EMORY
HEALTHCARE

PROTOCOL TITLE: Antibody Mediated Rejection Protocol for Heart Transplant Recipients							
APPLICABLE FACILITIES:							
☒EHC	☐EDH	☐EHH	☐EHI	☐EHN	☐EJCH	☐ELTAC	☐ESJH
☒EUH	☐EUHM	☐EUHS	☐EUOSH	☐EWWH	☐RJV-ERH	☐RJV-ESOP	☐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:

DIAGNOSIS OF AMR REQUIRES 2 OF THE FOLLOWING:

1. Biopsy Findings of pAMR ≥1 +/- concomitant ACR:
2. De novo or increase in existing DSAs
    a. Note the MFI pre and post-transplant
3. Graft Dysfunction:
    a. Noted by TTE or RHC
4. Elevated Allosure > 0.2

CONCERN FOR AMR WITHOUT CLINICAL SIGNIFICANCE:

1. Optimize immunosuppression (especially DMARD, steroids)
    a. Can consider a long prednisone taper over a month
2. Repeat Heartcare, Immuknow, DSAs, biopsy in 2-4 weeks

CLINICALLY SIGNIFICANT AMR WITH GRAFT DYSFUNCTION +/- HEMODYNAMIC SIGNIFICANCE

PROTOCOL RELATIVE CONTRAINDICATIONS:

Commented [MAB1]: Maybe "Biopsy findings including some combination of:" as I don't think you have to have all features to diagnose AMR. Or, maybe just leave it all out and indicate the biopsy grades of pAMR ≥1...i.e., "Biopsy grade pAMR ≥1" without any of the other details.

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- Moderate-to-severe neuropathy at baseline
- Absolute neutrophil count (ANC) < 1000 in last 7 days
- Platelets < 100,000 in last 7 days
- Allergies/adverse reactions to rituximab previously
- Current or recent (< 2 weeks) severe systemic infections
- Recent MI, uncontrolled angina/ischemia, Class IV CHF, uncontrolled arrhythmias

BASELINE PRE-TREATMENT:

- LABS:
  - CBC with Diff
  - CP Comp, Mag
  - PRA/DSA (order STAT)
  - Prograf/Cyclo/Rapa levels
  - CMV PCR, EBV PCR
  - Tetanus Ab
  - Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc)
  - Immuknow, Heartcare
- Biopsy for grading/C4d & RHC
- ECHO
- EKG
- Admission to one of the cardiac telemetry floors or CICU.
- IR order to place VasCath.
- Hold all anti-hypertensive medications on admission. May resume post Rituximab administration or as clinically indicated.
- Reduce Cellcept or Myfortic dose by 50% on admission; reassess for cytopenias prior to discharge and consider re-initiation at original or increased dose on discharge.
- Discontinue all ACE inhibitors/ARBs until after plasmapheresis has been completed.
- Opportunistic infection prophylaxis:
  a) PCP/Toxo:

Commented [MAB2]: Could add "or admission to CICU" as the Vascath can be placed faster there, especially for less stable patients.

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a. Bactrim DS (renal dose SS) MWF -or-
b. Atovaquone 1500mg daily -or-
c. Dapsone 100mg daily x 3 months

b) CMV: Valcyte 900 (renal dose 450 daily) x 3 months D+/R- or preemptive monitoring
c) Candida/yeast: consider Nystatin S&S x 1 month

If patient in cardiogenic shock, significant compromise, or combined cellular rejection (ACR), consider lymphocytic therapy in conjunction with the following protocol +/- proteasome inhibitor (thymoglobulin +/- bortezimib)

Timeline of Activities in EUH AMR Protocol

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 11	Day 19	1 Month
Biopsy w/ RHC/Hemodynamics, HeartCare, Immuknow	X								X*	X*
CMV PCR, EBV PCR, Tetanus Ab, HepB	X									
DSA/PRA (Stat)	X					X				X
ECHO	X									
Methylprednisolone 1000mg IV qDay x 3		X	X	X						
Plasmapheresis 1.5 PV qDay x 5		X	X	X	X	X				
IVIG 2Gm/kg x1 (Draw PRA prior admin)						X				
Rituximab 375 mg/m2 IV x 1						X				
Prednisone po taper (starting Day #4)					X					
Bortezomib**		**x**			**x**		**x**	**x**		**x**

**additional agent for refractory AMR
*timing of biopsy, heartcare, immuknow will be based on duration of therapy but ranges 2-4 weeks from end of treatment

TREATMENT PROTOCOL

Day # 1: _____

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

Step # 2: **Plasmapheresis** 1.5 PV (*remove preformed Ab*)

Step #3: **Bortezomib** 1.3 mg/m2 SQ (if using)

Commented [MAB3]: Just FYI; transfusion medicine has their own protocol for plasmapheresis, and I believe they do every other day (which is what we did at BWH). The last time I did pheresis several months ago, they were insistent on doing it every other day. HT guidelines propose several possible regimens including daily and QOD. Might be best to run this by Sullivan, who was involved the last time I did pheresis, so that the protocols don't clash and cause confusion/problem between us and them.

