	UCMC Heart Transplant Immunosuppression Guideline
	Version: 12/11/2024
PURPOSE:	To establish guidelines for immunosuppression in adult heart transplant recipients to reduce the risk of graft rejection.
	Immunosuppression will be given according to each transplant patient's risk individual stratification

Induction Therapy

Low Risk Induction	**Low Risk patients: (PRA-0%, and negative cross match)**
Mycophenolate:	1500 mg PO or IV administered before OR arrival
Methylprednisolone	500 mg IV in CVICU on call to OR + 500 mg IV intraop before cross clamp release

Intermediate Risk Induction	**Intermediate Risk Patients: Antibody positive but NO donor specific antibodies, and negative crossmatch; or assessed to be at intermediate risk after MD review**
Basiliximab (Simulect)	20 mg in 50 ML 0.9% NS (IVPB) x 1 dose on call to OR (POD 0 and POD #4)
PLUS	
Mycophenolate	1500 mg PO or IV administered before OR arrival
Methylprednisolone	500 mg IV in CVICU on call to OR + 500 mg IV intraop before cross clamp release

High Risk Induction Therapy	**High Risk patients: – All patients with Donor Specific Antibodies and positive Crossmatch; or assessed to be at high risk after MD review**
Thymoglobulin	1 mg/kg x 1 dose on call to OR (Pre-medication to be given prior to OR)
PLUS	
Mycophenolate:	1500 mg PO or IV administered before OR arrival
Methylprednisolone	500 mg IV in CVICU on call to OR + 500 mg IV intraop before cross clamp release

Intra-OP and POST-OPERATIVE MEDICATION DOSING REGIMEN

Methylprednisolone: 125 mg every 8 hours x 3 doses on return to the ICU on POD 0

- Initiate no later than 8 hours after the intra-operative methylprednisolone dose
  - Followed by steroid taper starting at 40 mg BID (max 1 mg/kg Q 12 hours)

Mycophenolate Mofetil (cellcept):

- 1500 mg IV every 12 hours starting postoperative day 0
- Dose 2 should be given approx. 12 hours after initial dose received
  - Oral and intravenous doses are equivalent due to 100% bioavailability of oral preparation
  - Change to oral form as soon as possible

Tacrolimus:

- The first dose of tacrolimus is administered as soon as the recipient can take oral medications and renal function is deemed to be stable (generally postoperative day 1-3)
- Initial dose is typically 0.5 to 1 mg BID d/t drug interactions
- Reduce dose by 30-50% when given in combination with a strong CYP 3A4 inhibitor (ie.voriconazole)

Antithymocyte Globulin (Thymoglobulin or ATG): Anti-lymphocyte Antibody (Cytolytic Induction)

- **For use as induction**:
  - Dosing is 1 mg/kg (range 0.5 mg-1 mg/kg) IV infusion over 6 hours (0.22 micron filter)
  - Dose based on ideal body weight or adjusted weight for weight greater than 120% of ideal
  - Preferred to administer via central line

- If central access is absolutely not available pharmacy must add heparin and hydrocortisone to thymo and administration given over 24 hours
- Dose rounded to the nearest 25 mg
- CBC with differential should be monitored daily
- Goal 5-7 days with goal absolute CD3 count less than or equal to 25
- For testing obtain daily CD3 counts [EPIC order: transplant monitor, heart] lab will run Mon-Sat
- Redose when CD3 count greater than 25
  - Consideration, if WBC between 2-3, give ½ dose. If WBC less than 2 hold dose
  - Consideration, if platelets between 50-75K, give ½ dose. If platelets less than 50K hold dose
- Premedicate 30-60 min prior to infusion to reduce adverse reactions (anaphylaxix, fever) with first several doses
  - Order from EPIC Thymoglobulin orderset to include prophylactic medications
  - Methylprednisolone (may use 500 mg dose intra-op)
    - If given intra-op, MUST be given 30 min prior to start of infusion
  - Diphenhydramine 25-50 mg IV prior to infusion
  - Acetaminophen 650 mg PO prior to infusion
- Consider starting calcineurin inhibitor 2-3 days prior to anticipated end of cytolytic induction therapy
- May be used in patients requiring delayed calcineurin inhibition (usually due to renal insufficiency)

