs and IV fluids. Administered by oncology nurse. Doses on call from Oncology satellite pharmacy. Premeds of antihistamine, acetaminophen, and -+/- methylprednisolone are given 60 minutes pre-dose.

Premeds: **Tylenol®:** 650mg PO/PR 60 min pre & q4h prn fever, HA.
Benadryl®: 25-50mg PO/IV 60 min pre & q4h prn chills, itching
+ Methylprednisolone: 1mg/kg IV

Monitoring: O2 saturation measured pre-infusion. VS: monitored pre and every 30 minutes x 2 hours, then hourly x 4 hours. Monitor for s/s of anaphylaxis (SOB, face swelling, hives, hypotension), rash, infusion-related reactions. Non-life threatening hypersensitivity reactions may respond to adjustments in infusion rate. Interrupt infusions for severe reactions; may be able to resume at 50% rate if reactions have completely resolved. Precaution is advised in patients who have significant cardiovascular risk factors. It is advised to hold blood pressure meds prior to infusion. Patients who develop clinically significant cardiopulmonary events should have infusion discontinued. Notify physician for T>37.8;BP>160/95 or <90/50, respiratory distress, pain in chest or abdomen, s/s of infection. Maintain WBC > 3.0; PLTs > 200K

Major Adverse Effects: Infusion related events: chills (33%), fever (5%), rash (15%), dyspnea (7%), bronchospasm (8%), hypotension (10%). Hematologic: lymphopenia (48%), neutropenia (14%), thrombocytopenia (12%), anemia (8%). Other: nausea (23%), infection (31%), HA (19%), myalgia/arthalgia (10%), angioedema (11%)

Other immuno: Continue maintenance or escalate doses: adjust to high target levels; often given in combination with other rejection treatments: plasmapheresis, IVIG, ATG, steroids

Blood glucose management: Hospital standard low dose lispro sliding scale.

Cost: 1gm = $6500

VIII. Acute Rejection Drug Treatment Guidelines

Alemtuzumab (Campath®) Treatment Guideline

Action: Immunosuppressant. Recombinant DNA-derived humanized monoclonal antibody directed against the cell surface glycoprotein, CD52. After binding to CD52(+) peripheral B & T lymphocytes, monocytes, macrophages, NK cells, an antibody-dependent lysis occurs. The mechanism of action includes complement-mediated lysis, cell mediated cytotoxicity, and induction of apoptosis of targeted cells. Indicated for treatment of B-cell chronic lymphocytic leukemia. Off label solid organ transplant uses include treatment of GVHD, induction immunosuppression, and treatment of rejection, treatment of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, vasculitis, ITP and scleroderma. Depression of CD4 and CD8 cell types lasts for 2 to >12 months.
When: Used for induction therapy, 2nd or 3rd line agent for severe or vascular (C4D+) rejection, or GVHD
Dose/Administration: (For non-SCCA patient)
Usual dosage range 10-30mg or 0.3mg/kg IV. Doses may be x 1 repeated to keep absolute lymphocyte counts<200 cells/μL. Dose escalation as with tx of B-CLL is not used. Standard dilution: 10-30 mg in 100 ml 0.9% NS (also compatible w/D5W). Infusion rate: over 2 hours via central or peripheral line. Stability: within 8 hours of dilution. Storage: may be stored at room temp or refrigerated; protect from light. Compatibilities: administer separately from other drugs and IV fluids. Doses on call from inpatient pharmacy. Drug is non-formulary.
Premeds of antihistamine, acetaminophen, and methylprednisolone are given 60 minutes pre-dose.
Premeds: **Tylenol®:** 650mg PO/PR 60 min pre & q4h prn fever, HA.
Benadryl®: 25-50mg PO/IV 60 min pre & q4h prn chills, itching
Methylprednisolone: 125mg IV pre
Monitoring: Monitor VS every 30 minutes for the first 2 hours, then hourly for 4 hours. Monitor for signs and symptoms of anaphylaxis (shortness of breath, swelling in face, hives, red skin, low blood pressure, syncope). Measure weight qd. Notify Physician for: Temp>37.8;BP>160/95 or <90/50; respiratory distress, pain in chest or abdomen, or signs and symptoms of infection. Hold for platelets < 25; ANC < 250. **Laboratory monitoring:** CBC with diff, platelet counts qd during tx; CD4 lymphocyte counts assessed regularly after tx completed until recovery to >=200 cells/μL
Major Adverse Events: (incidence based on patients tx for B-CLL)
Because of the humanization of alemtuzumab, the first-dose effect is relatively mild. First infusion reactions (fever, rash, nausea, vomiting, headache and rigors) due to cytokine release syndrome can be limited with steroid pre-treatment. Infusion related: rigors (89%), fever (83%), rash (33%), dyspnea (28%), hypotension (15%); Hematologic: neutropenia (70%), thrombocytopenia (62%), anemia (47%), pancytopenia (5%) (higher risk for doses >90mg/week). Other: N/V (41-54%), infections (37%), fatigue (34%), diarrhea (22%)
Other immuno: Continue maintenance or escalate doses: adjust to high target levels when used for rejection
Blood glucose management: Hospital standard low dose lispro sliding scale.