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Day # 2: _____

Toxicity Assessment
- GI:
- NEURO:
- HEME:
- DOSE REDUCTION NECESSARY?

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

Step # 2: **Plasmapheresis** 1.5 PV

Day # 3: _____

Toxicity Assessment
- GI:
- NEURO:
- HEME:
- DOSE REDUCTION NECESSARY?

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

Step # 2: **Plasmapheresis** 1.5 PV

Day # 4: _____

Toxicity Assessment
- GI:
- NEURO:
- HEME:

Step # 1: 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.

Step # 2: **Plasmapheresis** 1.5 PV

Step #3: **Bortezomib** 1.3 mg/m2 SQ (if using)

Day # 5: _____

Step # 1: **Plasmapheresis** 1.5 PV

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Step # 2: Check Stat DSA ****CRITICAL/ Draw before IVIG administration

Step # 3: Pre Medicate prior to IVIG & Rituximab
Acetaminophen 650 mg PO x 1 dose
Diphenhydramine 50 mg PO x 1 dose

Step # 4: **IVIG** 2Gm/kg (*block Ab function*)
Dose based on IBW, max dose 140mg

Step # 5: **Rituximab** 375 mg/m2 IV rounded to nearest 100mg (*monoclonal Ab against CD20 on B cells, B cell destruction*)

Step #6: Post-Treatment (Day 5) to be done after last plasmapheresis

LABS: CBC with diff, CP Comp, Mg, IS levels, PRA/DSA, CMV PCR, EBV PCR, Tetanus Ab Echo

If no cytopenias, increase Cellcept/Myfortic back to original or increased dose. Can consider changing Cellcept to rapamune considering risk of CAV in patients with AMR

Day # 8: _____
Step #1: **Bortezimib** 1.3 mg/m2 SQ

Day # 11: _____

Step #1: **Bortezimib** 1.3 mg/m2 SQ

1 month post: _____

Step #1: Check Immuknow, Heartcare, DSA/PRA labs.

Persistent Refractory AMR: consider Eculizumab (protocol written separately), Photopheresis, or TLI (Total Lymphoid Irradiation). Will need to be discussed on a case by case basis.

COMMON SIDE EFFECTS TO MONITOR FOR: (GI effects, cytopenias, neuropathy, fevers)

a. **Plasmapheresis**:
    a. Hypotension/volume depletion
    b. Allergic reactions
b. **Rituximab** (Rituxan):
    a. Life-threatening infusion reactions have been reported and result in bronchospasm, anaphylactic shock, ARDS, Hypotension, VFib, etc. These typically occur with 30-120 minutes

b. Angioedema, pruritis, urticaria – pretreatment with diphenhydramine

c. Fevers and chills – pretreatment with acetaminophen

d. GI effects (nausea, vomiting, diarrhea, Abd pain) – VERY common – order PRN meds for these effects

e. Cytopenias – thrombocytopenia, neutropenia, lymphopenia

c. **Bortezimib** (velcade)

a. Life threatening reactions: ARDS, cardiac arrest, arrhythmias, severe hypotension, angioedema

b. CHF

c. Neuropathies/neurologic issues – peripheral neuropathy, optic neuropathy, blindness, PRES,

d. Cytopenias

e. Pulmonary issues – pneumonia, pneumonitis, ARDS, interstitial pneumonia\

f. HUS

g. GI effects – diarrhea, hepatotoxicity, ileus, pancreatitis

DEFINITIONS:
N/A

REFERENCES AND SOURCES OF EVIDENCE:

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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.
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Commented [MAB4]: I think we should cite more current data than 1988-95:
HT guidelines: Costanzo JHLT 2010
ISHLT path guidelines: Berry JHLT 2013
AHA AMR Sci Statement: Colvin Circ 2015
Review on AlloSure in heart: Khush JHLT 2021

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5. Agbor-Enoh S, Shah P, Tunc I, Hsu S, Russell S, Feller E, Shah K, Rodrigo ME, Najjar SS, Kong H, Pirooznia M, Fideli U, Bikineyeva A, Marishta A, Bhatti K, Yang Y, Mutebi C, Yu K, Kyoo Jang M, Marboe C, Berry GJ, Valantine HA; GRAfT Investigators. Cell-Free DNA to Detect Heart Allograft Acute Rejection. Circulation. 2021 Mar 23;143(12):1184-1197.

KEY WORDS:
Heart Transplant
Antibody Mediated Rejection
Immunosuppression