DukeMedicine
Division of Cellular Therapy

ADULT AND PEDIATRIC BLOOD AND MARROW TRANSPLANT PROGRAM

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Cytomegalovirus (CMV) Monitoring, Prophylaxis and Management in Pediatric Hematopoietic Stem Cell Transplant Recipients

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Cytomegalovirus (CMV) Monitoring, Prophylaxis and Management in Pediatric Hematopoietic Stem Cell Transplant Recipients

Background/Purpose

This guideline outlines monitoring and treatment of Cytomegalovirus (CMV) in pediatric hematopoietic stem cell transplant (HSCT) recipients.

CMV is a beta herpes virus, which commonly circulates and can remain latent in the body after primary infection. Reactivation of latent virus or acute primary infection post-transplant can lead to disseminated disease and be associated with significant end organ damage, including pneumonitis, hepatitis, enteritis, retinitis, myelitis, ventriculitis and encephalitis in the HSCT population and is associated with increased non-relapse mortality. Antiviral therapies that are effective against CMV are associated with significant adverse effects and should be used judiciously. Various factors affect CMV risk status, including donor CMV status, recipient CMV status, immunosuppression (steroids, T cell depletion), and type of transplant. High levels of reactivation have been described after umbilical cord blood transplant in recipients who are seropositive. Special consideration regarding treatment should also be given in cases of delayed engraftment, renal impairment, impaired T cell function, and graft versus host disease (GVHD).

Diagnosis

CMV plasma quantitative polymerase chain reaction (PCR) is currently the test of choice for monitoring CMV levels in the blood, as it is highly sensitive and specific. This non-invasive test has been standardized in international units, which allows for easy comparison across laboratories and the ability to trend levels over time. However, tissue histopathology still remains the gold standard in diagnosing CMV disease as there can be end organ disease with low levels of DNAemia.

1. **Histopathology remains the gold standard for diagnosis of CMV disease if clinical suspicion for end organ involvement is high.**
2. Plasma quantitative PCR is the preferred non-invasive test for diagnosis and monitoring of CMV DNAemia.
3. Note on PCR testing: whole blood, serum, and plasma can be sent for CMV PCR. As values can vary depending on the sample type, the same test should be used within a patient for consistency. **Duke performs plasma PCR in house, and this is the preferred sample type**.

Prevention

Transplants with any CMV-seropositivity, in donor or recipient, are at risk for CMV DNAemia. Acyclovir and valacyclovir have been used in the pediatric HSCT population for CMV prophylaxis, given the potential bone marrow suppressive effects of ganciclovir and valganciclovir. However, with acyclovir and valacyclovir, there is limited activity for prevention of CMV at prohibitively high doses, minimal benefit, and

increased risk in patients with renal dysfunction. Therefore, while low dose acyclovir is helpful for prevention of HSV and VZV disease, we do not recommend acyclovir for prevention of CMV disease. Letermovir is FDA approved for the prophylaxis of CMV infection and disease in CMV seropositive recipients following allogeneic hematopoietic cell transplant Who are 6 months of age and older and weigh at least 6 kg.