Basiliximab (Simulect): IL-2 receptor Antibody

- For use as induction therapy or 20 mg IV in the OR (on postoperative day 0, preferably in OR but no later than 4-6 hours post-op) and on postoperative day 4
- Basiliximab therapy will be discontinued for patients receiving the addition of antilymphocyte preparations
  - (i.e. ATG)

Maintenance Immunosuppression Therapy

The following is a review of immunosuppression medications and recommended monitoring for the heart transplant patient

Steroid Therapy:

Prednisone:

- 1 mg/kg/day (with a maximum 80 mg per day) dosed twice daily in divided doses starting on postoperative day 1.
- An equivalent dose of methylprednisolone may be used if patient is unable to take oral medications
  - (5 mg prednisone = 4 mg methylprednisolone)
- Taper begins once tacrolimus levels are ≥ 5.
- Then the dose is tapered by 10 mg every 3 days until patient reaches 30 mg per day.
- Daily dosing can be considered when reaching 30 mg daily.
- Further weaning based on biopsy results, acceptable to wean as long as ISHLT grade 0R, immunofluorescence <1+ capillary C4d, AlloMap <30 and Allosure < 0.15%
- Weaning may be delayed for biopsy ISHLT grade 1R, ≥ 1+ C4d staining, AlloMap >30 and Allosure >0.15%
- Patients with biopsies ISHLT Grade 2R or greater or findings consistent with acute antibody medicated rejection not appropriate to wean.
- Weaning may continue as described above following histologic resolution of patients first rejection episode.
- Prednisone should not be weaned lower than 5 mg/day following second rejection episode unless patient has had histologic resolution for 6 months.
- The goal is to discontinue or reduce the dose of prednisone to the lowest dose necessary by six months post-transplant.
- Prednisone may be used long term for patient cases including
  - positive crossmatch (prospective or retrospective)
  - two or more treated rejection episodes within the previous 2 years

- persistent LV dysfunction following rejection
- inability to tolerate target doses of other immunosuppressive therapies
- any two of the following
  - donor specific HLA antibodies
  - persistent ≥1+ capillary C4d positive biopsy
  - persistent endothelial activation on biopsy
- when benefit outweighs risk in the clinical decision of the provider

- Patients on long term, low dose prednisone may be weaned off according to the following schedule
  - Decrease 5 mg alternating with 2.5 mg/day
  - Obtain echocardiogram at 6 weeks
  - Decrease to 2.5 mg/day
  - Obtain echocardiogram at 6 weeks
  - Decrease prednisone to 2.5 mg every other day
  - Obtain echocardiogram at 8 weeks
  - Discontinue prednisone, return in 2 weeks for RHC/Bx with immunofluorescence
  - Consider cosyntropin stimulation test to evaluate for adrenal insufficiency in patients with hypotension or significant fatigue

Steroid Taper

Prednisone 40 mg BID until Tacrolimus level =5

Initiate prednisone wean once Tacrolimus level = 5
Prednisone 35 mg BID x 6 doses (3 days)
Prednisone 30 mg BID x 6 doses (3 days)
Prednisone 25 mg BID x 6 doses (3 days)
Prednisone 20 mg BID x 6 doses (3 days)
Prednisone 30 mg daily until next biopsy with further wean based on biopsy

Antimetabolites:

Mycophenolate Mofetil:

