

UNIVERSITY OF PITTSBURGH MEDICAL CENTER



**LUNG TRANSPLANTATION MANAGEMENT
GUIDELINES**

August 2016

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MAINTENANCE IMMUNOSUPPRESSION AFTER ALEMTUZUMAB (CAMPATH) INDUCTION

MONTHS	1-12	12-24	> 24 & CKD	NOTES:
Prednisone (mg/day)	5 Begin AM post-op day 1	5	5	
Tacrolimus *□ (blood level) 1 st choice	10-15 (10-12 hour trough)	8-12	6-10	Begin 1 mg PO bid. Give 1 st dose 6 hours after arrival to ICU
Cyclosporine ~□ (usually Neoral) (blood level)	200-300 (10-12 hour trough)	200-250	100-200	Use if intolerant to Tacrolimus
Cellcept (250 mg /tablet)	Begin 500mg PO bid			Monitor neutropenia; Adjust dose accordingly
Myfortic (180 mg /tablet)	Begin 360 mg PO bid			Use if GI intolerance to Cellcept
OTHER MEDICATIONS				
Azathioprine † (WBC > 3.5)	1 – 2 mg/kg/d			Start 50 mg/day, increase to goal after one week if WBC acceptable and tolerating
Sirolimus + (blood level)			4-12 ⁺⁺ in combination with calcineurin inhibitors	Steady-state concentrations occur 5-7 days after dose change
Everolimus	3-8		3-8 in combination with CNI	Steady state concentrations occur 5 days after dose change

* Increase by 0.5 mg to achieve target blood level

~ Increase by 25 mg to achieve target blood level

+ Separate dosing by 4 hours from cyclosporine.

⁺⁺ *Sirolimus/Everolimus Dosing paradigm*: When using sirolimus or everolimus to decrease FK dose, we target a sirolimus/everolimus level of approximately 6-8 or 3-8 with an FK level of 4-6. This would add together to an additive goal of 10-12. The target levels are usually determined by calculating what the ideal FK level would be post-transplant, and then having a total FK + TOR inhibitor dose equal to that level. Avoid starting sirolimus or everolimus during the first three months after transplant, or when a major surgical procedure is anticipated over the next month.

† Avoid concomitant use of allopurinol and azathioprine.

Avoid dosing calcineurin inhibitors within 2 hours of magnesium, phosphorus and calcium.

Consider lower trough calcineurin inhibitor level target in patients > 65 years old if no history of rejection on serial biopsies or opportunistic infection

MAINTENANCE IMMUNOSUPPRESSION AFTER SIMULECT INDUCTION

Induction: 2 doses of 20 mg basiliximab, the first dose in the OR and on post-op day 4, methylprednisolone 1 gram iv in the OR and 125 mg for 6 doses; MMF 1g bid and Cyclosporine or prograf and prednisone taper as below.

MONTHS	1-12	12-24	> 24 & CKD	NOTES:
Prednisone (mg/day)	Begin gradual taper [#] after post-op routine taper, 20 mg by day 7	5-10	5	Prednisone taper beginning after first negative biopsy for ACR: generally 5 mg by month 6
Tacrolimus *□ (blood level) 1 st choice	10-15 (10-12 hour trough)	8-12	6-10	Begin 1 mg PO bid. Give 1 st dose 6 hours after arrival to ICU
Cyclosporine ~□ (usually Neoral) (blood level)	200-300 (10-12 hour trough)	200-250	100-200	Use if intolerant to Tacrolimus
Cellcept (250 mg /tablet)	750 mg PO bid			Monitor neutropenia; Adjust dose accordingly
Myfortic (180 mg /tablet)	540mg PO bid			Use if GI intolerance to Cellcept
OTHER MEDICATIONS				
Azathioprine † (WBC > 3.5)	1.0 – 2 mg/kg/d			Start 50 mg/day, increase to goal after one week if WBC acceptable and tolerating
Sirolimus + (blood level)			4-12 ⁺⁺ in combination with calcineurin inhibitors	10-16 ⁺⁺ Without calcineurin inhibitors Steady-state concentrations occur 5-7 days after dose change.
Everolimus	3-8		3-8 in combination with CNI	Steady state concentrations occur 5 days after dose change

#Pace of prednisone tapered is modified based on rejection history and complications (egs., prolong taper if early rejection; accelerate taper if no rejection and wound or infection complications) . Usually 20mg BID for two weeks then 20mg daily for the first two months

* Increase by 0.5 mg to achieve target blood level

~ Increase by 25 mg to achieve target blood level

+ Separate dosing by 4 hours from cyclosporine.

++ *Sirolimus Dosing paradigm*: When using rapamycin to decrease FK dose, we target a rapamycin level of approximately 6-8 with an FK level of 4-6. This would add together to an additive goal of 10-12. The target levels are usually determined by calculating what the ideal FK level would be post-transplant, and then having a total FK + Rapa dose equal to that level.

T Avoid concomitant use of allopurinol and azathioprine

Avoid dosing calcineurin inhibitors within 2 hours of magnesium, phosphorus and calcium.

Consider lower immunosuppression in patients > 65 years old if no history of rejection on serial biopsies in the first few months after transplant; this could include lower CNi trough target levels or lower dose/holding antimetabolite

Common Drug Interactions and Effects on FK/CsA levels

Increase FK/CsA Level	Decrease FK/CsA Level
diltiazem, nicardipine, verapamil	Magnesium oxide, sodium bicarbonate, antacids (take 2 hours before/after Prograf)
fluconazole, itraconazole, ketoconazole	Nafcillin
voriconazole, posaconazole	Rifampin >>> rifabutin
clarithromycin, erythromycin	carbamazepine
lanzoprazole, rabeprazole	phenobarbital
cimetidine	phenytoin
methylprednisolone	octreotide
allopurinol	ticlodipine
bromocriptine	orlistat
metoclopramide	St. John's Wort
colchicines	
amiodarone	
danazole	
grapefruit juice	

- This is not all-inclusive – for a more thorough drug interaction search, use any online pharmacy resource or ask clinical pharmacist

Post-transplant Pulmonary Surveillance for Rejection/Infection

- Microspirometry
- Spirometry
- Bronchoscopy and transbronchial biopsy

Time post transplant	PFTs (spirometry)	Bronchoscopy Frequency	Home Microspirometry
Year 1	Q 1 month	Q 2-3 mos	3 times weekly
Year 2	Q 1 month	Q 4 mos	3 times weekly
Year 3	Q 1 month	At least once end of year 3	3 times weekly
> 3 years	Q 1-2 month	as indicated by PFTs/symptoms	3 times weekly

Bronchoscopy q 2-3 month initially; reduce frequency to q3-4 months if 3 consecutive biopsies show no ACR and there is no clinical indication for bronchoscopy.

**First PFTs at first pulmonary clinic visit after discharge. Monthly spirometry
Bronchoscopy 2-3 weeks after treatment for biopsy-proven ACR.**

REJECTION

Definitions

Acute Cellular Rejection:

- Probable
 - At least 10% fall in FEV₁
 - Absence of another explanation (e.g. infection) for symptoms or decline in FEV₁
 - No histological evidence of acute rejection
- Definite
 - At least 10% fall in FEV₁
 - Absence of another explanation for symptoms or decline in FEV₁
 - Histological confirmation of Grade 1 or greater rejection
 - OR Histological confirmation of Grade II or greater rejection found on surveillance biopsy in the absence of clinical findings

Histological Grading of Acute Cellular Rejection (ACR)

Pathologic classification and grading of pulmonary allograft rejection

Nomenclature	Classification	Grading
A	acute rejection	0 – none 1 – minimal 2 – mild 3 – moderate 4 – severe x –ungradable
B	airway inflammation	0 – none 1R – low grade 2R – high grade x –ungradable
C	chronic airway rejection	0 – absent 1 – present x –ungradable
D	chronic vascular rejection	Accelerated graft vascular sclerosis

From: Stewart A, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transplant 2007; 26: 1229-42.

Definition of Acute Rejection according to Response to Treatment

Responsive to treatment	1 episode of \geq grade 2 acute rejection with return to A0 or A1 after treatment
Recurrent rejection	At least two treated episodes of \geq grade A2 acute rejection with return to A0 or A1 between episodes
Persistent rejection	Two consecutive, treated episodes of \geq A2 acute rejection without return to A0 or A1 between episodes
Refractory rejection	At least three consecutive, treated episodes of \geq grade A2 acute rejection without return to A0 or A1 between episodes

Treatment of Acute Cellular Rejection

Asymptomatic ACR Grade 2 or symptomatic grade 1

- Prednisone 550 mg taper (100 mg PO then decrease by 10 mg daily until back to baseline steroid maintenance dose)
- Bronchoscopy with biopsy 2-3 weeks after completion of taper.