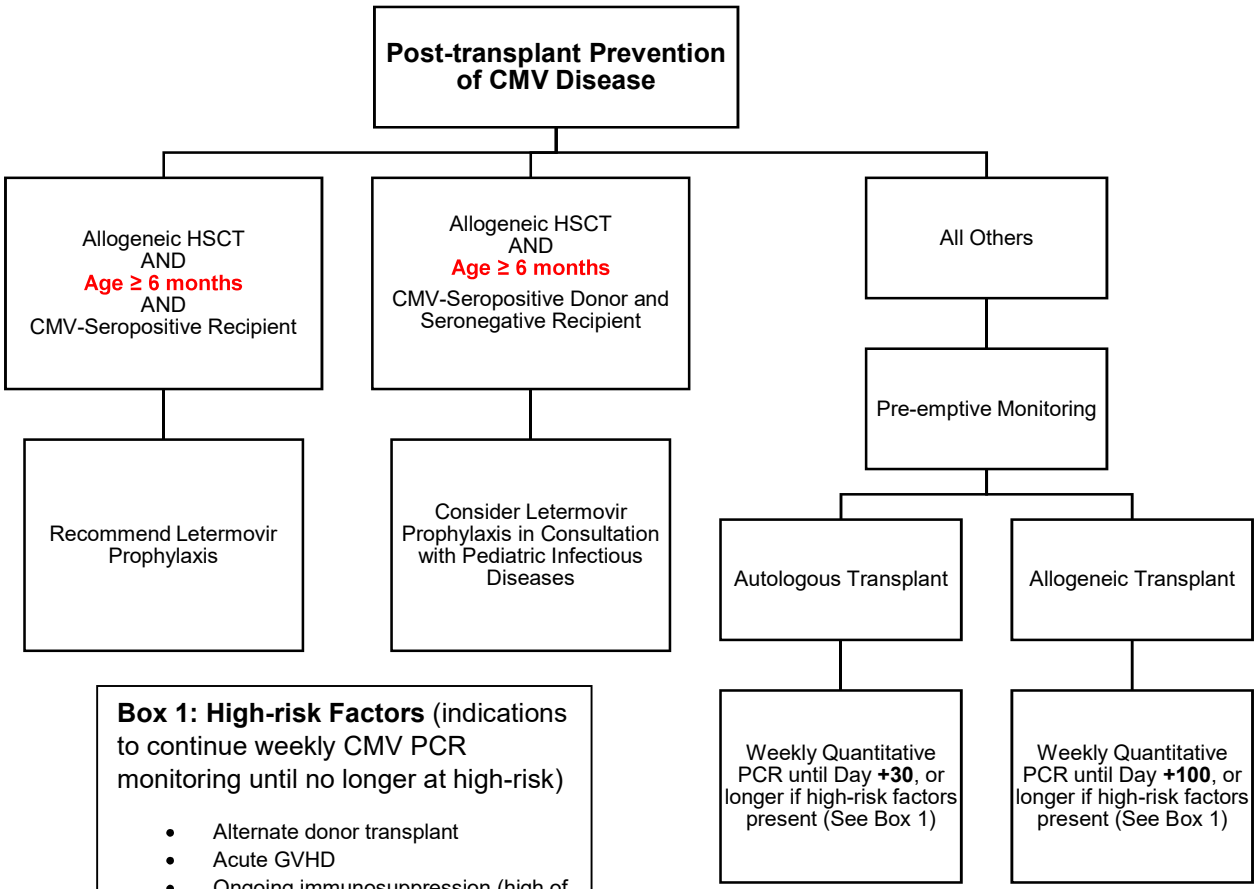
Prevention: Monitoring and Prophylaxis

Prior to transplant:

- CMV IgG should be obtained in the recipient prior to cytoreduction.
- Obtain a plasma CMV PCR within the week prior to start of cytoreduction to avoid active DNAemia during transplant.
- Leukocyte reduced blood products are recommended for all HSCT recipients.

Following transplant:

Stem cell transplant patients are at high risk for CMV infection. In the post-transplant period, we recommend 1) **preemptive monitoring** and 2) **consideration for prophylaxis** in certain patients, as detailed below. Note: **Plasma CMV PCRs can be considered at any point for any clinical signs and symptoms concerning for CMV infection** and not explained by any other cause (fevers, pneumonitis, hepatitis, colitis/diarrhea, retinitis, etc).