- Oral and intravenous doses are equivalent due to 100% bioavailability of oral preparation
- Concomitant administration with iron and/or antacids can lower levels
- Consider checking AUC if concern for intolerance (such as GI symptoms or leukopenia [ANC<1000])
- Obtain AUC at 3 months then annually, adjust MMF for goal 40-60
  - Following dose adjustment repeat AUC should be performed in 6-12 weeks
  - It is reasonable to trend AUC for patients on myfortic however goals are not well defined in literature
- In intolerant of MMF consider change to myfortic (MMF 500 mg = MPA 360 mg)
- After two years may consider decreased dose to 1000 mg BID and after 5 years 500 mg BID
- In the setting of acute infection it is not necessary to decrease or withdraw MMF therapy, in the setting of chronic infection consideration for off protocol immunosuppression goals should be considered

Azathioprine:

- May be used in lieu of mycophenolate or MPA therapy due to intolerable adverse effects
- Could consider sirolimus as acceptable alternative in select patients
- Dose is typically 1-3 mg/kg/day in divided doses
- Consider checking thiopurine S-methyltransferase (TPMT) activity level prior to initiation
- Patients on azathioprine will need counseling on skin cancer risk and annual skin checks

Calcineurin Inhibitor: Tacrolimus

Tacrolimus:

- The first dose of tacrolimus is administered as soon as the recipient can take oral medications and renal function is deemed to be stable (generally postoperative day 1-3)

- Initial dose is typically 0.5 to 1 mg BID
- Dose is titrated based on clinical response, serum levels, adverse effects, and tolerance.
- The goal is to achieve a therapeutic tacrolimus level by discharge following initial transplant hospitalization.
- Trough levels should be obtained prior to dose administration of tacrolimus
- Reduce dose by 30-50% when given in combination with a strong CYP 3A4 inhibitor (ie.voriconazole)

Tacrolimus Troughs:

- Goal trough tacrolimus levels are shown below.
- Trough levels may be adjusted to each patient case depending on parameters such as renal function, adverse effects, tolerance of other immunosuppressants, and risk of rejection.

Time from transplant	Level
0 – 3 months	12-15
3 – 6 months	10-12
6 – 12 months	8-10
1 – 2 years	6-8
2 years and beyond	5-7

Other dose forms

Liquid solution:

- Dosing is the same as capsules
- If liquid is needed as outpatient it will need to be sent to compounding pharmacy, and will require insurance appeal
- Supplied as 1mg/mL concentration

Sublingual:

- If the recipient remains intubated or can't take oral medications, sublingual tacrolimus may be used
- This formulation is preferred over liquid solution
- Sublingual tacrolimus dose is calculated using a dosing ratio of 1:2 or 50% of the oral dose given sublingual

Long acting/extended-release tacrolimus (Astagraf XL):

Extended-release tacrolimus (Astagraf XL) not interchangeable or substitutable with immediate release tacrolimus

- Dosing conversion is not 1:1, but rather somewhere between 1:1 and 1:1.25
- Optimal conversion is unknown
- Estimated conversion is total daily dose of twice daily tacrolimus
  - Dose of Extended-Release Tacrolimus is calculated at a dosing ration of 1:1.25 or 125% of total daily dose from BID dosing.
    - (Tacrolimus 5 mg BID= TDD 10 mg)
    - (10 mg x 125% = 12.5 mg daily of Astagraf XL)

- Once-daily formulations (Astagraf XL and Envarsus XR) are not interchangeable with each other due to significantly different pharmacokinetic properties.

Extended-release tacrolimus (Envarsus XR)

- Extended-release tacrolimus (Envarsus XR) is not interchangeable or substitutable with immediate release tacrolimus
  - Dosing conversion is not 1:1
  - Optimal conversion is unknown
  - Estimated conversion is 1:0.85 or 85% of total daily dose from BID dosing
    - Dose of Extended-Release Tacrolimus is calculated at a dosing ration of 1:0.85 or 85% of total daily dose from BID dosing.
      - (Tacrolimus 5 mg BID= TDD 10 mg)
      - (10 mg x 85% = 8.5 mg daily of Envarsus XL)

- Once-daily formulations (Astagraf XL and Envarsus XR) are not interchangeable with each other due to significantly different pharmacokinetic properties.