Cost: 30mg =$1800

IX. Acute Rejection Guidelines: Prophylactic Meds Post Rejection

Type of Prophylaxis	Steroids only	Antibody therapy (ATG, alemtuzumab)	Bortezomib	Rituximab
CMV	None	If donor or recipient (+), Valganciclovir 900mg po qd x 3 months.	None	None
HSV/VZV	None	If not on Valganciclovir, Acyclovir x 3 months.	Acyclovir x 3 months	None
Candida	Clotrimazole 10mg po qid, continued until Prednisone dose is < 10mg/day.	Clotrimazole 10mg po qid, continued until Prednisone dose is < 10mg/day.	None (if pt is on high dose steroids, use clotrimazole)	None (if pt is on high dose steroids, use clotrimazole)
Pneumocystis	Continue lifelong Trim/sulfa single strength po qhs.	Continue lifelong Trim/sulfa single strength po qhs.	Continue lifelong Trim/sulfa single strength po qhs.	Continue lifelong Trim/sulfa single strength po qhs.
Other				Check hep B serologies (HBsAG, anti-HBc) prior to initiation. Refer to table on next page for interpretation.

The durations above may be individualized according to the patient's specific clinical situation. If the rejection episode occurs within the period of routine post-transplant prophylaxis (i.e. 3-6 months), the patient should remain on the prophylaxis indicated for their transplant (See II. Infectious Disease Prophylaxis Guidelines). If the guideline above would add or extend their prophylaxis beyond what is routine, the start date for the above time frames is from the initial dose of antirejection therapy.

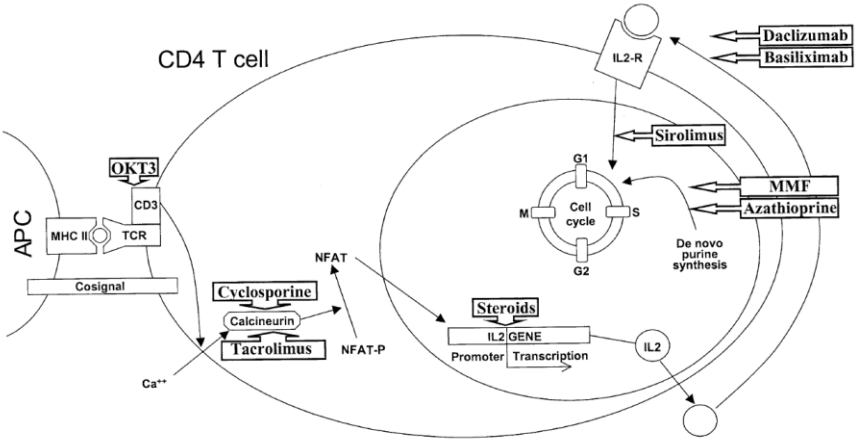
For Rituxaimab Patients, Interpretation of Hepatitis B Serologic Test Results

(accessed via CDC.gov)

Serology	Result	Interpretation	Recommendation
HBsAG **Anti-HBc**	+ +	Possible acute or chronic infection.	Consult ID and hepatology.
HBsAG **Anti-HBc**	- +	Possible resolved infection, "low level chronic infection, or resolving acute infection	Check Hep B PCR, consult ID and hepatology. - If Hep B PCR (-), initiate Hep B prophylaxis (typically lamivudine or entecavir) x 2 years. - If Hep B PCR (+), initiate Hep B prophylaxis/treatment (typically lamivudine or entecavir lifelong for prophylaxis)

HBsAG= Hepatitis B surface antigen
Anti-HBc= Total Hepatitis B core antibody

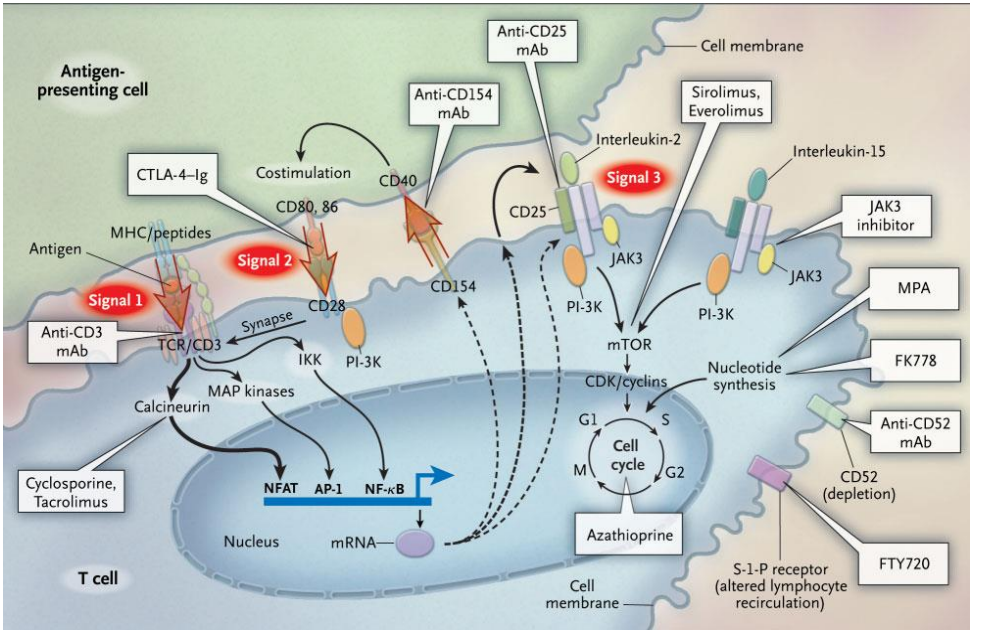
X. Immunosuppressive Medication Guide



Ann Thorac Surg 2004;77:354-62

Immunosuppressive Drugs and Sites of Action in the 3 signal Model

(NEJM 351:26 December 23, 2004)



N Engl J Med 2004;351:2715-29.