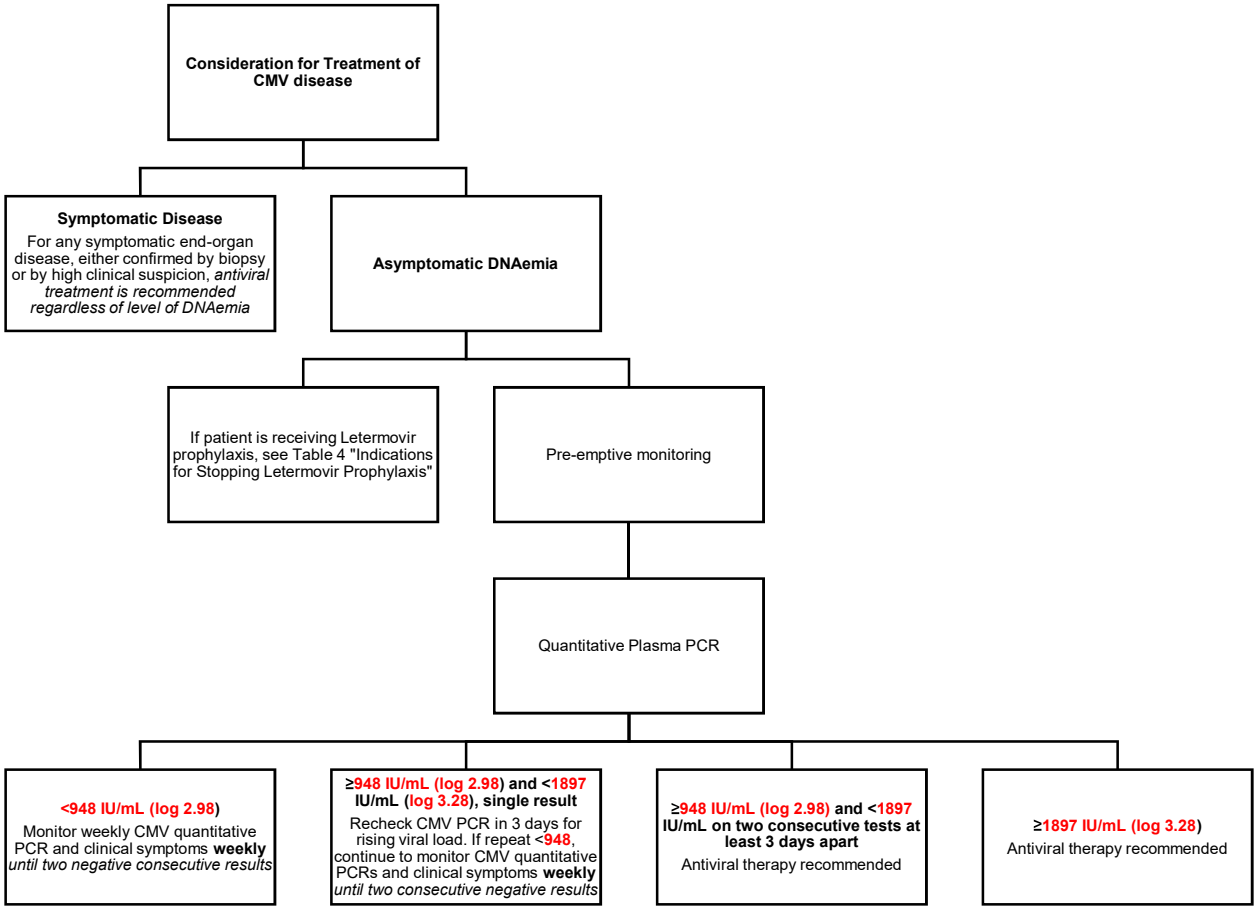


Box 1: High-risk Factors (indications to continue weekly CMV PCR monitoring until no longer at high-risk)

- Alternate donor transplant
- Acute GVHD
- Ongoing immunosuppression (high of high-dose steroids, recent ATG or alemtuzumab)
- Decreased CD4 count

Treatment

Patients may have some low-level DNAemia after transplant, which may represent reactivation and does not always require treatment. It is also important to note that levels of DNAemia can increase during the first two weeks of treatment, especially in patients who are significantly immunocompromised, and this does not necessarily represent resistance. In patients previously on letermovir prophylaxis for CMV who have detected DNAemia, however, we should consider resistance testing (see Table 4, Indications for Stopping Letermovir Prophylaxis). **Pediatric Transplant Infectious Diseases should be consulted for: treatment of CMV viremia, treatment of CMV disease with end organ involvement, significant increase of CMV viremia after > 2 weeks on initial treatment, and suspicion of antiviral resistance**.



Treatment recommendations:

Treatment options for CMV disease and DNAemia include Ganciclovir and Foscarnet. Due to its low barrier to resistance, letermovir should not be considered as first-line therapy for the treatment of CMV DNAemia. Ganciclovir is the preferred anti-CMV antiviral due to its efficacy and safety profile. Foscarnet may be preferred during the peri-engraftment period due to concerns for cytopenias associated with ganciclovir. Please note that foscarnet has also been associated with thrombocytopenia, headaches, fever, neuropathy, electrolyte disturbances, and significant nephrotoxicity in pediatric HSCT recipients. Thus, once engrafted, foscarnet should be transitioned to ganciclovir therapy.