Intravenous:

- Not recommended due to increased risk of renal dysfunction and adverse effects
- IV tacrolimus should not be used without Attending approval
- If the recipient remains intubated or can't take oral medications, intravenous tacrolimus may be used at dose of 0.01 mg/kg/day as continuous infusion
- If transitioning from oral to IV tacrolimus the intravenous dose is about 20-33% of oral dose or $1/5^{th}$ of oral dose administered as continuous infusion over 24 hours
- Wait at least 8-12 hours when switching from intravenous to oral dosing
- All blood for drug concentration should be drawn via peripheral stick or central line that has never been used to infuse tacrolimus

Calcineurin inhibitor: Cyclosporine

Cyclosporine:

- Cyclosporine microemulsion may be used in lieu of tacrolimus.
- The first dose is administered as soon as the recipient can take oral medications and renal function is deemed to be stable (generally postoperative day 1-3)
- Initial dose is 2-5 mg/kg/day dosed twice daily in divided doses
- Dose is titrated based on clinical response, serum levels, and tolerance
- Ensure the patient remains on a consistent manufacturer because preparations are not interchangeable [Neoral/Gengraf (cyclosporine modified) vs Sandimmune (Cyclosporine non-modified)]

Other dose forms:

- IV cyclosprorine should not be used without attending approval
- If the recipient remains intubated or can't take oral meds intravenous cyclosporine may be used at dose of 1 mg/kg/day as continuous infusion.
    - Note that intravenous dose is approximately 1/3 of oral dose

Cyclosporine Troughs

- Trough levels should be obtained prior to dose administration of cyclosporine
- Trough levels may be adjusted to each patient case depending on parameters such as renal function, adverse effects, tolerance of other immunosuppressants, and risk of rejection
- Goal trough cyclosporine levels are shown below

Time from transplant	Level
0 – 3 months	250-350
3 – 6 months	200-300
6 – 12 months	150-250
1 year – 2 years	100-200
2 years and beyond	50-100

CNI dosing and monitoring when discontinuing voriconazole therapy

A decrease in CNI level is expected with the discontinuation of voriconazole. Voriconazole inhibits intestinal and hepatic CYP3A4 enzymes, reducing CNI metabolism and increasing its bioavailability. Therefore, when voriconazole is discontinued, CNI metabolism is expected to increase, which will result in the need for higher doses of CNI to maintain

goal levels. Pharmacokinetic changes in CNI metabolism can be seen approximately 7-10 days after initiation or discontinuation of voriconazole and should be monitored accordingly.

For patients with therapeutic CNI levels at the time of voriconazole discontinuation:

- **Dosing**:
  - Increase CNI dosing by 25 to 50%, first dose the following day
- **Monitoring**
  - Follow up CNI levels every 3-5 days until patients have therapeutic CNI level
  - Minimum of two levels within goal weekly, then return to routine monitoring

- **For patients with supratherapeutic CNI levels at the time of voriconazole discontinuation**
- **Dosing**:
  - Increase CNI dosing by 25%, first dose the following day
- **Monitoring**
  - Follow up CNI levels every 3-5 days until patients have therapeutic CNI level
  - Minimum of two levels within goal weekly, then return to routine monitoring

For patients with subtherapeutic tacrolimus levels at the time of voriconazole discontinuation

- **Dosing**:
  - Increase CNI dosing by at least 50% starting with the next dose
- **Monitoring**
  - Follow up CNI levels every 3-5 days until patients have therapeutic CNI level
  - Minimum of two levels within goal weekly, then return to routine monitoring

mTOR Inhibitors

Indications for mTOR conversion:

- mTOR in place of a calcineurin inhibitor (CNI) as part of a **CNI free regimen** in patients with renal dysfunction who are greater than 12 months post-transplant with no evidence of rejection

- mTORs used in place of antimetabolite therapy (mycophenolate or azathioprine) or as adjunctive therapy in patients with **coronary allograft vasculopathy** (CAV)

  - [Defined as IVUS >0.5 in one or more vessels, may consider if IVUS 0.2-0.4 cm].