X. Immunosuppressive Medication Guide

Class: Non-specific inhibitors of T-cell proliferation					
Drug	**MOA/PK**	**Dosing/Admin**	**Side Effects**	**Monitoring**	**Charge (cost)**
Azathioprine (Imuran®, AZA)	**Purine analogue** Blocks DNA synthesis Parent compound T ½ = 3h Metab to 6-MP; T ½= 3h 60min	**Maintenance** 1-2mg/kg PO/IV QPM Rarely use >3mg/kg **Range:** 25-175mg /day IV = PO in heart and lung transplant Round to nearest 25mg	↓WBC ↓RBC ↓PLT **Other:** Alopecia N/V Diarrhea Hepatotoxicity pancreatitis	**Labs**: CBC Adjust dose based on WBC: <2.5 adjust ↓ Major drug interaction with Allopurinol.	IV= $250 ($45)/ day PO= $1.50/day (generic)
Mycophenolate mofetil (Cellcept®, MMF) **Mycophenolate sodium (Myfortic®, MPA, EC-MPS)**	**Purine and DNA synthesis blockade** Absorption 94%; Metab to MPA (active) T ½=18h Elim as MPAG MMF 1gm= MPA 720mg	**Maintenance** MMF: 1gm PO BID MPA: 720mg PO BID **Range:** **MMF:** 500mg-2gm/day MPA 360-1440mg/day IV = PO dose (MMF only) IV over 2h Peripheral/ Central Flush w/D5W	↓□WBC ↓RBC ↓PLT Diarrhea N/V	**Labs:** CBC **Levels:** MPA 2-5 mcg/ml	IV= $230 ($45)/ Day PO= $8.5/day (generic MMF) PO=$30/ day (Myfortic)

Class: non-specific inhibitor of B & T-cell proliferation					
Drug	**MOA/PK**	**Dosing/Admin**	**Side Effects**	**Monitoring**	**Charge (cost)**
Cyclo-phosphamide (Cytoxan®)	**Alkylating agent**; interferes with DNA synthesis Affects both T & B cells; may be used when AZA contraindicated or ABO incompatible graft	**Maintenance:** 25-50mg/day	↓WBC ↓RBC ↓PLT Other: Alopecia N/V hemorrhagic cystitis	**Labs**: CBC Adjustments based on WBC count	PO= $3.5/ day

X. Immunosuppressive Medication Guide

Class: Non-specific inhibitor of immune function					
Drug	**MOA/PK**	**Dosing/Admin**	**Side Effects**	**Monitoring**	**Charge (cost)**
Cortico-steroids (prednisone, methyl-prednisolone)	Blocks numerous cytokine synthesis including IL-1 which activates T-cells	**Ind**: 500mg-1gm MP IVPB in OR **Maintenance Heart**: Methylpred 125mg IV q12h x 3 doses then prednisone 0.15mg/kg/dose po BID (Based on ABW). Taper per MD.	Mood disturbances, ↓WBC, ↑BP, ↑BS, hallucinations,↓wound healing, edema, moon face,↑ acne, ↑appetite, N/V , muscle weakness, ↑wt, osteoporosis, ↑lipids,cataracts	**Labs:** lipids, BS **General:** BP, edema, vision, bones, wound, skin, wt	IV= $50-100 ($1-8)/day PO= $0.3/day

Class: Inhibitors of early T-cell activation					
Drug	**MOA/PK**	**Dosing/Admin**	**Side Effects**	**Monitoring**	**Charge (Cost)**
Cyclosporine (Microemulsion or Modified = Neoral®, Gengraf®, Eon Labs, Pliva) (Original formulation = non-modified= Sandimmune®, Apotex)	**Calcineurin inhibitor** Inhibits synthesis of IL-2 Absorption 30%; Lipoprotein bound; metab by P450 gut/liver; T1/2= 8h	**IV:**1-2mg/kg/day IV continuous infusion **IV = 1/3-1/4 PO** dose **PO** 2-3mg/kg PO q12h **Std gtt:** 125mg/250ml NS/D5W	nephrotoxicity, ↑K, ↓Mg, ↑BP, ↑BS, neurotoxicity, hirsutism, paresthesias, ↑lipids, HUS, gum hyperplasia	**Labs**: renal, K, Mg, lipid. LFT, BS **Levels:** See target blood level tables in guideline handbook	IV= $110 ($8)/day PO= $15/day
Tacrolimus (Prograf®, FK506)	**Calcineurin inhibitor** Inhibits synthesis of IL-2 Absorption 15-30%; Met by P450 gut/liver; T1/2= 8h	**IV:** 0.01mg/kg/day IV continuous infusion **IV = 1/3-1/4 PO** dose **PO**: usual starting dose 0.5-1mg PO q12h post transplant. Titrate to level. **Std gtt:** 2.5mg/250ml NS/D5W	nephrotoxicity, neurotoxicity, ↑K, ↓Mg, ↑BP,↑BS. anorexia, alopecia, ↑lipids	**Labs**: renal, K, Mg, lipid, LFT, BS **Levels:** See target blood level tables in guideline handbook	IV= $250 ($50)/day PO= $15/day