See Table 1 for treatment recommendations.

1. Consult Pediatric Transplant Infectious Diseases
2. Dosing assumes normal renal function. Please consult Pharmacy if there is renal impairment.
3. Continue weekly plasma CMV quantitative PCR testing to monitor DNAemia.

Table 1. Antiviral selection for treatment of CMV[1]			
Antiviral	**Prior to Initiation**	**Dosing[2]**	**Duration**
Ganciclovir*		5 mg/kg q12h	At least 2 weeks AND until quantitative levels decrease to <239 IU/mL twice
Foscarnet	Obtain nuclear medicine GFR scan prior to initiation of therapy. Monitor BUN, Cr, and electrolyte disturbances while on therapy	60 mg/kg q8h* Dose adjusted to GFR	At least 2 weeks AND until quantitative levels decrease to <239 IU/mL twice Transition to Ganciclovir **once patient is stably engrafted**
*Valganciclovir can be considered in patients who are stably engrafted, have asymptomatic DNAemia, and who are tolerating enteral feeds without concerns for insufficient enteral absorption.			

Maintenance therapy:

The need for and duration of maintenance or suppressive dosing, with ganciclovir or valganciclovir, should be considered on a case-by-case basis with discussion with Peds Transplant ID. See **Table 2** for dosing.

Table 2. Maintenance Anti-CMV Antiviral Dosing and Duration Recommendations			
	Antiviral	**Dosing**	
Maintenance	**Ganciclovir** OR **Valganciclovir[1]** OR **Foscarnet**	5 mg/kg once daily 7 x BSA x CrCl once daily 90 mg/kg/day once daily	The need for and the duration of maintenance regimens may vary. We would continue maintenance therapy until the risk of reactivation is decreased (no evidence of acute GVHD, decreased dose of immunosuppression).

1. Alternative dosing for valganciclovir is 15-17 mg/kg once daily, but the 7 x Body Surface Area (BSA) x Creatinine Clearance (CrCl) dosing is preferred.

Special considerations:

Consider **Ophthalmology** consult as per clinical judgment for concern of CMV retinitis.

Antiviral resistance testing:

If after two weeks on initial treatment, CMV Quant PCR plasma level has significantly increased **(> 1.0 log or > 10-fold increase), decrease immunosuppression if possible, consider CMV antiviral resistance testing, and consider a change to alternative antiviral treatment for possible treatment failure.**

While resistant CMV is still rare in the pediatric stem cell transplant population, it is important to consider such testing in clinical scenarios where the CMV level continues to rise and there could be significant consequences to inappropriate treatment. **A minimum of 2 weeks of treatment is recommended before sending CMV antiviral resistance testing if patient is clinically stable and CMV viremia is still significantly increasing (> 1.0 log or > 10-fold increase).** The decision to test for resistance should also be balanced with the costs of testing. Of note, the level of CMV also has to be sufficient enough in order to perform antiviral resistance testing. There is no consensus on how often antiviral resistance testing can be done, but it should be considered no more than once monthly and only as clinically indicated (**Table 3**).

Table 3	**Clinically stable?**	**Send for antiviral resistance testing?**	**Empiric change of antiviral therapy?[1]**
CMV viral load increase ≥ 1 log from initial testing over 2 weeks[2]	Yes	Yes	No
	No	Yes	Yes
CMV viral load increase ≥ 0.5 and < 1.0 log from initial testing over 2 weeks	Yes	No	No
	No	**Per clinical judgment**	**Per clinical judgment**
CMV viral load increase < 0.5 log from initial testing over 2 weeks	Yes	No	No
	No	No	No
CMV viral load increase ≥ 1 log from initial testing over **less than 2 weeks**	Yes	No	No
	No	**Per clinical judgment**	**Per clinical judgment**

1. If on foscarnet, change to ganciclovir. If on ganciclovir, change to foscarnet.
2. Consult Pediatric Transplant Infectious Diseases

Graft versus Host Disease (GVHD)

GVHD poses a unique risk for reactivation of CMV disease due to increased and long-term immunosuppression. Once grade II-IV GVHD has been diagnosed, we recommend the following:

1. Weekly CMV Quantitative PCR Plasma monitoring, as outlined previously.
2. Once treatment is started, recommend continuing for 2 weeks and until resolution of viremia.
3. After completing treatment (minimum 2 weeks of therapy), recommend continuing with once daily maintenance therapy with ganciclovir or valganciclovir until immunosuppression is decreased.