Symptomatic ACR grade 2 or grade 3-4

- Solumedrol 1 gram IV times 3 days (~15 mg/kg/day for weight <50 kg); adjust dose for patients who are on azoles at time of solumedrol given prolongation of half life (Usually reduced to 750mg IV times 3 days)
- Bronchoscopy with biopsy 2-3 weeks after treatment
- Consider fungal and/or CMV prophylaxis if history of fungal infection/CMV mismatch or high risk environment
- Check CMV-PCR weekly for two months after steroid bolus (based on the in vitro data of steroid effects on PBMC function, as well as clinical experience at UPMC)

Persistent or Refractory Rejection - Options

- Thymoglobulin (RATG)
- Alemtuzumab (Campath)
- Sirolimus (Rapamycin) or Everolimus (Zortress)
- Solumedrol
- Photophoresis
- Total lymphocytic radiation

Anti-lymphocyte Therapy *Consider lymphocytic characterization prior to starting*

- **Thymoglobulin** (Rabbit Anti-Thymocyte Globulin) No skin test required
 - Start 1.5 mg/kg IV as a 4 to 12 hour infusion daily for 7 days.
 - First infusion over 6 hours and subsequent 4 hours
 - Premedicate with:
 - Methylprednisolone (Solu-medrol) 1000mg IV (1st dose only); decrease by 250mg per day until 100mg prior to each dose
 - Diphenhydramine 25mg IV or PO 1 hour prior to dose and q6 hours PRN
 - Acetaminophen 650mg PO 1 hour prior to dose and q6 hours PRN
 - Reduce dose by one half if WBC count is between 2000-3000/mm³ or platelet count is 50,000 – 75,000. Discontinue if count lower.
 - Discontinue if ANC < 1000.
- **Alemtuzumab** (Campath)
 - 30 mg IV times one dose only
 - Adjust dose to 15-20 mg IV for patient < 40 kg
 - Premedicate one hour prior to administration with
 - Methylprednisolone (Solumedrol) 1000mg IV
 - Acetaminophen (Tylenol) 650mg PO
 - Diphenhydramine (Benadryl) 50 mg IV
 - Famotidine (Pepcid) 20 mg IV

Humoral (antibody-mediated) rejection

Antibody mediated rejection (AMR) occurs when the recipient develops antibodies against donor specific antigens. Antibody mediated rejection is a diagnosis consisting of several criteria including:

- Circulating donor specific antibodies (DSA)
- Allograft dysfunction
- Tissue pathology
- C4d deposition and/or C1q positivity
- Exclusion of all other causes of allograft dysfunction

Classification

- Clinical
 - Definite: Presence of all 5 criteria
 - Probable: Allograft dysfunction in the presence of 2 of the 3 following criteria: presence of DSA; positive histology suggestive of AMR; and positive C4d staining
 - Possible: Allograft dysfunction in the presence of 1 of 3 following criteria: presence of DSA; positive histology suggestive of AMR; and positive C4d staining
- Recent review by our group and others has demonstrated that development of donor-specific antibodies (DSA) detected by HLA antibody screen is associated with a markedly increased risk of chronic rejection and premature mortality.

Diagnosis of Antibody-Mediated Rejection (AMR)

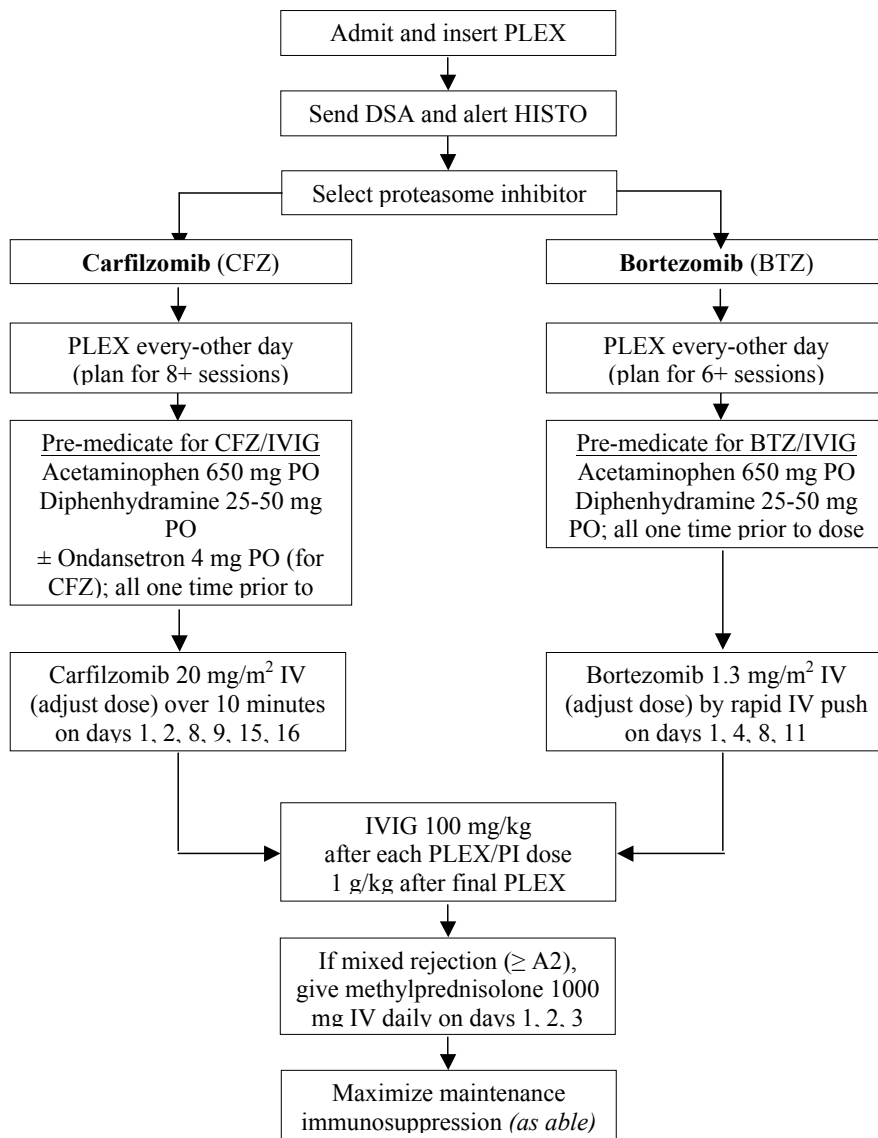
- Presentation:
 - Mostly mixed-rejection (ACR + AMR)
 - Rare isolated AMR (~5% of cases)
- AMR diagnosis requires:
 - + Presence of DSA (anti-HLA or non-HLA, high-strength/high-titer/C1q-positive)
 - + Allograft dysfunction (in the absence of another identifiable cause)
 - ± Pathologic findings consistent with AMR (Capillaritis, neutrophilic septal margination, C4d pericapillary deposition, etc.)
- Patients at elevated-risk for AMR/Antibody-mediated allograft dysfunction:
 - Sensitized patients with preformed DSA
 - Early de novo DSA production
 - Presence of increasing-strength/increasing-titer or high-strength/low-titer DSA
 - Recurrent ACR episodes
 - Alemtuzumab induction

Treatment Indications

- Requires empiric therapy:
 - Any upper-moderate antibodies crossed at the time of transplant
 - Positive virtual or CDC crossmatch
- Requires AMR treatment:
 - Diagnosis of AMR
 - Recurrent/refractory ACR in the presence of DSA
- Consider AMR treatment:
 - Presence of high-strength/high-titer/C1q-positive DSA without allograft dysfunction
 - Rapidly increasing-strength/increasing-titer DSA

AMR Treatment

For patients with the diagnosis of AMR or recurrent/refractory ACR in the presence of DSA. Consider for patients with presence of high-strength/high-titer/C1q-positive DSA without allograft dysfunction or rapidly increasing-strength/increasing-titer DSA.



Caveats and details of AMR Treatment

- Total-plasma exchange/plasmapheresis (PLEX)
 - 1.5 exchanges per session
 - Replacement fluids
 - Not bleeding/not anticoagulated: 5% albumin (100%)
 - If bleeding or anticoagulated and cannot stop/reverse: mixed FFP and 5% albumin (50%:50%)
 - PLEX duration is NOT fixed
 - Each Luminex-IgG dilution corresponds to 1 PLEX session (e.g., neat serum diluted 1:2 corresponds to 1 session of PLEX)
 - If MFI on initial Luminex-IgG has not fallen at 1:16 dilution, more than 5 sessions are likely needed for clinically meaningful DSA depletion
- Follow ANY PLEX with IVIG
 - Use 4th generation Gammagard 10% liquid
 - Round dose to the nearest 2.5 grams
- Proteasome inhibitor caveats
 - Requires HSV prophylaxis with acyclovir 400 mg BID (or as adjusted) during treatment and for 3 additional months, unless on lifelong HSV prophylaxis or CMV prophylaxis with valganciclovir
 - Dosage adjustments:

Toxicity	Parameters	CFZ dose adjustment	BTZ dose adjustment
Neutropenia	ANC < 1000	Hold until > 1000 and reduce to 15 mg/m ²	Hold until > 1000 and reduce to 1 mg/m ²
Thrombocytopenia	< 50,000	Reduce to 15 mg/m ²	Hold until > 50,000 and reduce to 1 mg/m ²
	< 25,000	Hold until > 25,000 and reduce to 15 mg/m ²	
Peripheral neuropathy	Affecting ADLs	Hold until resolved and reduce to 15 mg/m ²	Reduce to 0.7 mg/m ²
Hepatotoxicity (attributable to CFZ)	AST/ALT > 5x ULN	Hold until resolved and reduce to 15 mg/m ²	None
	Bili > 3x ULN		
Nephrotoxicity	SCr > 2x baseline	Hold until resolved and reduce to 15 mg/m ²	None

- DSA testing
 - Alert the HISTO lab to concern for AMR
 - Send Luminex-IgG and Luminex-C1q before starting any PLEX

- Send Luminex-IgG with dilution to 1:16 and Luminex-C1q after the second to last planned PLEX session to determine if additional sessions are required
 - Additional sessions will be required if DSA MFI > 2000 at 1:16 dilution or C1q-positive
- Send Luminex-IgG with dilution to 1:16 and Luminex-C1q 14 and 28 days after completion of treatment
- Maximize maintenance immunosuppression as able
 - Maximize MMF dose to 1000-1500 mg BID
 - Consider conversion of MMF to MPS 720-1080 mg BID to improve mycophenolate pharmacokinetics
 - Maximize T-cell suppression
 - Change cyclosporine to tacrolimus
 - Increase CNI trough target
 - Augment with mTOR or PO cyclophosphamide as 4th agent (enhanced accommodation)
- Asymptomatic DSA (latent humoral response, silent humoral rejection or subclinical humoral rejection)
 - Add antimetabolite, preferably mycophenolate if not currently on
 - Assess for hypogammaglobulinemia, and replete with IVIG if low (<700)
 - Consider rituxan

Evaluation and Management of Decline in FEV₁

- Commonly suspect infection or acute rejection in first 12 months; and chronic rejection after 12 months
 - Pulmonary function lab spirometry (preferably UPMC) plus CXR and sputum culture if feasible
 - Consider HRCT without contrast and inspiratory/expiratory images (BOS protocol CT) to assess for changes of chronic rejection such as air trapping
 - HLA antibody screen to assess for donor-specific HLA antibodies as marker of potential antibody-mediated rejection
 - Empiric therapy for bacterial pneumonia, particularly if sufficiently ill to require hospital admission
 - Bronchoscopy with BAL and transbronchial biopsy (TBBx) to assess for anastomotic stenosis/malacia, rejection, infection
 - If no evidence of infection and strong clinical suggestion of rejection, treat as per acute rejection with solumedrol or further therapies as indicated. May cover with antibiotics
 - Review maintenance immunosuppression and consider increase in maintenance immunosuppression
 - Repeat spirometry in no later than 2-3 weeks.