X. Immunosuppressive Medication Guide

Class: inhibitor of late T-cell activation & maturation					
Drug	**MOA/PK**	**Dosing/Admin**	**Side Effects**	**Monitoring**	**Charge (Cost)**
Sirolimus (Rapamune®, rapamycin, Rapa)	**MTOR inhibitor** Inhibits response of T-cell to IL-2 Absorption 15-27%; Met by liver; T1/2= 46-78h	**Induction:** not indicated **Maintenance:** 1-5mg PO qd IV not available	↑lipids (cholesterol, TG), ↓WBC, ↓RBC,↓PLT, mouth ulcers, ↓wound healing, ↑BS, LE edema, dermatitis, joint pain, pleural effusion	**Labs**: CBC Lipids LFT **Levels**: 5-15ng/ml	PO = $35/day
Everolimus (Zortress®)	**MTOR inhibitor** Inhibits response of T-cell to IL-2 Met by liver; T1\2=30h	**Induction:** Not indicated **Maintenance:** Initial: 0.75mg po q12h IV not available	Peripheral edema HTN, Nausea Anemia,↑lipids Constipation	**Labs:** CBC Lipids LFT **Levels:** 3-8mcg/ml	PO = $35/day

Class: Inhibitors of antigen recognition					
Drug	**MOA/PK**	**Dosing/Admin**	**Side Effects**	**Monitoring**	**Charge (Cost)**
Antithymocyte Globulin, rabbit (ATG, Thymoglobulin®) **Equine antithymocyte globulin (Atgam®) is NOT used in solid organ transplants.**	**Polyclonal Antibodies** that block T-cell function by blocking multiple CD sites and through removal or lysis of T-cells Thymo T1/2= 14-45d Duration: 1-4 wks	**Ind/Rejection: Thymo:** 1-1.5mg/kg IV qd Infuse over 6h via central preferred (periph in 500ml NS, HC 20mg heparin 1000units) Premeds: 1mg/kg MP, Benadryl, APAP	↓WBC, ↓RBC, ↓PLTs, fever, chills, headache, diarrhea, SOB, ↓↑BP, rash (allergy to rabbit or horse)	**Labs**: CBC, CD3 count (<0.1)	Thymo: 100mg = $2000 ($500)

Class: Modulation of Anti-HLA antibodies					
Drug	**MOA/PK**	**Dosing/Admin**	**Side Effects**	**Monitoring**	**Charge (Cost)**
Immune globulin (IVIG) (Gammunex®, Flebogamma®, Gammagard®)	**Uses:** Suppression of anti-HLA antibody mediated rejection; Desensitization protocols pre-tx *See IVIG comparison table	**Dose:** 2g/kg IV divided into multiple doses, ie. 1mg/kg IV qd x 2 days; 100mg/kg (~10 gm) replacement after PP Premeds: APAP, Benadryl	↓BP, SOB, ARF anaphylaxis, chest tightness, tachycardia, HA, nausea, fever, chills, back pain, facial flushing **Gammunex® preferred in RF**	Infusion rate related-slow escalation recommend epinephrine should be available	400mg/kg = ~30gm =$7400 2gm/kg =~140gm =$20,000

X. Immunosuppressive Medication Guide

Class: Inhibitor of B cells					
Drug	**MOA/PK**	**Dosing/Admin**	**Side Effects**	**Monitoring**	**Charge (Cost)**
Rituximab (Rituxan®)	**Monoclonal ab** Chimeric (mouse) anti-CD20 ag on surface of B cells results in lysis. **Tx uses:**↓ABO or PRA ab titers in pre- conditioning for tx; treatment of antibody mediated rejection in heart tx; treatment of PTLD	**Tx Dose:** 375mg/m^2 or 1gm IV q7-14 days, duration to be determined Premeds: APAP, Benadryl, + steroid 1mg/kg	Infusion related: (↓BP. fever, chills, rigors- responds to ↓rate, supportive care), lymphopenia, hypersensitivity rxns, cardiac arrhythmias, renal toxicity, tumor lysis syndrome	**Labs:** Anti-ABO antibodies CBC, PLT's, human antichimeric antibodies, SCr	1gm = $8000 ($2700)

Class: Inhibitor of B & T cells					
Drug	**MOA/PK**	**Dosing/Admin**	**Side Effects**	**Monitoring**	**Charge (Cost)**
Alemtuzumab (Campath®) **(Campath-1H)**	**Monoclonal ab** Humanized anti-CD52 ag results in B & T cells lysis **Tx uses:** Lymphocyte depleting agent to induce tolerance, induction or treat GVHD in SOT T1/2= 7 days	**Conditioning or induction:** 30mg IV x 1 **GVHD:** Consult attending for dose Premeds: steroid, APAP, Benadryl	↓WBC (neutropenia), ↓RBC, ↓PLTs, Infusion related-fever, rigors, dyspnea, ↓BP, headache, nausea, rash	**Labs:** ALC, CD4 lymphocytes, CBC, PLTs,	30mg = $5000 ($1200)

Class: Proteosomal inhibitor					
Drug	**MOA/PK**	**Dosing/Admin**	**Side Effects**	**Monitoring**	**Charge (cost)**
Bortezomib (Velcade®)	**Proteosome inh** ↓ability of B & T cells to degrade proteins and perform functions leading to cell death **Indications:** Multiple myeloma **Tx use:** humoral rejection	**MM:** 1.3mg/M^2 IVP BIW x 4 doses	↓BP N&V Rash ↓WBC ↓PLTs Peripheral neuropathy	**Labs:** WBC PLT LFT DSA	1.6mg= $1400 (340)