Contraindications to mTOR conversion:

- Major open wounds or known impaired wound healing
- Anticipated need for surgical intervention

Lab Tests (complete PRIOR to conversion) :

- CBC
- Renal Panel
- Lipid panel
- Urine protein/creatine ratio
- Chest X ray
- PFTs (acceptable if obtained withing 3 months prior to initiation)

Preferred mTOR and Initiation Regimen: Sirolimus

- Sirolimus (Rapamune®) - available in 0.5, 1 and 2 mg tablets, and 1 mg/ml oral solution
  - To standardize, please use the 0.5 mg or 1 mg tablet strength

- Initial dosing: simultaneously initiate Sirolimus based on regimen listed below while decreasing CNI

CNI Free Regimen

- Initiate Sirolimus 2 mg daily while simultaneously decreasing CNI.
- Decrease CNI level by approximately 50% or per physician preference
- Document adequate sirolimus level prior to discontinuing calcineurin inhibitor

Sirolimus + Antimetabolite Regimen (CNI Free regimen) Target Goals	
# months post-transplant	Sirolimus Goal
1 year (12-23 months)	8-12 ng/ml
Year 2 and beyond (24+ months)	6-10 ng/ml

CNI + sirolimus for CAV risk reduction regimen

- Discontinue antimetabolite therapy (unless high risk for rejection)
- Initiate sirolimus 1 mg daily while simultaneously decreasing CNI.
- Decrease CNI dose by approximately 50% or per physician preference
- Dose at least 4 hours following calcineurin inhibitor dosing if any evidence of neurotoxicity, otherwise may be given concomitantly
- If triple therapy is necessary recommendation for aiming for lower range of goals below

	Sirolimus + tacrolimus CAV risk reduction Target Goals		
# months post-transplant	Tacrolimus Goal	Sirolimus goal	Combination goal
1-2 years (12-35 months)	4-7 ng/ml	4-7 ng/ml	8-14 ng/ml
3 years (36+ months)	3-6 ng/ml	3-6 ng/ml	6-12 ng/ml

OR

	Sirolimus + cyclosporine CAV risk reduction Target Goals	
# months post-transplant	Cyclosporine Goal	Sirolimus goal
1-2 years (12-35 months)	100-200 ng/ml	4-7 ng/ml
3 years (36+ months)	50-100 ng/ml	3-6 ng/ml

Alternative mTOR Regimen: Everolimus

Everolimus (Zortress®) - available in 0.25, 0.5, 0.75, and 1 mg tablets

- Initial dosing: simultaneously initiate Everolimus 0.75 mg twice daily based on regimen listed above (CNI free or CAV Regimens) while decreasing CNI

CNI-Free Regimen:

- Initiate Everolimus 0.75 mg twice daily while simultaneously decreasing CNI.
- Decrease CNI level by approximately 50% or per physician preference
- Document adequate everolimus level prior to discontinuing calcineurin inhibitor

Everolimus + Antimetabolite: CNI Free Regimen Target Goals	
# months post-transplant	Everolimus Goal
1 year (12-23 months)	6 - 10 ng/ml
Year 2 and beyond (24+ months)	4 - 8 ng/ml

CNI and Everolimus for CAV risk reduction regimen

- Discontinue antimetabolite therapy (unless high risk for rejection)
- Initiate everolimus 0.75 mg twice daily while simultaneously decreasing CNI.
- Decrease CNI dose by approximately 50% or per physician preference
- Dose at least 4 hours following calcineurin inhibitor dosing if any evidence of neurotoxicity, otherwise may be given concomitantly
- If triple therapy is necessary recommendation for aiming for lower range of goals below

	Everolimus + tacrolimus: CAV risk reduction Target Goals		
# months post-transplant	Tacrolimus Goal	Everolimus goal	Combination goal
1-2 years (12-35 months)	4-7 ng/ml	3-7 ng/ml	7-14 ng/ml
3 years (36+ months)	3-6 ng/ml	3-6 ng/ml	6-12 ng/ml

