

PROTOCOL TITLE: Acute Cellular Rejection Protocol for Heart Transplant Recipients	
APPLICABLE FACILITIES: <input checked="" type="checkbox"/> EHC <input type="checkbox"/> EDH <input type="checkbox"/> EHH <input type="checkbox"/> EHI <input type="checkbox"/> EHN <input type="checkbox"/> EJCH <input type="checkbox"/> ELTAC <input type="checkbox"/> ESJH <input checked="" type="checkbox"/> EUH <input type="checkbox"/> EUHM <input type="checkbox"/> EUHS <input type="checkbox"/> EUOSH <input type="checkbox"/> EWWH <input type="checkbox"/> RJV-ERH <input type="checkbox"/> RJV-ESOP <input type="checkbox"/> TEC/ESA	
EFFECTIVE DATE: 5/4/2020	ORIGINATION DATE: 8/4/2022

CATEGORY:

Choose One or More: Medication Guidelines

LEVEL:

Choose One: Interdependent

CONTENT: This protocol applies to heart transplant recipients who are determined to acute cellular rejection.

Policy Statement: The Emory Transplant Center and all the solid organ transplant programs will comply with all applicable federal, state, and local laws, regulations, policies and protocols regarding the management of transplant patients.

Basis: This protocol is necessary for the protection of patients, physicians and staff

Administrative Responsibility: All transplant program physicians, practitioners and clinical staff members are responsible for compliance with this clinical protocol.

RELATED POLICIES / PROCEDURES:

Initial assessment:

1. Grade 1R ACR:
 - a. Optimize oral immunosuppression strategy
2. First episode of $\geq 2R$ ACR?
 - a. Hemodynamically stable? Follow **Steroid Pulse Protocol**
 - b. Hemodynamically unstable (newly decreased LVEF, SBP < 90 with signs/symptoms of heart failure and/or requiring inotropes, or at the discretion of the transplant cardiologist)? Follow **Thymoglobulin Protocol + Steroid Protocol**
3. Recurrent episode of ACR?
 - a. Patient has not received thymoglobulin previously for ACR?
 - i. Repeat **methylprednisolone** pulse. Increase **Cellcept/Mycophenolate** dose if not already on maximum dose; initiate **prednisone** po taper following methylprednisolone pulse.
 - ii. Pulse therapy with **methotrexate** po (2.5 mg to 20 mg once weekly)
 - iii. Cytolytic therapy with **thymoglobulin +/- steroid**
 - d. Patients has received thymoglobulin previously for ACR?
 - iv. Repeat cytolytic therapy with **thymoglobulin +/- Steroid**
 - v. **Photopheresis**

Commented [HM1]: Do we want to include rejection grade?

Commented [MAB2]: I have several comments here:
 (1) Maybe it is presumed, but for hemodynamically unstable, we should always give BOTH steroid pulse and thymo at the same time. Little data to support, but this is what everyone does. It is also what is stated in the HT management guidelines (says for HD unstable to give cytolytic therapy "in addition to IV CS").
 (2) Also, steroids can be given faster – first dose can usually be given <1hr after being ordered whereas thymo requires an order template be completed, and then takes pharmacy at least an hour to prepare – in my experience here it is usually a few hours before the thymo is finally hanging.
 (3) Do you want to provide a specific comment on grade 3R? We don't see too many because we're slow to biopsy here, but the majority of these will present with HD instability, making it a moot point. But, in the instance that it doesn't, I would suggest we say to favor thymo +CS but ultimately up to the treating physician's discretion.

Commented [HM3]: Think we would need consensus on when to go to thymo first instead of steroids.

Commented [MAB4]: Numbering is off here...2 number 2s.

vi. **Total lymphoid irradiation (TLI)**

A. Steroid Pulse

Day # 1: _____

Step # 1: **Methylprednisolone** 1000 mg IVPB

Step # 2: Start opportunistic infection prophylaxis

- a) **PCP/Toxo:** Bactrim DS (renal dose SS) MWF, Atovaquone 1500mg daily, or Dapsone 100mg daily until prednisone dose < 10 mg daily x 1 month
- b) **Valcyte prophyl for CMV D+/R-, D-/R+, D+/R+** patients x 4 weeks with weekly labs for cbc, cmp, and CMV PCR

Day # 2: _____

Step # 1: **Methylprednisolone** 1000 mg IVPB

Day # 3: _____

Step # 1: **Methylprednisolone** 1000 mg IVPB

Day # 4: _____

Step # 1: Resume **prednisone** po at previous dose if first episode of rejection. If recurrent rejection or at the discretion of transplant cardiologist, start **prednisone** po taper 20mg po qDay x 4 weeks, then 15mg qDay x 1 week, then 10mg qDay x 1 week, then 5mg daily indefinitely.

2 weeks post: _____

Step # 1: Repeat biopsy

B. Thymoglobulin

Day # 1-10*: _____

**Total Duration of thymoglobulin treatment to be determined by transplant cardiologist*

Step # 1: Order rabbit anti-thymocyte globulin via transplant order set. Standard dose **thymoglobulin 1.5 mg/kg** rounded to the nearest 25 mg (Central line preferred*)

Commented [MAB5]: I would reverse the order here so someone doesn't delay the first dose of steroids while waiting for Bactrim to be given. If only CS, I'd vote no more than 1 month of treatment with OI proph. I think medium risk (D-/R+ and D+/R+) should also receive CMV prophylaxis...little downside as long as CBC is monitored, especially with a short course.

Commented [MAB6]: If doing an extended taper, how long, if at all, do we extend OI prophylaxis?