XI. Immunosuppressive Drug Interactions^

^Reported drug interaction data may conflict, not a comprehensive list of interactions

Drug Name	P-glyco-protein	P450 3A4	Additive toxicity	Effect on other drugs	Effect on warfarin
Azathioprine (Imuran®)			BM toxins	↓ **CSA**	↓
Corticosteroids	Substrate	Substrate	GI toxins	↑**CSA/FK** ↓calcium abs	↓↑
Cyclosporine (Neoral®, Sandimmune®)	Substrate Inhibitor	Substrate Inhibitor	Renal toxins: -NSAIDs -aminoglycosides -contrast, -amphotericin Neurotoxins ↑Potassium: -ACEIs -ARBs, -K supps -spironolactone	↑ statin levels (except pravastatin) (contraindicated w/simvastatin) **corticosteroids** colchicine caspofungin bosentan methadone fentanyl amiodarone Digoxin **Sirolimus** **MPA**	NS
Everolimus (Zortress®)	Substrate	Substrate	BM toxins	ACEI-angioedema ↑ statin levels	
Mycophenolate (Myfortic®), Cellcept®)			BM toxins GI toxins	↓OCPs ↑acyclovir, ganciclovir	NS
Sirolimus (Rapamune ®)	Substrate Inhibitor	Substrate Inhibitor	Bone marrow toxins	↑ statin levels (except pravastatin) ↓**FK**	NS
Tacrolimus (Prograf®, FK506)	Substrate Inhibitor	Substrate Inhibitor	Renal toxins: -NSAIDs -AG -contrast -amphotericin Neurotoxins ↑Potassium: -ACEIs -ARBs -K supps, -spironolactone	↑ statin levels (except prava), **corticosteroids** colchicine, digoxin, bosentan, **MPA**	NS

XI. Immunosuppressive Drug Interactions^

^Reported drug interaction data may conflict, not a comprehensive list of interactions

Drug Name	Drugs that ↑ levels	Drugs that ↓ levels	Effect of food on absorption	Drug-food interaction
Azathioprine (Imuran®)	Allopurinol **(avoid or ↓ dose AZA by 75%) febuxostat - contraindicated**		No effect	
Corticosteroids	*Macrolides, *Azoles, *CCBs, *Protease inh, Nefazodone, **CSA**	&Anticonvulsants rifampin > rifabutin, efavirenz nevirapine		↑ levels: Grapefruit (Pomegranate)
Cyclosporine (Neoral®, Sandimmune®)	*Macrolides, *Azoles, *CCB, *Protease inh, metoclopramide, metronidazole, amiodarone, fluvoxamine, nefazodone, OCPs quinupristin **corticosteroids**	&Anticonvulsants rifampin > rifabutin bosentan St. John's Wort **azathioprine**	↓	↑ levels: Grapefruit (Pomegranate)
Everolimus (Zortress®)	*Macrolides, *Azoles, *Protease inh Digoxin, **CSA**	&Anticonvulsants rifampin > rifabutin Efavirenz St. John's Wort	↓ Take with or w/o food	↑ levels: Grapefruit (Pomegranate)
Mycophenolate (Myfortic®, Cellcept®)	**FK**	antacids-Mg/Al, PPIs-MMF only) metronidazole, iron cholestyramine, colestipol, **CSA** rifampin, echinacea	Delays Cmax, Tmax Not extent	
Sirolimus (Rapamune) ®)	*Macrolides, *Azoles **voriconazole contraindicated**, *CCBs, *Protease inh, metoclopramide, Amiodarone, fluvoxamine, nefazodone, OCPs Quinupristin**,** micafungin, **CSA**	&Anticonvulsants rifampin > rifabutin efavirenz nevirapine bosentan St. John's Wort	↑	↑ levels: Grapefruit (Pomegranate)
Tacrolimus (Prograf®, FK506)	*Macrolides, *Azoles, *CCB, *Protease inh, metoclopramide, metronidazole, amiodarone, fluvoxamine, nefazodone, OCPs, quinupristin, **corticosteroids**	&Anticonvulsants rifampin > rifabutin efavirenz nevirapine bosentan St. John's Wort caspofungin **sirolimus**	↓	↑ levels: Grapefruit (Pomegranate)

***Drug Classes:**

Azoles: ketoconazole/voriconazole > posiconaozle/itraconazole > clotrimazole/fluconazole
CCB: calcium channel blockers (verapamil, diltiazem, nicardipine)
Macrolides: erythromycin, clarithromycin
Protease inhibitors: atazanavir, amprenavir, indinavir, nelfinavir, ritonavir, saquinavir, boceprevir, telaprevir,
Anticonvulsants: phenytoin, phenobarbital, primidone, carbamazepine, oxcarbazepine

XII. Conversion Tables

Immuno PO → IV Conversion

Drug	PO	IV	Comment
Prednisone Methylprednisolone	1mg	1mg	Use Prednisone for PO steroid dosing; MP for IV dosing
Cyclosporine (CSA)	4mg	1 mg	IV as continuous infusion
Tacrolimus (FK506)	4mg	1mg	Avoid using IV ; consider IV CSA @1-2mg/hr CI
Mycophenolate mofetil (Cellcept®, MMF)	500mg	500mg	IV divided q12h =360mg Myfortic, MPA
Mycophenolate sodium (Myfortic®, MPA)	360mg	Not available	Must convert to MMF for IV administration =500mg Cellcept, MMF
Azathioprine	1mg	1mg	Kidney and liver transplants may use 1mg PO:0.5mg IV conversion.