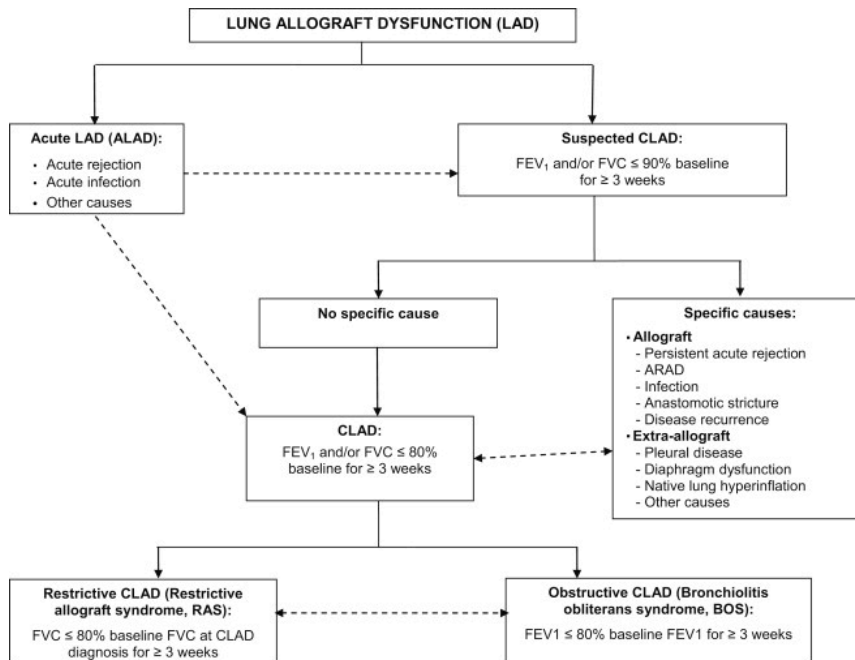
If no improvement:

- Consider repeat bronchoscopy or open lung biopsy
- Upper GI, pH probe, and manometry to assess for GERD and contribution to allograft dysfunction
- Consider repeating Solumedrol

If no improvement:

- Consider repeat bronchoscopy or open lung biopsy
- Cytolytic therapy with alemtuzumab or thymoglobulin
- Change in immunosuppression – see BOS protocols
 - Consider prednisone increase
 - If persistent proven pathology of ACR consider RATG, Campath, rapamycin, or photopheresis.

Lung Allograft Dysfunction Classifications:



From: G. Verleden et al. Journal Heart Lung Transplant, 2014

Bronchiolitis Obliterans Syndrome Classification System

Classification of bronchiolitis obliterans syndrome after lung transplantation

Stage	Pulmonary function criteria
BOS 0	FEV ₁ > 90% baseline* & FEF ₂₅₋₇₅ > 75% baseline*
BOS 0-p (potential)	FEV ₁ 81-90% baseline* &/or FEF ₂₅₋₇₅ ≤ 75% baseline*
BOS 1	FEV ₁ 66-80% baseline*
BOS 2	FEV ₁ 51-65% baseline*
BOS 3	FEV ₁ ≤ 50% baseline*

Baseline FEV₁ = avg of 2 best FEV₁ values after transplant

Baseline FEF₂₅₋₇₅ = avg of 2 best FEF₂₅₋₇₅ values after transplant

Decline is determined by two measurements at least one month apart

From: Estenne M et al. Bronchiolitis obliterans syndrome 2001: An update of the diagnostic criteria. J Heart Lung Transplant 2002; 21: 297-310.

Treatment strategies for Bronchiolitis Obliterans Syndrome (BOS)

- Review immunosuppression and bronchoscopy results; exclude infection and antibody-mediated rejection
- Exclude significant gastroesophageal reflux disease (GERD)
- Assess for humoral rejection with HLA antibody screen
- Consider Solumedrol (for possible “missed ACR”)
- Consider altered immunosuppression:
 - Azithromycin 250mg PO three times weekly, especially if neutrophilia present on BAL
 - Increase Cellcept/Myfortic
 - Add mTOR inhibitor (rapamycin or everolimus), or change MMF to mTOR inhibitor
 - Inhaled steroids, particularly if neutrophilic inflammation, with bronchodilators
 - Statin, unless contraindication
 - Leukotriene receptor antagonist (montelukast)

Progressive BOS consider:

- Cytolytic therapy with alemtuzumab or thymoglobulin
- Inhaled cyclosporine (if able to obtain)
- Photopheresis
- Plasmapheresis and IVIG

Switching Calcineurin Inhibitors

- Indications: Usually intolerance of tacrolimus (neurologic, gastrointestinal, or psychiatric complications, TTP/HUS, refractory neutropenia, chronic kidney disease)
- Caution that change from tacrolimus to cyclosporine may be associated with increased incidence of ACR. Frequent rejection surveillance after change is essential.
- Tacrolimus to cyclosporine OR cyclosporine to tacrolimus
Discontinue first drug then start alternative drug with the next dose.
Check drug level at Day 3
As a starting dose: 50 mg cyclosporine \approx 1 mg prograf

Initiating Sirolimus or Everolimus

- **Avoid in first 3 months post-transplant or if anticipate surgery in near future**
- Sirolimus with continuation of calcineurin inhibitor, and with or without discontinuation of antimetabolite. Check UA before starting rapamycin to assess for proteinuria. Avoid sirolimus if proteinuria as it can worsen the renal function.
- Adjust dosing if patient is on voriconazole. Rapamycin should not be taken within 4 hours of cyclosporine. Prograf and rapamycin can be taken together.

Sirolimus

For less than 55kg or CKD stage \geq 3

6 mg loading dose
2 mg/day thereafter
1st level 1 week after loading
Goal level 6-12

3 mg loading dose
1 mg/day thereafter
1st level 1 week post loading
Goal level 6-12

Everolimus

Start at 0.75mg BID
Can check level 3-4 days after initiation

Monitor: triglycerides before starting rapamycin, then monthly thereafter

Belatacept

Uses:

- CNI replacement: direct contraindication to continued CNI therapy
- CNI sparing: reduced dose CNI
- Add-on immunosuppression for rejection where additional myelotoxins are contraindicated
- MUST be EBV R+ (EBV mismatch [D+/R-] is a direct contraindication to belatacept use)

Pharmacokinetics:

- Half-life = 10 days

Dosing:

- Within 6 months of transplantation or immediate CNI replacement
 - Belatacept 10 mg/kg IV on days 1 and 5, weeks 2, 4, 8, 12
 - Belatacept 5 mg/kg IV once every 4 weeks starting at week 16
- Transition from CNI to belatacept
 - Belatacept 5 mg/kg IV on day 1 and weeks 2, 4, 6, 8, 12 and once every 4 weeks thereafter
 - Taper CNI: decrease dose/trough target by 50% at 2 weeks, by 75% at 3 weeks, and off at 4 weeks.
- CNI sparing
 - During year 1: Reduce FK to 6-8, CSA 100-150
 - After year 1: Reduce FK to 4-6, CSA 50-100
- Other immunosuppressants per routine protocol.
- Usually given in an infusion center. Nulojix-Network infusion center locator available at: <http://www.nulojix.com/hcp/support/locator/infusion-center-locator.aspx>.

Concomitant drugs:

- HSV/VZV prophylaxis if not on CMV prophylaxis: acyclovir 400 BID or renal equivalent
- Triazole fungal prophylaxis – posaconazole/isavuconazole > voriconazole > itraconazole

Relevant Adverse Effects:

- Infections, viral/fungal
- Progressive multifocal leukoencephalopathy (PML)
- Post-transplant lymphoproliferative disorder (PTLD)
- Alopecia

REMS

- **MUST** provide each patient with medication guide available at:
http://packageinserts.bms.com/medguide/medguide_nulojix.pdf.

Immunosuppression in the patient with Cancer or Opportunistic Infection

- Skin Cancer – Basal/Squamous/Non-aggressive
 - No change in immunosuppression
- PTLD – Reduce immunosuppression
 - Example: FK goal 4-6 if no recent ACR
 - FK goal 6-10 if recent ACR, or transplanted within 1 year
 Consider addition of mTOR
- Other cancers
 - Consider reducing immunosuppression and substituting mTOR inhibitor
- Nocardia/Invasive Fungal Infection, or active CMV infection
 - Consider holding 3rd agent (MMF or azathioprine) until acute infection IS controlled.
 - Consider reducing immunosuppression goals.
 - Example: FK goal 4-6 if no recent ACR
 - FK goal 6-10 if recent ACR, or transplanted within 1 year
 - Consider incorporating mTOR inhibitor for persistent CMV infection based on anti-CMV activity
- Consider addition of inhaled cyclosporine when opt for significant reduction of maintenance immunosuppression (see transplant pharmacist or Dr. Johnson for administration and dosing guidelines)

PROPHYLAXIS

CYTOMEGALOVIRUS (CMV).

- Valganciclovir (Valcyte) started on Post-op Day 1
- Dosing is based on CMV donor and recipient status and renal function.

