EMORY HEALTHCARE

PROTOCOL TITLE: Heart Post Transplant CMV Protocol							
APPLICABLE FACILITIES:							
☒EHC	☐EDH	☐EHH	☐EHI	☐EHN	☐EJCH	☐ELTAC	☐ESJH
☒EUH	☐EUHM	☐EUHS	☐EUOSH	☐EWWH	☐RJV-ERH	☐RJV-ESOP	☒TEC/ESA
EFFECTIVE DATE:				**ORIGINATION DATE:** 12/18/19			

CATEGORY:
CPOE, Diagnostic/Therapeutic/Preventive, Medication Guidelines,

CONTENT:

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.

Scope/Procedure:

Protocol:

1. All patients undergoing heart transplantation will have the CMV status (antibody) rechecked at the time of transplantation.

2. CMV status of donor and recipient will be documented in EeMR.

3. All patients will be informed of their donor/recipient CMV status and risk for CMV disease by the post-transplant coordinator during the patient's transplant admission and documented on the appropriate clinical transplant pathway.

4. Please do not start valganciclovir prophylaxis unless previous CMV PCR tests have been "Undetected."

    A. If the patient has a detectable CMV viral load (<35 or any quantified CMV level), do not start prophylaxis dose of valganciclovir or ganciclovir. These patients should either continue pre-emptive monitoring or start treatment dosing of vanganciclovir/ganciclovir.

5. **Post-Transplant Prophylaxis** (for eGFR >60 ml/min):

Donor/Recipient Status	Prophylaxis Regimen	Duration
D+/R-	Valganciclovir 900 mg po daily starting on POD 21	3 months
Any R+	Preemptive monitoring AND Valacyclovir 1000 mg po daily Or Acyclovir 400mg q 8 hours If unable to comply with monitoring OR if receiving belatacept, then Valganciclovir 900 mg po daily starting on POD 21	3 months
D-/R-	Valacyclovir 1000 mg po daily Or Acyclovir 400mg q 8 hours	3 months

Note: D = donor, R = recipient, (+) = positive, and (-) = negative

Prophylaxis dosage adjustment for renal function is as follows:

CrCl (ml/min)	**Ganciclovir Prophylaxis**	**Valganciclovir Prophylaxis Dose**	**Valacyclovir / Acyclovir Dose**
>60	5mg/kg IV q24h	900 mg po daily	1000 mg daily / 400 mg q 8 hour
40-59	2.5mg/kg IV q24h	450 mg po daily	1000 mg daily / 400 mg q 12 hours
25-39	1.25mg/kg IV q24h	450 mg po 3 times/week	500 mg po daily / 400 mg daily
10-24	0.625mg/kg IV q24h	450 mg po 3 times/week	500 mg po daily / 400 mg daily
< 10 or dialysis dependent	0.625mg/kg 3 times weekly (post-HD)	450 mg po post-hemodialysis or 2-3 times/week	500 mg po daily / 400mg daily, administer post-hemodialysis on HD days

Note: HD = hemodialysis

6. Patients on prophylaxis who are unable to take oral medications may be given parenteral ganciclovir as above or have weekly CMV PCRs checked until able to take oral medication.

7. Leukopenia: Do **NOT** reduce the dose of valganciclovir or ganciclovir for leukopenia.

A. If Absolute Neutrophil Count (ANC) drops below 1000, consider administration of G-CSF (Neupogen/Granix) until ANC > 1000

B. If patient is not a candidate for G-CSF administration, then consider placing patient on pre-emptive strategy

8. CMV Monitoring by plasma PCR testing

A. CMV PCR will be performed, in addition to below, in any patient regardless of CMV status when CMV disease is suspected and when clinically indicated (i.e., patient presents with fever, leukopenia, diarrhea, malaise, respiratory symptoms, or if immunosuppression is augmented).

B. **D+/R-** patients on ganciclovir or valganciclovir prophylaxis

i. CMV PCR at days 7, 14, and 21, then months 1, 2, 3, 4, 5, 6, 8, 10, 12

C. **R+** patients on ganciclovir or valganciclovir prophylaxis

i. CMV PCR at months 1, 2, 3, 4, 5, 6

D. **D-/R-**

i. No per protocol testing

ii. However, if the patient has received extensive transfusion of blood products, then initiate weekly CMV PCR monitoring for 4 weeks

E. **Pre-emptive monitoring (for all D+/R- and R+ patients NOT on ganciclovir or valganciclovir prophylaxis)**

i. This strategy will be used for patients who are intolerant to valganciclovir or cannot obtain valganciclovir

ii. D+/R- patients: weekly CMV PCR through month 3, then q 2 week PCR through month 6, then month 8, 10, and 12

iii. R+ patients: weekly CMV PCR through month 3, then at months 4, 5, 6.

iv. All patients on pre-emptive monitoring should receive Valacyclovir or Acyclovir for HSV/VZ prophylaxis for at least 3 months