Glucocorticoid Systemic Equivalencies

Glucocorticoid	Approximate Dose (mg)	Relative Antiinflammatory potency	Relative Mineralocorticoid potency
Hydrocortisone	20	1	1
Prednisone/Prednisolone	5	4	0.8
Methylprednisolone	4	5	0.5
Dexamethasone	0.75	25-30	0
Fludrocortisone	-	10	125

XIII. Table for Dosing Ganciclovir/Valganciclovir in renal dysfunction

CrCl (ml/min)	Ganciclovir Treatment Dose (mg/kg)*	Dosing Interval (hours)	Ganciclovir Prophylaxis Dose (mg/kg)*	Dosing Interval (hours)
≥70	5.0	12	5.0	24
50-69	2.5	12	2.5	24
25-49	2.5	24	1.25	24
10-24	1.25	24	0.625	24
<10	1.25	On dialysis days-give after dialysis	0.625	On dialysis days-give after dialysis

* Use Total Body Weight (Adapted from Package Insert)

CrCl (mL/min)	Valganciclovir Treatment Dose	Valganciclovir Prevention Dose
≥60	900mg twice daily	900mg once daily
40-59	450mg twice daily	450mg once daily
25-39	450mg once daily	450mg every 2 days[1]
10-24	450mg every 2 days[1]	450mg twice weekly
<10 (on hemodialysis)	Not recommended[2]See text below	Not recommended[2]See text below

[1]For patients with CrCl 10-24 requiring Valganciclovir Treatment dosing, or for patients with CrCl 25-39 requiring Valganciclovir Prophylaxis dosing (for patients requiring every 2 days dosing) MWF dosing may be used if every 2 days dosing is considered a threat to treatment adherence

[2]For pts with CrCl <10 (i.e. where Valganciclovir is not recommended):

1. Preferred option
   a. Prophylactic dosing
      i. IV ganciclovir per package insert (0.625mg/kg iv 3x/week, give after HD if on HD)
      ii. If available: Oral ganciclovir 500mg po 3x/week, give after HD if on HD
   b. Treatment
      i. IV ganciclovir iv on days of dialysis, given after HD. (For example, if pt dialyzes 5 times a week, then the dose should be given 5 times a week)
      ii. If available: Oral ganciclovir 500mg po 3x/week, give after HD if on HD
2. **Alternative options should only be considered if recommended by Transplant ID.**

For alternative renal replacement therapy (i.e. CVVH, SLED, SCUF) please contact clinical pharmacist for recommendations

Product Information: Cytovene(R), ganciclovir injection and capsules. Roche Laboratories, Inc., NutleyNJ, 2000.
Product Information: Valcyte™, valganciclovir. Roche Pharmaceuticals, Nutley, New Jersey, 2001.
Czock, D; Scholle C; Rasche, FM, et al. Pharmacokinetics of valganciclovir and ganciclovir in renal impairment. Clinical Pharmacology& Therapeutics 2002 Aug;72(2):142-50.

XIV. Bacterial Endocarditis Prophylaxis: Dental Procedure Guidelines

Antibiotic prophylaxis with dental procedures is reasonable only for patients with cardiac conditions associated with the highest risk of adverse outcomes from endocarditis, including:

- Prosthetic cardiac valve or prosthetic material used in valve repair
- Previous endocarditis
- Congenital heart disease only in the following categories:
    - Unrepaired cyanotic congenital heart disease, including those with palliative shunts and conduits
    - Completely repaired congenital heart disease with prosthetic material or device, whether placed by surgery or catheter intervention, during the first six months after the procedure*
    - Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation recipients with cardiac valvular disease

High Risk Dental Procedures (Definition): those that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa.

Situation	Agent	Single Dose 30-60 minutes before procedure (Adult recs)
PO	Amoxicillin	2 g PO
NPO	Ampicillin **OR**	2 g IM or IV
	Cefazolin **OR** Ceftriaxone	1 g IM or IV
PO: Allergic to penicillins or ampicillin	*#Cephalexin **OR**	2 g PO
	Clindamycin **OR**	600 mg PO
	Azithromycin **OR** Clarithromycin	500mg PO
NPO: Allergic to penicillins or ampicillin	*Cefazolin **OR** *Ceftriaxone	1 g IM or IV
	OR Clindamycin	600mg IM or IV

*Cephalosporins should not be used in a person with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin
#Or other first or second generation oral cephalosporin in equivalent adult dosage.