CMV Table –Valganciclovir (Valcyte) Prophylaxis with Induction Therapy

CMV Status	Dose				Duration
	GFR ≥ 60	GFR 40-59	GFR 25-39	GFR 10-24	
D+/R- (primary mismatch)	900 mg qD	450mg qD	450mg qOD	450mg biweekly	Campath induction - minimum of 12 months. Simulect induction – 6 months
D-/R+ or D+/R+	450mg qD	450mg qOD	450mg qMWF	450mg qMTh	6 months
D-/R- or Herpes prophylaxis	Acyclovir (zovirax) See HSV below				

For R+

- Monitor CMV PCR every 1-2 weeks X 3 months then monthly until valcyte is discontinued.
- After D/C of valcyte, monitor CMV PCR every 1-2 weeks X 3 months
- Discontinue CMV PCR surveillance after three months of negative PCRs
- Patients over age 50 should be transitioned to acyclovir 400 mg BID after valganciclovir prophylaxis period is complete

For primary CMV mismatch (D+/R-) –

- Monitor CMV PCR every 1-2 weeks X 1.5 year, then monthly if maintained on valcyte
- Patients over age 50 should be transitioned to acyclovir 400 mg BID after valganciclovir prophylaxis period is complete

HERPES SIMPLEX VIRUS (HSV)

- All CMV D-/R- patients should receive acyclovir 400 mg PO bid or valacyclovir if acyclovir shortage for 3 months post-transplant. Valacyclovir or acyclovir is not needed in those receiving treatment for CMV or EBV, as ganciclovir and valganciclovir have good anti-HSV activity. Patients over age 50 should be transitioned to acyclovir 400 mg BID after valganciclovir prophylaxis period is complete

Ensor 7/17/16 1:33 PM

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	Dose			Duration
	GFR \geq 30	GFR <30	On HD	
Herpes prophylaxis for CMV D-/R-				
Valacyclovir dosing	500 mg BID	500 mg qD	500 mg qD (given after HD)	3 months minimum
Acyclovir dosing	400 mg BID	200 mg BID	200 mg BID	3 months minimum

VARICELLA ZOSTER VIRUS (VZV)

Screening:

- All patients should have varicella zoster (VZV, sometimes listed as HZV) serology tested prior to transplant. The test to order is VZV IgG.

Vaccination:

- Candidates who are not immune to varicella (VZV IgG negative) and have LAS of < 35 should be vaccinated with the live attenuated VZV vaccine (Varivax® Merck & Co.) with standard two doses 4-6 weeks apart if feasible. While it is preferable that the vaccination series be completed by 4 weeks prior to transplant, candidates vaccinated < 2 weeks can still be safely transplanted when an organ becomes available; call TID to clear these patients for transplant. All patients should have VZV IgG checked 1 month after completing the vaccine.
- Patients who are pre-transplant and have a high LAS score should not be vaccinated because the vaccine is live. For this same reason, no post-transplant patients on immunosuppression should be vaccinated for VZV.

Post-exposure prophylaxis:

If a patient reports potential varicella exposure:

- No prophylaxis is necessary for those who are known to have positive pre-transplant varicella serology or those who have received varicella vaccination with documented post-vaccination serology.
- For those with no documented VZV (sometimes recorded as HZV) serology on records, send a blood test for varicella serology as soon as an exposure is reported. Contact Transplant ID to evaluate patients.
- For documented seronegative recipients with significant varicella exposure, consider 1) acyclovir 800 mg PO four times a day or valacyclovir 1g PO tid for 7 days or 2) varicella immunoglobulin (VariZIG®, Cangene Corporation) within the first 96 hrs of exposure (now only available through investigative new drug protocol submitted to FDA). Contact Transplant ID to evaluate patients.

Zoster prophylaxis

- Continue acyclovir or valacyclovir prophylaxis **indefinitely** in patients over the age of 50 and patients with one episode of herpes zoster.

PCP (*Pneumocystis jirovecii*, formerly known as *Pneumocystis carinii*)

- Prophylaxis drug:
 - Trimethoprim/Sulfamethoxazole (eg. BactrimTM) 1 SS tab po daily (or one DS tab MWF) for eGFR >30; dose adjust (half the regular dose) for eGFR <30.
- In TMP-SMX allergic patients:
 - First choice:
Dapsone 100 mg po qd
 - Check G6PD before starting dapsone therapy.
 - In heart-lung transplant patient, add pyrimethamine 50 mg po weekly (for toxoplasmosis prophylaxis, especially in Toxo mismatch patients).
Leucovorin is recommended to prevent bone marrow suppression.
 - Second choice:
 - Atovaquone (Mepron) 1500 mg po qd with food.
 - Third choice:
 - Aerosolized pentamidine 300 mg per month is by Respigard II jet nebulizer using 6 ml sterile water. Administer bronchodilator 15 minutes before inhalation.
 - In heart-lung transplant patient, add pyrimethamine 50 mg po weekly. Leucovorin is recommended to prevent bone marrow suppression.
- Duration: lifelong.

FUNGAL PATHOGENS

Duration of and Indications for Antifungal Prophylaxis after Lung Transplantation

- Immediate Post-Transplant Prophylaxis
 - Basiliximab
 - Current Mold Era: Isavuconazole x 3 months
 - No history of SCCA: Voriconazole X 3 months
 - History of SCCA: Posaconazole ER 300 mg X 3 months
 - Lytic agents (alemtuzumab/anti-thymocyte globulin)
 - Current Mold Era: Isavuconazole x 4 months
 - No history of SCCA
 - Posaconazole ER 300mg x 3 months
 - Voriconazole X 4 months
 - History of SCCA
 - Posaconazole ER 300 mg X 4 months
 - (Itraconazole is another option if difficulty getting insurance coverage)

- Prophylaxis for rejection
 - Lytic agents (alemtuzumab/anti-thymocyte globulin/others)
 - No history of SCCA: Voriconazole X 3 months
 - History of SCCA: Posaconazole or itraconazole X 3 months
 - Steroids: None

Isolation of mould in BAL in asymptomatic patients with clear chest CT +/- sinus (“preemptive therapy”)

If “potentially pathogenic” mould is isolated:

- Inhaled amphotericin B X 1 month (preferred choice)
 - Amphotericin B/Fungizone 25mg NEB BID
 - Liposomal Amphotericin B/Ambisone 25mg NEB TIW
- Itraconazole, posaconazole, or voriconazole X 1 month (2nd choice)
- No treatment warranted if “potentially hypo-virulent” mould isolated
- Note: All non-*versicolor* *Aspergillus* species, *Fusarium*, *Scedosporium*, and dematiaceous moulds should be considered “pathogenic”. Examples of “potentially hypo-virulent” moulds are *Paecilomyces*, *Penicillium*, and *Aspergillus versicolor*. For organisms outside those listed, call Transplant ID to assess whether preemptive therapy is warranted.

Prophylaxis for patients with stents (past the first 3-4 months of transplant)

- Presence of ischemic reperfusion injury: If necrotic plaque and biopsy/cytology/culture suggestive of presence of fungal pathogen: Voriconazole (or itraconazole or posaconazole) + inhaled amphotericin B X 1 month. If lesion no longer present on follow-up BAL, continue with inhaled amphotericin until ischemic reperfusion injury resolves.
- Colonization with mould:
 - Preferred agent: Inhaled amphotericin B X 3 months (if repeat BAL negative)
 - Amphotericin B/Fungizone 25mg NEB BID
 - Liposomal Amphotericin B/Ambisone 25mg NEB qweek
 - Alternative: itraconazole or posaconazole
- Stent with no ischemic reperfusion injury, no suggestion of invasive fungal infection, and no colonization with mold: no prophylaxis

Additional Notes:

- If the patient is intolerant of voriconazole due to adverse effects (such as severe LFT elevation, moderate to severe light intolerance, periostitis, squamous cell carcinoma, etc) consider posaconazole or inhaled amphotericin B (AmB).
- If the patient is intolerant of voriconazole due to GI intolerance or mild to moderate LFT abnormalities, consider posaconazole, itraconazole, or AmB nebulizer.

- In the event of mild to moderate elevation in LFTs, recommend to wait for LFTs to normalize before starting another tri-azole agent
- Consider cumulative exposure to voriconazole in patients who are at risk for squamous cell carcinoma, (age > 65 years old, history of skin cancer, lives in high UV states). In such patients, consider itraconazole, posaconazole, or AmB nebulizer instead.
- If possible, a systemic antifungal is recommended for the first 3 months post-transplant until the anastomotic site is healed.
- Note regarding itraconazole formulations:
 - Capsule absorption is optimized if given in the fed state with high gastric acidity. Use capsule if patients are not receiving PPI (or can be switched to H-2 blocker). Capsule should be taken with juice or cola beverage (to increase gastric acidity) and food.
- Solution absorption is optimized in the fasting state, but is not affected by gastric acidity. If patient must receive a PPI, give solution.
- Recommend to pursue therapeutic drug monitoring (TDM) in patients being treated for active infection, preemptive therapy, and in specific cases to assess whether supra-therapeutic levels are contributing to hepatotoxicity or neurotoxicity. General recommendations for lower limits are:
 - Voriconazole: ≥ 1
 - Posaconazole: ≥ 1
 - Itraconazole + Hydroxy-itraconazole: ≥ 1
- Dosing recommendations for AmB nebulizer:
 - Prophylaxis
 - AmB deoxycholate 25 mg bid
 - For patients intolerant of AmB deoxycholate, liposomal AmB can be considered (25 mg three times a week X 1 week, followed by 25 mg once a week)
 - Treatment or preemptive Therapy
 - AmB deoxycholate 25 mg bid
 - For patients intolerant of AmB deoxycholate, liposomal AmB can be considered (25 mg three times a week)
- Lung transplant patients who are infected or colonized pre-transplant should receive antifungal based on the effective pre-transplant regimen.
- Due to squamous cell skin cancer (SCCA) risk associated with prolonged use, voriconazole is not recommended to be prophylactically used longer than 3 months unless clinically essential. If duration longer than 3 months is required, use alternative agents such as itraconazole or posaconazole if possible. Consult Transplant ID for advice. For the following patients, would avoid the use of ≥ 3 months of voriconazole unless absolutely indicated: 1) ≥ 65 year old; 2) lives in sun-exposed areas; 3) previous history of cancer. If an anti-mould antifungal is necessary, change to itraconazole or posaconazole after 3 to 6 months of voriconazole. Call Transplant ID for recommendations.