OR

	Everolimus + cyclosporine: CAV risk reduction Target Goals	
# months post-transplant	Cyclosporine Goal	Everolimus goal
1-2 years (12-35 months)	100-200 ng/ml	3-7 ng/ml
3 years (36+ months)	50-100 ng/ml	3-6 ng/ml

mTOR Monitoring

mTOR and CNI levels

- Obtain mTOR trough level 5-7 days post conversion along with CNI level
- Checking mTOR level earlier than 5 days post conversion provides inaccurate information and should not be done
- mTOR level should be a trough level (i.e. patient gets AM lab draw BEFORE taking morning dose of mTOR)

Titrate mTOR and CNI doses to achieve target levels as follows:

- mTOR level at target: continue mmTOR dose and discontinue CNI
    - Monitor mTOR levels every 5-7 days until stable level is achieved
- mTOR level sub-therapeutic
    - increase sirolimus 0.5 to 1 mg daily and continue current CNI dose
    - increase everolimus by 0.5 mg twice daily and continue current CNI dose
    - varies per situation depending on CNI level
    - Continue to monitor mTOR and CNI levels every 5-7 days until stable level is achieved for mTOR
    - When therapeutic mTOR level occurs, then discontinue CNI
- If mTOR level is supra- therapeutic
    - decrease sirolimus dose by 0.5-1 mg daily and discontinue CNI
    - decrease everolimus dose by 0.5 mg twice daily and discontinue CNI
    - Continue to monitor mTOR levels every 5-7 days until stable dose/level is achieved

Once stable mTOR level is achieved monitor monthly and then at frequency of regular maintenance lab

mTOR Monitoring and Considerations

mTor Dose Reduction Considerations

- Reduce dose by approximately 1/3 in patients with hepatic impairment
- Reduce dose by 50-90% when given in combination with a strong CYP 3A4 inhibitor (ie. **voriconazole**, ketoconazole, Clarithromycin, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, Posaconazole, ritonavir, saquinavir, tipranavir)

mTor Common Side Effects

- Adverse events are most likely to occur during the initial conversion / dose titration period

Commonly observed adverse events and recommended therapy:

- Pulmonary Edema – if radiographically confirmed, then target a lower Sirolimus level
- Mouth ulcers – initiate therapy (possible options listed below) and may need to target a lower Sirolimus level
    - Chlorhexidine 0.2% (10ml swish and spit two times daily for pain)
    - Benzydamine 0.15% (10-15ml rinsed in mouth every 3 hours for pain)
    - Steroid topical ointment or mouthwash applied twice daily (i.e. hydrocortisone, betamethasone, clobetasol, fluocinolone; consult PharmD for specific doses)
- Peripheral edema— target a lower Sirolimus level
- Leukopenia—target a lower Sirolimus level
- Bone pain – target a lower Sirolimus level (if clinically indicated)
- Elevated triglycerides (isolated)- TRICOR® 1 tab (145mg) daily (dose adjust for renal dysfunction)
    - Other options: Lovaza® (prescription) or OTC fish oil formulations, statin therapy
    - In those with Type 2 diabetes, check hemoglobin A1C. Elevated A1C may also exacerbate triglyceride level
    - Shortness of breath

mTor Discontinuation Criteria

Consider discontinuation when:

- Severe adverse events continue despite target level modifications
- Triglycerides > 500 despite therapy and strict control of diabetes mellitus
- Abnormal LFT's
- Proteinuria defined by PCR > 3 (OR) when PCR doubles from baseline
- Abnormal PFTs- worsening SOB
- For elective major surgery
    - Discontinue mTOR 6 weeks prior to surgery
    - If CNI free regimen resume CNI and default back to CNI only goals
    - If on mTOR and CNI regimen, discontinue mTOR and resume antimetabolite if contraindication does not exist
    - If unable to tolerate MMF prednisone should be considered
    - When wound healing is complete (approximately 6-8 weeks) you may revert to pre-operative strategy