Adapted from: Wilson W et al.Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, council on Cardiovascular Disease in the Young, and the council on clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. **Circulation 2007; 116(15): 1736-1754.**

XV. Low Molecular Weight Heparin Dosing Guidelines

See UWMC ACC web site: http://depts.washington.edu/anticoag/home/ for complete details and/or consult pharmacist

Indications	Enoxaparin (Lovenox®)
Initial treatment of VTE	1mg/kg SQ q12h Minimum course - 5 days and INR > 2 *CrCl 30-60 = 0.85mg/kg SQ q12h* *CrCl <30 = IV unfractionated heparin preferred; may use Enoxaparin 1mg/kg q24h as alternative* *See monitoring guidelines below.*
Bridge therapy * If this is being done as an outpatient peri-procedurally, please consult the anticoagulation clinic that manages pt to coordinate care.	1mg/kg SQ q12h Treatment until INR ≥ lower limit of therapeutic range *CrCl 30-60=0.85mg/kg SQ q12h* *CrCl <30= IV unfractionated heparin preferred; may use 1mg/kg q24h as alternative* *See monitoring guidelines below.*

LMWH Dosing in Renal Impairment

If Anti-Xa monitoring is NOT available: Avoid use if CrCl < 30 ml/min
If Anti-Xa monitoring is available: consider the following initial dosing and adjust PRN based on trough Anti-Xa activity levels:
CrCl >60: Enoxaparin 1mg/kg SQ q12h
CrCl 30-60: Enoxaparin 0.85mg/kg SQ q12h
CrCl <30: IV unfractionated heparin is preferred; Enoxaparin 1mg/kg SQ q24h is an alternative

Trough Anti-Xa Goal: <0.5 units/ml. Monitoring may be indicated to evaluate accumulation.

Short Term Monitoring Guidelines

- Baseline PT/aPTT
- Baseline hematocrit and q3-5 days (then prn if bleeding is suspected or confirmed)
- Baseline platelet count, and q3-5 days during first 2 weeks of LMWH therapy
- Baseline serum creatinine, and q3-5days, (then prn if change in renal function is suspected, or if bleeding is suspected or confirmed)

Recommendations on Enoxaparin Use in Cardiac Biopsy

- Please consult attending physician and pharmacist for guidance as management is tailored to the individual's bleeding risk, renal function, and indication for anticoagulation.
- If receiving q12h Enoxaparin, last dose of Enoxaparin is given 36 hrs prior to biopsy. Hold both doses day before biopsy, AM of biopsy, and PM dose immediately after biopsy. Do not resume until at least the morning after day of biopsy.
- If receiving q24h Enoxaparin, last dose of Enoxaparin is given 48h prior to biopsy, but the dose should be reduced by 50%. Hold doses day before biopsy and on day of biopsy. Do not resume Enoxaparin until at least the morning after day of biopsy.

XVI. Vaccines in Solid Organ Transplant

Summary recommendations:

Timing of Immunizations — The waiting period pre-transplant should be used to maintain or boost antibody concentrations for all recommended vaccines. Although vaccination responses in some patients awaiting transplantation are suboptimal, antibody responses are usually even more attenuated when vaccines are administered after transplantation. Other reasons to immunize patients before transplantation include the fact that live virus vaccines (eg, measles, mumps, rubella, varicella, and the intranasal influenza vaccine) are usually avoided posttransplant. The American Society of Transplantation (AST) recommends waiting a minimum of four weeks between live virus vaccine administration and transplantation. An important issue is the optimal timing to resume immunization following solid organ transplantation. As stated in the AST guidelines, most transplant centers restart vaccination at approximately three to six months after transplantation, once maintenance immunosuppression levels have been attained.

Inactivated vaccines — Inactivated vaccines are generally considered to be safe following solid organ transplantation, although there has been concern about their potential for triggering organ rejection. However, this has not been substantiated by clinical studies. Routine seasonal administration of the inactivated influenza vaccine is recommended for all transplant candidates and recipients every year, including the first year after transplantation. The intranasal live-attenuated influenza vaccine is contraindicated in transplant recipients. **Inactivated Vaccines:** Tetanus toxoid (Td), Tetanus diphtheria pertussis (Tdap), Poliomyelitis (injectable only), Pneumococcal, Hepatitis B, Hepatitis A, Meningococcal, Haemophilus influenza type B (pediatric), Influenza (injectable only), Japanese encephalitis, Typhoid (injectable only), HPV (Gardasil®) age 9-26.

Live virus vaccines — AST recommends waiting a minimum of four weeks between live virus vaccine administration and solid organ transplantation. Live organism vaccines are generally avoided following solid organ transplantation given the potential for active infection. **Live Vaccines:** Measles/Mumps/Rubella (MMR), Oral poliomyelitis, Oral Typhoid, BCG vaccine (Bacillus Calmett-Guerin), Varicella (Chickenpox), Zoster (Shingles), Vaccinia (Smallpox), Yellow Fever, Nasal Influenza, Nasal H1N1 Influenza

Live virus vaccines in household contacts — Family members should be immunized fully, and in particular should receive annual influenza vaccines. Inactivated vaccine options are preferred. With the exception of small pox and oral polio vaccines, there is little to no risk from the close contacts receiving live vaccines. It is preferred that household and close contacts be vaccinated against measles/mumps/rubella, and varicella. Rotavirus vaccines also pose a theoretical risk of transmission. Good handwashing is recommended after diaper changes. Vaccinees who develop a rash should avoid contact with transplant recipients for the duration of the rash.

***Recommended vaccinations for adult solid organ transplant candidates and recipients:**
*(see table 2 in reference for full prescribing recommendations for these vaccines)

Vaccine	Inactivated/ live attenuated	Recommended before transplant	Recommended after transplant	Monitor vaccine titers
Influenza	I	Yes	Yes	No
	LA	No	No	No
Hepatitis B	I	Yes	Yes	Yes
Hepatitis A	I	Yes	Yes	Yes
Tetanus	I	Yes	Yes	No
Pertussis (Tdap)	I	Yes	Yes	No
Inactivated Polio vaccine*	I	Yes	Yes	No
S. pneumoniae	I	Yes	Yes	Yes
N. meningitides* (conjugate vaccine)	I	Yes	Yes	No
Human papilloma virus (HPV)*	I	Yes	Yes	No
MMR	LA	Yes	No	No
Varicella (live-attenuated; Varivax)	LA	Yes	No	Yes
Varicella (live-attenuated;Zostavax)	LA	Yes	No	No
Varicella (recombinant-adjuvanted; Shingrix)	I	Yes	No	No

* Recommended only in certain populations; please refer to reference.