- Lung transplant patients with fungus ball or mould infection in the explanted lungs should receive prolonged antifungal prophylaxis. Consult TID for input.
- Patients who are intolerant to oral/intravenous voriconazole due to adverse effects such as gastrointestinal tolerability, elevations in liver transaminases, and/or persistent visual disturbances can be changed to oral itraconazole or posaconazole.
 - **Voriconazole**
 - A loading dose of 6 mg/kg IV q12h x 2 doses, followed by 200 mg PO bid (for patients weighing > 40 kg) or 100 mg PO bid (<40kg).
 - When initiating therapy with voriconazole in patients already receiving tacrolimus, reduce the tacrolimus dose to one-third of the regular dose and follow with frequent monitoring of tacrolimus blood levels. When voriconazole is discontinued, tacrolimus concentrations must be frequently monitored and the dose increased as necessary.
 - When initiating therapy with voriconazole in patients already receiving cyclosporine, reduce the cyclosporine dose to one-half of the regular dose and follow with frequent monitoring of cyclosporine blood levels. When voriconazole is discontinued, cyclosporine concentrations must be frequently monitored and the dose increased as necessary.
 - **Itraconazole**
 - A loading dose of 200mg PO TID x 3 days (using the capsule formulation), followed by a maintenance dose of itraconazole 200mg PO BID. When initiating therapy with itraconazole in patients already receiving tacrolimus, reduce the tacrolimus dose to 1/3 of the regular dose. Follow with frequent monitoring of tacrolimus blood levels.
 - When initiating therapy with itraconazole in patients already receiving cyclosporine, reduce the cyclosporine dose to 1/3 of the regular dose. Follow with frequent monitoring of cyclosporine blood levels.
 - All unnecessary acid suppressive medications must be discontinued (preference is given to antacids and H₂ receptor antagonists)
 - Administration of the capsules should always be given with a meal and preferably with an acidic beverage (ie. Coca-cola, orange juice, etc.) to increase the bioavailability of itraconazole.
 - Therapeutic drug monitoring will be done routinely, beginning of day 7 of therapy and weekly thereafter. The goal trough level of itraconazole for prophylaxis is >0.5mcg/mL.
 - Patients who cannot take medication by mouth may receive the itraconazole solution (same doses) to be given via a PEG, NG, G, or GJ tube with no regard to enteral/parenteral feeding.
 - For patients who remain subtherapeutic, it is recommended to change the itraconazole formulation to the solution (100mg/10mL) at the same dose without regard to meals and without a loading dose.
 - **Posaconazole:**

- Dosing: Prophylaxis Posaconazole DR 300mg daily. Avoid suspension use due to questionable absorption.
- When initiating therapy with posaconazole in patients already receiving tacrolimus, reduce the tacrolimus dose to 1/2-1/3 of the regular dose. Follow with frequent monitoring of tacrolimus blood levels.
- When initiating therapy with posaconazole in patients already receiving cyclosporine, reduce the cyclosporine dose to to ¼ of the regular dose. Follow with frequent monitoring of cyclosporine blood levels.
- Obtain posaconazole serum level at day 7 of therapy, then weekly until goal concentration is obtained.
 - The target trough level is > 1mcg/mL. If serum concentration is below target levels, increase dose accordingly.

Caveats with posaconazole suspension:

- optimal absorption with high fat meal. If poor diet, use nutritional supplement with at least 14 grams of fat (Ensure, Boost, etc.).
- Diarrhea also shown to decrease AUC
- Avoid use with phenytoin and rifabutin

Gastrointestinal prophylaxis

- Famotidine 20 mg po BID or qhs – adjust for renal dysfunction
- Proton pump inhibitor – Need to assess risk/benefit ratio given recent reports of renal dysfunction in patients taking PPIs

DVT prophylaxis

- Inpatient: per standard of care (typically heparin, or unfractionated heparin)
- Duration: until mobile and central venous line discontinued. Continue indefinitely if indwelling central venous line unless contraindication.
- Consider prolonged prophylaxis if on mTOR inhibitor (significantly increased incidence of DVT with sirolimus or everolimus)

C difficile colitis prophylaxis indications:

- If prior severe infection history, institute prophylaxis for every course of systemic antibiotics
- Drug: metronidazole 500 mg TID
- If intolerant or prior metronidazole treatment failure, vancomycin 125 mg QID

TREATMENT OF COMMON PROBLEMS

CYTOMEGALOVIRUS (CMV)

Definitions:

- Infection – Evidence of active CMV replication (i.e. positive PCR) regardless of symptoms.
- Disease - evidence of CMV infection with attributable symptoms. CMV disease can be further categorized as either a viral syndrome or as tissue invasive disease (e.g. pneumonitis, hepatitis, retinitis, gastrointestinal disease).

Viral Syndrome: CMV PCR positive with at least 2 of the following:

- Fever
- Leukopenia < 3.0 or thrombocytopenia <100
- Arthralgias, myalgias

Pneumonitis:

- Probable: Appropriate clinical syndrome with positive viremia with CXR changes, having ruled out other possible causes.
- Proven: Histopathologic examination demonstrating inclusion bodies in lung biopsies or with or without CXR changes.

Extrapulmonary CMV: GI, hepatitis, retinitis, etc. Appropriate positive cultures, histopathological confirmation or specific clinical or test findings.

Treatment:

A. Treatment of asymptomatic CMV infection (i.e., CMV PCR positive) in R+ patients.

CMV Status	Valganciclovir (Valcyte) Treatment Dosing				Duration
	GFR > 60	GFR 40-59	GFR 25-39	GFR 10-24	
D-/R+ D+/R+	900 mg BID	450mg BID	450mg qD	450mg q48h	Until 2 consecutive CMV PCR a week apart are negative. After completion of treatment, a 1–3 month course of secondary prophylaxis is recommended.

B. Treatment of CMV infection in symptomatic patients or patients with primary CMV mismatch or previously R-

- Consult Transplant Infectious Disease
- If uncontrolled CMV disease, consider holding the third immunosuppressive agent (mycophenolate or azathioprine) if no recent history of ACR until infection or disease is controlled.
- Intravenous ganciclovir is preferable to oral valganciclovir in patients with severe or life-threatening disease, or in patients who may have a problem with gastrointestinal absorption of oral drug (e.g. significant diarrhea). The typical dose of intravenous ganciclovir for treatment is 5 mg/kg twice a day. The dosing should be adjusted according to the renal function .

Renal Dosing of Ganciclovir used for treatment:

Creatinine Clearance (ml/min)	Dose of Ganciclovir (IV)
≥ 70	5 mg/kg IV q 12
50-69	2.5 mg/kg IV q 12
25-49	2.5 mg/kg IV q 24
10-24	1.25 mg/kg IV q 24
<10 or hemodialysis	1.25 mg/kg IV after each HD

- Duration: minimum of 2-4 weeks. Patients should be maintained on therapy until disease is controlled (clinical resolution of symptoms) and 2 consecutive CMV PCRs a week apart are negative.
- After completion of treatment, a 3 month course of secondary prophylaxis with valganciclovir should be considered
- The addition of CMV Immune Globulin (CMV-IG) to existing antiviral treatment regimens is questionable and in general has minimal benefit for lung transplant recipients.
- Consider drug-resistant CMV (UL97/54 mutations) among patients who develop CMV disease after prolonged courses of ganciclovir or valganciclovir prophylaxis, and those failing to respond to standard ganciclovir treatment. Genotypic testing for resistance should be performed. Therapeutic options include increasing the dose of intravenous ganciclovir (up to 10 mg/kg two times a day) or foscarnet (alone or in combination with low dose ganciclovir) or Cidofovir. Consider CMV-IG. Consult Transplant Infectious Diseases.
- Consider incorporating a mTOR inhibitor into maintenance immunosuppression in patients who have refractory or ganciclovir-resistant CMV disease.

EBV MISMATCH

EBV IgG negative recipients of EBV positive donors are at increased risk of EBV-related viral syndrome and Post-transplant Lymphoproliferative Disease (PTLD). Early identification of reactivation and timely intervention may reduce morbidity.

PROPHYLAXIS:

- ✓ Antiviral agents (valganciclovir) may have a role in prophylaxis in EBV-seronegative organ transplant recipients as they can block EBV production in donor B cells and subsequent infection of recipient B cells. Moreover, long-term prophylaxis with antiviral agents or intravenous immunoglobulin may decrease the incidence of PTLD by limiting intercellular virus transmission; several centers use prophylactic valganciclovir or intravenous immunoglobulin in the first 6 months after allograft, during which time the immunosuppression is most intense. The value and effectiveness of valganciclovir or IVIG prophylaxis are unclear, as PTLD is observed among patients receiving prophylaxis

PRE-EMPTIVE THERAPY:

- ✓ The use of preemptive strategies in high-risk populations may lower PTLD incidence rates; reduction in immunosuppression is the best-documented intervention strategy. There is insufficient data to determine the efficacy of other intervention strategies such as antivirals, anti-CD20 antibody (rituximab) or adoptive immunotherapy. The role of pre-emptive therapy with rituximab requires further prospective study to determine its overall safety and efficacy. (Reference: Martin SI, et al. Monitoring infection with Epstein-Barr virus among seromismatch adult renal transplant recipients. Am J Transplant. 2011;11:1058-63).
- ✓ Proposed pre-emptive strategy in high-risk patients/EBV mismatches:
 - Monitor EBV PCR monthly in the first six months after transplant, then at least every 2-3 months when clinically indicated. If a rising titer is noted, more aggressive monitoring may be warranted.
 - Monitor EBV PCR in any EBV mismatch patient who has viral syndrome, unexplained fatigue, fevers/sweats, weight loss, failure to thrive, diarrhea or lymphadenopathy/pulmonary nodules.
 - If EBV PCR becomes positive with high suspicion of disease, reduce immunosuppression if possible, as well as continue to check EBV PCR every week. If viral load increases rapidly or PCR level reaches the third quartile (>16,000), obtain CT chest/abdomen/pelvis +/- PET scan, and consult Transplant Infectious Disease.