F. **Rejection**

i. Patients who are treated with T-cell depleting antibody therapy will receive 3 months of CMV prophylaxis with valganciclovir or IV ganciclovir (see dosage table above)

ii. CMV PCR will be drawn every two weeks for two months, then monthly for months 3 – 6 following each documented rejection episode treated with T-cell depleting antibody

9. **Treatment of CMV Disease**:

A. Any patient with CMV disease should be treated with IV ganciclovir or oral valganciclovir.
   i. Patients with severe disease, including most patients with tissue invasive CMV disease, should be initially treated with intravenous Ganciclovir. CMV disease with mild clinical symptoms may be treated with oral Valganciclovir.

   ii. Dose reduction of immunosuppressive therapy should be considered in severe CMV disease, non-responding patients, those with high viral loads, and leukopenic patients.

   iii. Consult Transplant ID after clearance of PCR for consideration for prophylaxis after treatment (secondary prophylaxis)

B. Asymptomatic CMV <u>negative</u> recipients (**D+/R- or D-/R-**)

   i. Low-positive (<35 IU/mL), repeat plasma CMV PCR weekly for 4 weeks and do not necessarily require immediate treatment

   ii. CMV PCR ≥ 35 IU/ml, regardless of symptoms, begin treatment with valganciclovir or IV ganciclovir (as below).

C. Asymptomatic CMV <u>positive</u> (**D-/R+ or D+/R+**) recipients

   i. CMV PCR less than 1000 IU/ml, repeat CMV PCR test weekly for 4 weeks and do not necessarily require immediate treatment

   ii. CMV PCR ≥ 1000 IU/ml, regardless of symptoms, begin treatment with valganciclovir or IV ganciclovir (as below).

D. Patients should have a CMV PCR checked weekly while on treatment.

E. Therapy should be continued for <u>at least 21 days</u> and until at least 2 consecutive undetectable CMV PCR tests or five consecutive undetectable or <35 IU/mL CMV PCR tests.

F. Consider CMV genotyping (CMV Resistance testing) for in patients with refractory CMV viremia or if CMV viral load continues to increase after 14 days of appropriate CMV treatment.

i. Consider Transplant ID consultation for any suspected CMV resistance.

G. Treatment Dosages:

CrCl (ml/min)	Valganciclovir (mg) – Oral	Ganciclovir (mg) - IV
> 60	900 mg po q12h	5 mg/Kg IV q 12 hours
40-59	450 mg po q12h	2.5 mg/Kg IV q 12 hours
25-39	450 mg po daily	2.5 mg/Kg IV daily
10-24	450 mg po every other day	1.25 mg/Kg IV daily
<10 or dialysis dependent	450 mg po post dialysis or 3 times per week	2.5 mg/Kg IV post dialysis or 3 times per week

H. **Leukopenia**: Do **NOT** reduce the dose of valganciclovir or ganciclovir for leukopenia.

i. If Absolute Neutrophil Count (ANC) drops below 1000, consider administration of G-CSF (Neupogen/Granix) until ANC > 1000

ii. If patient is not a candidate for G-CSF administration, consult Transplant ID.

iii. Consider reducing mycophenolate/azathioprine and/or changing Bactrim to an alternate agent for PJP prophylaxis.

I. Once treatment ends, PCR surveillance will continue monthly for 3 months after treatment or secondary prophylaxis is discontinued.

J. Secondary prophylaxis after treatment for CMV disease may be considered for select patients, such as those who develop CMV viremia/disease while on prophylaxis, those with tissue-invasive disease, those with recurrent CMV viremia, or high-risk mismatch (D+/R-) recipients. Dosing should be adjusted for renal function (see “Prophylaxis Post-Transplant” above). Prophylaxis should continue for 3 months, though extended prophylaxis may be considered in certain situations, including recurrent viremia/disease.

10. Transplant ID Clinic

A. Any patients with CMV may be referred for follow up in the Transplant ID Clinic.

B. Patients with CMV tissue invasive disease, with resistant CMV, or those treated with an alternative agents should be followed in Transplant ID clinic

C. For patients experiencing leukopenia with CMV or while on treatment for CMV viremia/disease, refer to Transplant ID clinic.

11. Policy Review:

A. As part of the QAPI program, policy compliance and CMV viremia rates for the first twelve months post-transplant will be reviewed every six months by the transplant program's clinical leadership and transplant infectious disease specialist.

RELATED POLICIES / PROCEDURES:
N/A

DEFINITIONS:
N/A

REFERENCES AND SOURCES OF EVIDENCE:

1. Kotton CN, Kumar D, Caliendo AM, et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation. 2018 Jun;102(6):900-931.
2. Fishman JA. Infection in Organ Transplantation. Am J Transplant. 2017 Apr;17(4):856-879.
3. Snydman DR, Limaye AP, Potena L, Zamora MR. Update and review: state-of-the-art management of cytomegalovirus infection and disease following thoracic organ transplantation. Transplant Proc. 2011 Apr;43(3 Suppl):S1-S17.

KEY WORDS:
Heart transplant
Cytomegalovirus
Prophylaxis