Reference:

Danzinger-Isakov L, Kumar D. Vaccination in Solid Organ Transplantation. Am J Transplant. 2013;13:311-317.

XVI. Vaccines in Solid Organ Transplant

Pneumococcal vaccines- Two main formulations are available for use: a 23-valent polysaccharide vaccine and a 13-valent protein-conjugated vaccine. The protein-conjugated vaccine may produce a greater antibody response. Thus, new ACIP recommendations state that patients should be vaccinated with a prime-boost strategy using both the conjugate followed by the polysaccharide vaccine 8 weeks later. For details on who is a candidate for this strategy and timing, please consult the Transplant Infectious Diseases service.

Reference:

1. http://www.cdc.gov/vaccines/pubs/ACIP-list.htm
2. UWMC Guidelines for Pneumonia Vaccine for Solid Organ Transplant Candidates/Patients.

XVII. Neutropenia Management Guidelines

ABSOLUTE NEUTROPHIL COUNT (ANC)	MANAGEMENT APPROACH
ANC < 1500	Ensure that Valganciclovir is renally adjusted.
ANC < 1000	Consult Cardiology attending and Transplant ID for further guidance on individualized management.

General dosing of Filgrastim:
5mcg/kg/day (round to nearest vial size: 300mcg or 480mcg vials) subcutaneous x 2 doses then recheck CBC.

XVIII. Electrolyte Supplements

Calcium Salts	% Ca++	Strength / route	mg Ca++	mEq Ca++
Calcium acetate	25 %	667mg capsule PO	169mg	8.4 mEq
Calcium carbonate	40 %	500mg tablet PO	200mg	10 mEq
Calcium chloride	27.3%	100mg/ml IV	27.3 mg/ml	1.36 mEq/ml
		1gm		**13.6 mEq = 1 amp**
Calcium citrate	21%	950 mg tablet PO	200 mg	10 mEq
Calcium glubionate	6.5%	360mg/ml soln PO	23.4 mg/ml	1.17 mEq/ml
Calcium gluconate	9.3%	100mg/ml IV	9.3mg/ml	0.465 mEq/ml
		1gm		**4.5 mEq = 1 amp**
	9.3%	500mg PO	45 mg	2.3 mEq

Phosphate Salts	Strength / route	mmol PO4	mg PO4	mEq Na or K
Sodium phosphate	250 mg tab PO	8 mmol	**250 mg/tablet**	Na- 13 mEq/ 298mg K- 1.1 mEq/ 45 mg
Sodium phosphate **(Phospho-Soda®)**	Solution	4.15 mmol/ml	130 mg/ml	Na- 4.82 mEq/ml
Sodium phosphate	3 mmol/ml IV	3 mmol/ml	93 mg/ml	Na- 4 mEq/ml (92mg/ml)
		30 mmol		**40 mEq NaPO4**
Sod/Pot phosphate **(Phos-Nak®, Neutra-Phos®)**	250 mg pwdr PO	8 mmol	**250 mg/pkt**	Na- 7.1 mEq / 164 mg K- 7.1 mEq / 278 mg
Potassium phosphate	3 mmol/ml IV	3 mmol/ml	93 mg/ml	K- 4.4 mEq/ml (170mg/ml)
		30 mmol		**44 mEq KPO4**
Milk		0.03 mmol/ml		

Magnesium Salts	% Mg++	Strength / route	mg Mg++	mEq Mg++
Mag hydroxide (MOM)	41.7%	400 mg/5ml PO	166.8 mg/5ml	13.7 mEq/5ml
Mag citrate	16.2%	291 mg/5ml PO	47 mg/5ml	3.8 mEq/5ml
Mag oxide	60.3%	400 mg tab PO	241 mg	19.5 mEq
Mag sulfate	9.9%	**1gm**/ 2 ml IV	99 mg	**8 mEq = 1 amp**
Mg amino acid chelate (Mg + protein®)	20%	665 mg tab PO	133 mg	10.7 mEq
Mg chloride hexahydrate (Slow-Mg)		64mg PO	64mg	5.3 mEq

Iron Salt/Complex	% Fe++	Strength / route	mg Fe++
Ferrous gluconate	12%	324 mg tablet PO	38 mg
Ferrous sulfate	20%	325 mg tablet PO	65 mg
Polysaccharide iron complex (Niferex®, Ferrex 150®)		150mg tablet PO	150mg
Iron dextran (Infed®)		50 mg/ ml IV	50 mg
Iron sucrose (Venofer®)		20 mg/ml IV (sucrose 300mg/ml)	20mg
Sodium Ferric gluconate complex (Ferrlecit®)		12.5 mg/ml IV (sucrose 195mg/ml)	12.5 mg

Sodium bicarbonate	Strength/route	mEq
	650mg PO	7.8 mEq
	83mg/ml IV (8.4%)	1 mEq/ml IV
	50ml IV (8.4%)	**50meq = 1 amp**