Post-Transplant Lymphoproliferative Disease (PTLD)

Epstein-Barr virus (EBV) is associated with the majority of PTLD cases. Risk factors for developing this complication include EBV mismatch, development of primary EBV infection after transplantation, and severity of immunosuppression. Most PTLD occurs in the first year after lung transplant, and cases occurring later may be EBV-negative and have cytogenetic abnormalities. EBV-associated PTLD encompasses a wide spectrum of clinical conditions

characterized by lymphoproliferation after transplantation. These syndromes range from uncomplicated infectious mononucleosis to true malignancies. Disease may be nodal or extranodal, localized or widely disseminated. Patients may be symptomatic or asymptomatic.

Management:

- Reducing immunosuppression
- Standard regimen is 4-8 cycles of rituximab (rituxan), 375 mg/m² weekly for CD20 markers in PTLD tissue.
 - Potential adverse events include a tumor lysis-like syndrome and prolonged depletion of B cells. CMV reactivation and protracted hypogammaglobulinemia are recognized complications of rituximab.
- Monitor weekly EBV serum viral load as a potential marker of response to rituximab
- Reserve standard chemotherapy for patients who fail rituximab or have severe disease
- Consult Transplant Infectious Disease and Hematology/Oncology for refractory cases

RESPIRATORY SYNCYTIAL VIRUS (RSV) and other paramyxoviruses -

In uncontrolled studies published thus far, combined therapy of ribavirin (nebulizer, PO or IV) with oral corticosteroid with or without IVIG reduces the severity of RSV disease, length of mechanical ventilation, and incidence of bronchiolitis obliterans. The role of palivizulab is not known in the setting of RSV infection in lung transplant recipients, and the cost of this monoclonal antibody is prohibitive.

Recommended management:

- Consult Transplant Infectious Diseases

Ribavirin treatment of Paramyxoviruses (RSV, hMNV, parainfluenza)

1. Antiviral treatment should be considered for:

- All symptomatic lung transplant recipients in order to prevent progression to a lower respiratory tract infections and for potential benefit in reducing the rate of chronic rejection.
- In other immunocompromised patients (such as transplant recipients other than lung) who have evidence of lower respiratory tract infection / respiratory failure.
- Duration of therapy: 7-10 days.

2. Choice of the route of ribavirin administration.

1) Oral ribavirin: can be used for most patients who meet the indication and have a functioning GI tract.

- Would recommend a TID consult for hospitalized patients requiring ribavirin therapy and for those cases where risk/benefit ratio is uncertain.
- Standard dose for those with normal renal function: 15-20 mg/kg/day divided into three doses (Reference: Pelaez, J Heart Lung Transplant 2009;28:67-71). Use the actual weight given the large volume of distribution of the drug. Note that oral ribavirin is provided as 200 mg tablets.

- For those who cannot swallow the pills, be advised that ribavirin cannot be crushed. Suspension form can be obtained if needed.

Renal adjustment (reference: modified from Hirsch, CID 2013;56:258-66, Gupta, Eur J Clin Pharmacol 2012;68: 415-418)

Creatinine Clearance	Dose
50 mL/min or higher	15-20 mg/kg/day in 3 divided doses; excepting those with extremes of weight, this usually translates to 400mg PO TID
30-50 mL/min	600 mg PO x 1 then 200 mg PO TID starting 8h post loading dose
10-30 mL/min	600 mg PO x 1 then 200 mg PO daily from day #2
ESRD on hemodialysis	600 mg PO x 1 then 200 mg PO qPM from day #2
CRRT	No data

*Clear-cut recommendation is lacking / inconsistent for CrCl < 50 or those with ESRD.

2) Intravenous ribavirin: reserved for critically ill patients unable to absorb/tolerate oral ribavirin. Please call Transplant ID as the use of IV ribavirin requires an Emergency IND.

3) Inhaled ribavirin: Not preferred due to significant resource requirement (negative pressure room, nursing precautions, prolonged administration time (6-18 hours/day), cost (\$6,000/day)). Ribavirin is a synthetic nucleoside use for the short term treatment of RSV and is FDA approved for pediatric use. Ribavirin is used off label for morbidity and mortality risk reduction in lung transplant recipients. Ribavirin is classified as pregnancy risk category X with the potential for carcinogenicity and teratogenicity in individuals who are exposed.

Indications:

- Contraindications to oral ribavirin
- Oral ribavirin failure/toxicity
- Severe PMV infection
 - Allograft failure
 - Mechanical ventilation
 - Hypoxemia requiring substantial oxygen ($\geq 4L$)

Procedures:

- Non-intubated patients
 - Deliver via mask and small particulate aerosol generator (SPAGII) circuit
 - Albuterol premedication for bronchospasm
 - Ribavirin 6 grams (in 150 mL sterile water) over 24 hours delivered in 3 divided doses, 2 grams every 8 hours, over 2-hour aerosol periods
- Intubated patients
 - Deliver via ventilator with small particulate aerosol generator (SPAGII) circuit
 - Albuterol premedication for bronchospasm
 - Ribavirin 6 grams (in 300 mL sterile water) over 18 hours delivered continuously in every 24 hour period

Room requirements:

- Intubated patients
 - Negative pressure room
- Non-intubated patients
 - Demystifier scavenger bed tent

3. Adjunctive therapy with corticosteroids (modified from the Peleaz paper.)

- Dose: 1 mg/kg/d, with maximum dose of 60 mg of prednisone equivalent/day x 48hrs, then taper by 10 mg every 2 days until the patient is on the baseline prednisone dose.
- If the patient has just received a Methylprednisolone pulse therapy for rejection < 1 week prior to the start of therapy, we can dispense with the steroid taper.
- Would also consider IVIG for severe disease, since better outcome has been shown with the combination of ribavirin and IVIG in HSCT patients with RSV pneumonia.

ASPERGILLOSIS –

Work-up for a positive respiratory culture for pathogenic *Aspergillus* spp.

- CT chest and sinus
- Bronchoscopy (if not yet performed)
- If patient is on an iazole at the time of culture, check trough drug level

Aspergillus colonization – Patients with a BAL culture positive for *Aspergillus* but with a normal bronchoscopic and chest and sinus CT scan findings

Proposed treatment for *Aspergillus* colonization:

- Inhaled amphotericin B/Fungizone (25 mg bid)
- Inhaled liposomal amphotericin/Ambisone (25 mg three times a week) for 1 month
- voriconazole – dose: 200 mg bid (for patients weighing > 40 kg), and 100 mg bid (for those < 40 kg). Duration: 1 month (longer if there is a stent) repeat BAL in 2 to 3 months (sooner if symptoms) –Consult Transplant ID if culture continues to grow *Aspergillus*.

Proposed treatment for *Aspergillus* invasive disease

- Typical therapy with Voriconazole + Caspofungin initially, then azole alone after therapeutic azole level is achieved and the patient is clinically improved. The voriconazole therapeutic level is defined as level between 1.5 to 4 ug/mL.
- Addition of inhaled amphotericin/Fungizone (25mg NEB BID) if evidence of endobronchial infection or severe pulmonary disease
- Sinus disease needs to undergo aggressive debridement.

COLONIZATION OR DISEASE DUE TO NON-ASPERGILLUS MOULDS –

Consult Transplant ID.

ORAL CANDIDIASIS -

- Nystatin (Nilstat[®], Mycostatin[®], others) or clotrimazole (Mycelex[®], others)
Dose: 5 ml Swish and swallow QID for 3 months if Campath
Do NOT eat or drink for 20-30 minutes after dose.
- Oral azoles (fluconazole, itraconazole, voriconazole, or posaconazole) are also effective
Caspofungin IV is reserved for refractory infection to topical therapy as well as to systemic azole agents.

Hypogammaglobulinemia

Common in patients with prolonged steroid use pre-transplant, malnutrition, or prolonged immunosuppression

Indications for replacement:

- IgG level < 700 and recurrent infections or rejection
- IgG level < 400 in the absence of infection history

Additional testing: IgG subclasses, quantitative IgM/IgG/IgA, tetanus and pneumococcal titers; consider serum protein electrophoresis/urine protein electrophoresis (SPEP/UPEP)

Treatment:

- Immune globulin intravenous (IVIG) 0.5gm/kg IV (divide over 2-3 days if renal insufficiency)
- Pre-medications: Tylenol 650mg PO x 1, Benadryl 25-50mg PO/IV x 1 30-60 minutes prior to dose (steroids not mandatory but use hydrocortisone 100 mg IV x 1 if prior history of reaction)

Delay repletion in acutely infected patients

Repeat IgG testing in one month. If recurrently low, refer to immunology for evaluation and consideration of regular subcutaneous/IV repletion.

Neutropenia

- Definition: ANC = WBC x % (PMNs + bands) /100; ANC < 1000 is significant neutropenia, however, significant risk of infections increases dramatically only when ANC is below 500
- Etiologies: mycophenolate, valgancyclovir, metronidazole, infection, prolonged bone marrow suppression following Campath induction or RATG, Bactrim
- Treatment:
 - avoid or dose adjust the offending agent.
 - Filgastrim (Neupogen) 300 mcg IV/SQ daily x 3days (dose escalate ANC <500 or if non-responsive)

Anemia:

- Definition: Hb <13 g/dl or Hct <41%

- Causes: Drug induced, hemolysis, chronic disease like CKD (when Ccr <30), malnutrition or infections like Parvo B19. GI loss.
- Anemia work up includes:
 - Haptoglobin, Iron (lower limit or % sat <25), TIBC, ferritin, folate B2 level, reticulocyte count, LDH, Transferrin. Parvovirus B19, EBV, CMV, HHV6 PCR. TSH, free T4 level. Stool hemocult testing
- Treatment
 - Oral iron when iron level is low: Ferrous sulfate
 - consider iv iron if patient has poor oral absorption (ferlicit 125 mg or venofer 200 mg iv qod x five doses)
 - B12 replacement when low blood levels and replace folic acid.
 - If blood results shows hemolysis: Hematology needs to be consulted.
 - If Parvo B19 PCR is positive: The treatment will be IVIG (total of gram/kg) using 0.5 grams/kg daily for 4 days with follow up reticulocyte count and a Parvo B19 pcr in one week. Repeat the same treatment if pcr remains positive