* If patient does not have central line and is hemodynamically stable, choose peripheral line formulation when ordering (contains heparin + hydrocortisone and defaults to run over 8 hours vs. 6 hours to prevent risk of extravasation)

Premedications prior to thymoglobulin

- a) **Acetaminophen** 650 mg PO daily
- b) **Diphenhydramine** 50 mg PO daily
- c) **Methylprednisolone** 500mg IV Day 1, 250mg IV Day 2, 125mg IV Day 3, followed by prednisone taper

Step # 2: Order CBC with differential daily to monitor for neutropenia and lymphopenia. Consider the following guidance for dose adjustments:

NOTE: CD3 monitoring not recommended to guide treatment due to the inability of EUH lab to report assessment of T cell subsets in presence of low number of lymphocytes and due to delay in reporting of results (may take up to 72 hours)

		Thymoglobulin Dosage Adjustment
WBC	> 1.5	No changes
	1 – 1.5	Reduce thymo dose 50%
	≤ 1.0	Reduce thymo dose 50% and give neupogen
	ANC ≤ 500	Hold thymo and give neupogen
PLT	> 60K	No changes
	30-60K	Reduce thymo dose 50%
	<30K	Hold thymo

Can also consider holding Thymo dose if ALC < 10% baseline or at discretion of the physician if there are clinical concerns with continued dosing.

Step # 3: Start opportunistic infection prophylaxis

- a) **PCP/Toxo**: Bactrim DS (renal dose SS) MWF, Atovaquone 1500mg daily, or Dapsone 100mg daily x 3 months
- b) **CMV**: Valcyte 900 (renal dose 450 daily) x 3 months for recipients who are CMV+ or CMV mismatch
- c) **Candida/yeast**: consider Nystatin S&S x 1 month

Step # 4: Consider reduction of Cellcept or Myfortic dose by 50% during thymoglobulin course

Step # 5 (on final day of thymoglobulin):

- a) Continue **prednisone** po taper 40 mg po qDay x 1 week, then 30 mg qDay x 1 week, then 20 mg qDay x 1 week, then 10 mg daily x 1 week, then 5 mg daily indefinitely
- b) If no cytopenias, increase **Cellcept/Myfortic** back to original or increased dose. Can consider changing Cellcept to sirolimus

2 weeks post: _____

Step # 1: Repeat biopsy

Commented [MC7]: Do we want to include consideration to hold thymo dose if ALC <10% baseline (given some data for not doing daily thymo if ALC/CD3 at goal?)

Commented [MAB8]: These seem like aggressive thresholds; is there data backing this? In my experience, once the WBC starts to fall, it starts to fall precipitously. Continuation depends more on the situation: i.e., if I've already managed to get in 5 doses, the pts hemodynamics have improved and the WBC went from 4.2 → 1.9, I'm going to stop giving thymo. Maybe we could just say cessation is at the discretion of the physician and in relation to the situation (e.g., dose number, trend in WBC, etc...) with an absolute lower limit cutoff beneath which we all should stop (1.0 seems good for that, IMO).

COMMON SIDE EFFECTS OF THYMOGLOBULIN TO MONITOR FOR:

- a. Life-threatening hypersensitivity and anaphylactic reactions have been reported. Stop infusion immediately if anaphylactic reaction occurs. Immediate treatment (including SQ epinephrine and corticosteroids) should be available during infusions for management of hypersensitivity
- b. Cytopenias – thrombocytopenia, leukopenia, anemia
- c. Cardiovascular – hyper-/hypotension, tachycardia, peripheral edema
- d. GI – abdominal pain, nausea, vomiting, diarrhea
- e. CNS – fever, chills, headache, pain, insomnia, malaise
- f. Neuromuscular– myalgia, arthralgia, weakness, back pain
- g. Respiratory – dyspnea
- h. Dermatologic – skin rash, pruritus

DEFINITIONS:

ANC – absolute neutrophil count

ALC – absolute lymphocyte count

REFERENCES AND SOURCES OF EVIDENCE:

1. Auphan N, DiDonato JA, Rosette C, Helmberg A, Karin M. Immunosuppression by glucocorticoids: inhibition of NF-kappa B activity through induction of I kappa B synthesis. *Science*. 1995 Oct 13;270(5234):286-90.
2. Burdick JF. The biology of immunosuppression with anti-lymphocyte antibodies. In: *Kidney Transplant Rejection: Diagnosis and Treatment*, Williams GM, Burdick JF, Solez K (Eds), Marcel Decker, New York 1988. p.307.
3. Cosimi AB, Delmonico FL. Antilymphocyte antibody immunosuppressive therapy. In: *Kidney Transplant Rejection: Diagnosis and Treatment*, Williams GM, Burdick JF, Solez K (Eds), Marcel Decker, New York 1988. p.335.
4. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S, Fedson S, Fisher P, Gonzales-Stawinski G, Martinelli L, McGiffin D, Smith J, Taylor D, Meiser B, Webber S, Baran D, Carboni M, Dengler T, Feldman D, Frigerio M, Kfoury A, Kim D, Kobashigawa J, Shullo M, Stehlik J, Teuteberg J, Uber P, Zuckermann A, Hunt S, Burch M, Bhat G, Canter C, Chinnock R, Crespo-Leiro M, Delgado R, Dobbels F, Grady K, Kao W, Lamour J, Parry G, Patel J, Pini D, Towbin J, Wolfel G, Delgado D, Eisen H, Goldberg L, Hosenpud J, Johnson M, Keogh A, Lewis C, O'Connell J, Rogers J, Ross H, Russell S, Vanhaecke J; International Society of Heart and Lung

Commented [MAB9]: Should also add the guidelines:
Costanzo JHLT 2010



Transplantation Guidelines. The International Society of Heart and Lung Transplantation
Guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2010
Aug;29(8):914-56.

KEY WORDS:

Heart Transplant
Cellular Rejection
Immunosuppression