Renal insufficiency

- Post transplant, etiology of kidney disease (acute and chronic) can be multifactorial. Our patients are at high risk, however, of calcineurin inhibitor nephrotoxicity (CIN).
- Mechanism: Acute renal failure: Increases in efferent and afferent glomerular arteriolar vasoconstriction. Chronic kidney disease: mechanism unknown.
- Dx: albuminuria common, although not nephrotic range proteinuria (if present, investigate other causes)
- While the K/DOQI guidelines have not been validated in transplant patients, since the mechanism of injury may be similar to non-transplant populations, it has been recommended to follow the consensus guidelines.
- Our general practice: When renal disease reaches CKD 3, we have generally added sirolimus in an effort to lower calcineurin inhibitor (FK or cyclosporine) dosing.
 - However, there are data to suggest that sirolimus may actually worsen calcineurin-induced nephrotoxicity in the setting of proteinuria, so this must be done with caution.
- Losartan or ACE inhibitors may have nephroprotective effects (reduce fibroproliferative disease) (Bloom RD, Reese, PP. Chronic kidney disease after nonrenal solid-organ transplantation. J Am Soc Nephrol 2007; 18:3031-3041)
- In monitoring renal dysfunction, it is essential to monitor GFR as well as (and even more important than) serum creatinine. To calculate GFR, we generally use the MDRD equation. To classify CKD stage, the patient must have a *stable* creatinine.
 - MDRD calculator: www.nephron.com

Stages in chronic kidney disease (Based on K/DOQI guidelines)

CKD Stage	Description	GFR (ml/min/1.73m ²)
1	Kidney damage w/ nml GFR	≥ 90
2	Kidney damage w/ mild decr GFR	60-89

3	Moderate decrease GFR	30-59
4	Severe decrease GFR	15-29
5	Kidney Failure	< 15

- Lab work: Lytes, BUN/Creat, Ca, Mg, Phos, serum protein, CBC with diff, iron studies, intact parathyroid hormone, 25-hydroxyvitamin D level, spot urine protein and creatinine to estimate proteinuria

Treatment of complications of CKD:

- Metabolic acidosis – to prevent bone buffering and skeletal muscle breakdown/hypoalbuminemia, give sodium bicarbonate to maintain serum bicarb > 22 mEq/L.
- Hyperphosphatemia – phosphate balance is usually maintained when GFR > 30, but at the expense of renal osteodystrophy/secondary hyperparathyroidism
 - Give calcium acetate to maintain phos 2.7-4.6 in Stage 3-4, and 3.5-5.5 in Stage 5
 - Keep serum calcium-phosphorous product < 55 mg²/dL²
 - Caution with sevelamer – it can impact calcineurin levels.
- Renal osteodystrophy – Parathyroid levels can begin to increase when GFR < 70. Check 25-hydroxyvitamin D to see if patient is absorbing Vitamin D, and once vitamin D replete, supplement with calcitriol (1,25-dihydroxyvitamin D), the active metabolite of vitamin D that is made in the kidney
 - Calcitriol should be dosed and titrated to target intact PTH (iPTH) level

CKD Stage	Target iPTH level
3	35-70 pg/mL
4	70-110 pg/mL
5	150-300 pg/mL

- HTN – Blood pressure goal < 125/80.
- Anemia – Evaluate anemia when Hgb < 12 in women and < 13.5 in men
 - Anemia common when GFR < 60 mL/min!
 - Labs: absolute retic count, serum iron, TIBC, % transferrin sat, ferritin, WBC and diff, Plt, stool occult blood
 - Make sure patient’s iron stores are replete:
 - ferritin > 100 ng/mL, %transferrin sat ≥ 20%
 - Administer weekly erythropoietic agent: erythropoietin (20-40,000 Units SQ) or darbopoeitin (1 mcg/kg weekly) to achieve a goal Hgb >9 g/dL
- Consider referral to nephrology when patients reach CKD Stage 3.

Nausea/anorexia +/- vomiting

- Commonly observed in the first few months after lung transplantation
- Multiple potential etiologies: gastroparesis related to vagal nerve dysfunction, cholestasis related to azole antifungals, gastritis, and medications (mycophenolate, voriconazole and other azole antifungals, tacrolimus are common offenders).

- Attempt to determine etiology: liver function and pancreatic enzyme measurement, gastric emptying study, CMV and EBV pcr
- GI consult if no apparent etiology
- Symptomatic treatment with Compazine, Zofran, and/or metoclopramide
- Consider domperidone (10 mg TID, obtain from on line pharmacies in Canada)
- Systematic trial off potential causative drugs: hold mycophenolate for 5-7 days if no recent ACR; if persistent, hold azole for 5-7 days; if refractory, and no apparent etiology, consider change from tacrolimus to cyclosporine

Diarrhea

- Causes:
 - Infectious causes:
 - Nosocomial: *Clostridium difficile*-associated diarrhea (most common), CMV
 - Community: *Clostridium difficile*, CMV, other bacteria (*Salmonella*, *Shigella*, *Campylobacter*, etc), parasites (Giardia, *Cryptosporidium*, *Entamoeba*), viruses (Norwalk virus, Rotavirus, Adenovirus)
 - Non-infectious causes:
 - medications (magnesium, Cellcept, antibiotics)
 - endocrine (hyperthyroidism, hypothyroidism, Addison's disease, gastrinoma, carcinoid)
 - others: ischemic colitis, malabsorption syndromes (celiac disease, Whipple's disease, short bowel syndrome, short bowel bacterial overgrowth), maldigestion (pancreatic insufficiency)
- Proposed work-up:
 - Stool studies
 - Nosocomial diarrhea: *C. diff* toxin, viral culture (especially with nosocomial outbreak), CMV PCR
 - Community diarrhea: fecal leukocytes, O&P (send 3 times), culture for *Salmonella*, *Shigella*, *Campylobacter*; viral studies (Norwalk, Rotavirus, Adenovirus, etc); stool for acid fast staining for *Cryptosporidium*, *Cyclospora*, *Isospora belli*, stool Giardia antigen ELISA, *C. difficile* toxin.
 - Blood studies – CMP, amylase, lipase, thyroid function tests, CMV PCR. Blood cultures for patients with systemic symptoms.
- Rx:
 - If known causes – treat accordingly
 - Put patient on lactose-free diet (many patients develop temporary lactase deficiency); treat underlying cause; fiber supplements, lactobacillus (Lactinex)
 - Patients with symptoms of colitis (abdominal pain, systemic symptoms such as fever, melena or bloody diarrhea) – CT abdomen, CMV PCR, *C. diff* toxin, GI consult for a colonoscopy, CMV PCR. Consult Transplant Infectious Diseases.
- *C. diff* prophylaxis: We often give patients with *any history* of *C. diff* or diarrhea flagyl 500mg TID or vancomycin 125mg PO QID with any antibiotic therapy

Osteoporosis and bone pain (+/- hypertrophic pulmonary osteoarthropathy (HPOA))

- Causes: corticosteroids, renal osteodystrophy, malnutrition/malabsorption

- Monitoring: DEXA scan yearly or every other year (frequency varies based on severity of condition)
- T-score : -1.5-2.5 = osteopenia & < -2.5 = osteoporosis
- Treatment: Calcium and Vitamin D (important to check and normalize 25-hydroxy-vitamin D levels); Bisphosphonates (relatively contraindicated in patients with CKD (GFR <50); consider dose reduction); Forteo
- In CKD patients, treat secondary hyperparathyroidism with vitamin D or vitamin D metabolites
- Refer severe or refractory cases to endocrinology
- Discontinue azole if bone pain or arthropathy for no other reason (reported alterations in fluoride metabolism resulting in bone pain akin to HPOA) (Reference: Wang TF, Wang T, Altman R, Eshaghian P, Lynch JP 3rd, Ross DJ, Belperio JA, Weigt SS, Saggar R, Gregson A, Kubak B, Saggar R. Periostitis secondary to prolonged voriconazole therapy in lung transplant recipients. Am J Transplant. 2009;9:2845-50).

Hyperlipidemia

- Common in transplant patients. Any lipid abnormalities, consider 1st line therapy as a statin (pravastatin), as there may be potential beneficial immunomodulatory effects (Johnson BA et al. AJRCCM 2003; 167: 1271-8)
- Hypertriglyceridemia can occur with sirolimus- must monitor triglycerides and cholesterol every few months in patients on sirolimus
- Caution when statin added to azole (increased risk of rhabdomyolysis)
- Patients on statin require AST/ALT monthly for 3 months, then every three months. Discontinue statin immediately and check CPK if any muscle weakness or unexplained myalgias.

Hypomagnesemia

- Calcineurin-inhibitors cause renal magnesium loss; diarrhea also contributes to magnesium loss
- When severe, hypomagnesemia causes muscle cramps
- Goal is magnesium > ~1.2 with oral replacement
 - Magnesium oxide 400-800 mg BID to TID or Slo-mag 64 mg BID or Magnesium gluconate 500-1500 mg BID to TID

Hyperkalemia

- Common after transplant and due to calcineurin inhibitor (other contributors include bactrim, and ACE inhibitor/ARB)
- Mild hyperkalemia (K 5.2-5.5 in PUH lab)
 - Potassium restrict diet
 - Consider lasix if hypertension history
 - Florinef 0.1 mg daily to BID if fails dietary restriction

- Moderate hyperkalemia (K 5.6 to 5.9)
 - Consider repeat if concern for hemolysis
 - Potassium restrict diet
 - Consider lasix if hypertension history
 - Florinef 0.1 mg BID
 - If abrupt increase from baseline - Kayexelate 15-30 gm and repeat potassium the following day
- Severe hyperkalemia (K 6 or greater) – immediate referral to ER for repeat and treatment
- Reduce florinef dose when K <5 to minimize fluid retention that is associated with florinef

Hypertension

- Common after transplant due to calcineurin inhibitor
- Goal BP is <140/80
- Drug options:
 - beta blocker (lopressor 25-200 mg BID, or other beta-1 selective blockers)
 - ACE inhibitor or ARB – preferred if no history of significant hyperkalemia as may have renal protective effects – lisinopril 2.5-10 mg daily; check potassium one week after initiation
 - loop diuretic (furosamide, others)
 - calcium-channel blocker (amlodipine(Norvasc)) – 2.5 -10 mg/day; avoid other calcium-channel blocker due to interference with calcineurin inhibitor metabolism

Pre-transplant Assessment of Sensitized Patient

Definitions

- Non-sensitized, no detectable anti-HLA antibodies present.
- Sensitized, detectable anti-HLA antibodies present.
 - Broadly sensitized, multiple detectable anti-HLA antibodies of class I and/or II irrespective of strength/titer (unlikely to result in elevated cPRA).
 - Highly sensitized, detectable high-strength/high-titer anti-HLA antibodies (may result in elevated cPRA depending on the antibody).
 - Highly and broadly sensitized, multiple detectable high-strength/high-titer anti-HLA antibodies (results in markedly-elevated cPRA).
- Calculated panel reactive antibodies (cPRA), indicates the inverse-percent likelihood of identifying an HLA-compatible donor in the donor pool (e.g., cPRA = 100% indicates a 0% likelihood of finding an HLA-compatible donor in the donor pool). OPTN cPRA calculator available at:
<http://optn.transplant.hrsa.gov/resources/professionalResources.asp?index=78>.
- Antibody strength, low strength = MFI < 2000, moderate strength = MFI 2000-8000, lower-moderate strength = MFI 2000-4000, upper-moderate strength = MFI 4000-8000, high strength = MFI > 8000 (MFI = mean fluorescent intensity on Luminex assay).
- Antibody titer, presence of anti-HLA antibody upon serial dilution at various strengths (e.g., HLA-A2, neat MFI = 8000, 1:16 MFI = 8000, this is a high-strength/high-titer antibody).
- Unacceptable antigens, all high-strength and/or high-titer anti-HLA antibodies on Luminex-IgG and all complement binding anti-HLA antibodies on Luminex-C1q.
- Donor-specific antibody (DSA), presence of anti-HLA antibodies directed at the HLA of the donor.
- Preformed DSA, presence of anti-HLA antibody pre-transplant, now DSA post-transplant.
- De novo DSA, formation of DSA post-transplant that was not present pre-transplant.
- Hypogammaglobulinemia, total serum IgG < 700.

Virtual Crossmatch

- All unacceptable antigens will be listed in UNOS
- All sensitized patients will undergo virtual crossmatch
- NO high-strength or C1q-positive anti-HLA antibodies will be crossed
- ≤ 2 upper-moderate (MFI > 4000) strength anti-HLA antibodies may be crossed if the patient's clinical condition is rapidly deteriorating and waiting for a fully HLA-compatible organ is determined imprudent
 - If any upper-moderate antibodies are crossed, empiric peri-transplant therapy MUST be initiated (page 3)

Induction Immunosuppression

- Sensitized patients with cPRA > 10% or with any moderate-strength antibodies (MFI > 2000) should receive rabbit antithymocyte globulin (rATG, Thymoglobulin) induction.

- Reduces biopsy-proven AMR episodes and de novo DSA production in moderately sensitized renal transplant recipients
- 1.5 mg/kg IV once allograft(s) are accepted and for 4 consecutive daily doses (5 doses)
- Reduce dose to 0.75 mg/kg for WBC < 3 or platelets < 75,000
- Hold dose for WBC < 2 or platelets < 50,000
 - Give filgrastim 300 mcg once for WBC < 2
 - If dose reduced or held, add on to end of therapy (7.5 mg/kg total)
- Premedicate with acetaminophen 650 mg, diphenhydramine 25 mg, and hydrocortisone 100 mg
- Patients with history of malignancy or > 65 years of age should receive basiliximab, irrespective of sensitization

Antibody Testing

- Pre-transplant
 - Non-sensitized patients
 - HLA assessment using LABScreen PRA every 6 months
 - Sensitized patients
 - HLA assessment using Luminex-IgG neat every 3 months
 - Highly-sensitized patients (in addition to b above)
 - Luminex-IgG neat and dilution to 1:16
 - Luminex-C1q neat
- Peri-transplant
 - Luminex-IgG upon admission for transplantation
 - Complement-dependent cytotoxicity (CDC)-crossmatch within 24 hours of transplant
- Post-transplant
 - ALL patients: Luminex-IgG on POD +7
 - Histocompatibility lab will determine need for IgG-dilution and/or Luminex-C1q
 - Sensitized patients pre-transplant with moderate or high-strength anti-HLA antibodies (MFI > 2000) irrespective of crossing: Luminex-IgG on POD +3 and +7 and +14
 - Histocompatibility lab will determine if need for more frequent testing and for IgG-dilution and/or Luminex-C1q
 - ALL patients: Luminex-IgG with each routine surveillance TBBx and BAL
 - ALL patients with multiple ACR episodes within 3 months
 - For cause: unexplained decline in lung function, after sensitizing event(s), etc.

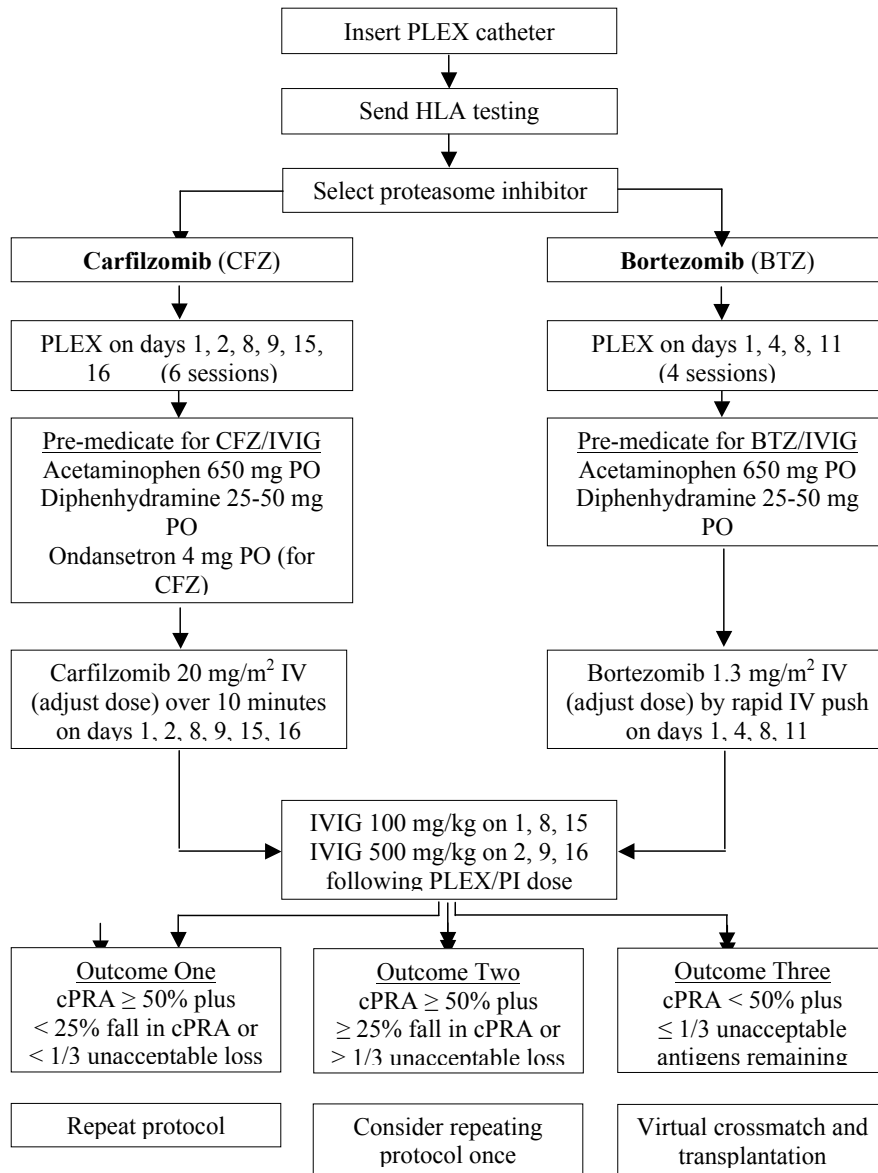
Hypogammaglobulinemia Testing

- Patients with any DSA should be screened monthly for hypogammaglobulinemia.
- Patients with DSA and IgG < 700 should undergo at least monthly supplementation with 4th generation IVIG, such as Gammagard 10% liquid, to achieve IgG trough > 700.
- ALL patients with suspected AMR must be screened for hypogammaglobulinemia upon admission for therapy.

- ALL patients treated for AMR must be screened for hypogammaglobulinemia 1-2 days following the last protocolized IVIG dose of 0.5 g/kg. If this IgG level is < 700, an additional dose of IVIG 0.5-1 g/kg should be given to achieve an IgG level > 700

Pre-transplant Desensitization/AMR Risk-Reduction

For patients with cPRA $\geq 50\%$ or ≥ 3 unacceptable antigens.



Caveats of desensitization:

1. Total-plasma exchange/plasmapheresis (PLEX)

- a. 1.5 exchanges per session
 - b. Replacement fluids
 - i. Not bleeding/not anticoagulated: 5% albumin (100%)
 - ii. If bleeding or anticoagulated and cannot stop/reverse: mixed FFP and 5% albumin (50%:50%)
 - c. Discontinue all ACE inhibitor use prior to PLEX
2. Follow ANY PLEX with IVIG
 - a. Use 4th generation Gammagard 10% liquid
 - b. Round dose to the nearest 2.5 grams
 3. Proteasome inhibitor caveats
 - a. See AMR Treatment, no. 3 (p.6)
 4. HLA testing
 - a. Alert the HISTO lab to desensitization
 - a. Send Luminex-IgG and Luminex-C1q before starting any PLEX
 - b. Send Luminex-IgG with dilution to 1:16 and Luminex-C1q on day 16 after all therapy complete
 - c. Send Luminex-IgG with dilution to 1:16 and Luminex-C1q 14 and 28 days after completion of therapy