Table 4: Letermovir use in patients >12 years

Criteria for Use	1) Demonstrated insurance coverage and/or other means of payment for letermovir prophylaxis in the outpatient setting. 2) Allogeneic HCT recipients ≥ 6 months of age who are CMV-seropositive. **Use in CMV-seropositive donor / CMV-seronegative recipients to be considered on case-by-case basis in discussion with Pediatric Transplant Infectious Disesaes.** 3) Initiation on day 0 to +1 with a documented plasma quantitative CMV PCR value < 239 IU/mL **within 5 days prior to the first dose of letermovir**. Initiation can be delayed up to day +28. Transplant infectious diseases (TID) consultation recommended if initiated after day + 28. 4) For oral (PO) administration a creatinine clearance (CrCl) > 10 mL/min is required. For intravenous (IV) administration, use with caution and closely monitor serum creatinine in patients with CrCl < 50 mL/min as accumulation of the IV vehicle (hydroxypropyl betadex) can occur.
Exclusion Criteria	1) CrCl ≤ 10 mL/min and/or on hemodialysis (see comment #4 above). 2) Severe hepatic impairment (defined as Child-Pugh Class C). 3) Concomitant use of IV foscarnet, IV ganciclovir, PO valganciclovir or IV cidofovir.
Dose	Based on patient's weight as follows: 6 kg to < 7.5 kg: 80 mg PO/IV daily 7.5 kg to < 15 kg: 120 mg PO/IV daily 15 kg to ≤ 30 kg: 240 mg PO/IV daily > 30 kg: 480 mg PO/IV daily For patients > 40kg receiving concomitant cyclosporine, 240 mg PO/IV daily. Monitor for increased cyclosporine levels closely. Preference for PO route of therapy for all patients unless unable to tolerate (e.g., severe nausea, vomiting, diarrhea and/or other NPO status). If IV therapy is utilized, a switch from IV to PO letermovir should occur once patients are able to take PO medications.
Duration of Therapy	Planned duration of prophylaxis is through day +100. Extension beyond day +100 to be considered on a case-by-case basis in discussion with Pediatric Transplant ID
Indications for Stopping Letermovir Prophylaxis	1) Clinically significant CMV infection (defined as): a. **CMV end-organ disease** (e.g., pneumonitis, gastrointestinal disease, hepatitis, retinitis, encephalitis/ventriculitis, cystitis, myocarditis, pancreatitis) **--OR--** b. **Quantitative plasma CMV PCR values exceeding designated threshold** as follows: i. **HIGH RISK** (haploidentical and cord transplant, anti-thymocyte globulin or alemtuzumab-inclusive regimen, *ex-vivo* T-cell depletion, GVHD requiring ≥ 1mg/kg/day of prednisone or prednisone equivalent and/or other mismatched transplant): **CMV PCR > 239 IU/mL** ii. **LOW RISK** (all others): **CMV PCR > 854 IU/mL** Patients with clinically significant CMV infection (as defined above) require CMV induction therapy with IV ganciclovir, IV foscarnet or PO valganciclovir. Pediatric Transplant Infectious Diseases consultation is

<table>
<tr><td></td><td>recommended in all patients developing clinically significant CMV infection on letermovir prophylactic therapy.
2) Concomitant non-CMV viral infection (e.g., HHV-6, acyclovir-resistant HSV) necessitating use of IV ganciclovir, PO valganciclovir, IV foscarnet or IV cidofovir.
3) CrCl reduction to ≤ 10 mL/min and/or need for hemodialysis.
4) Development of severe hepatic impairment (defined as Child-Pugh Class C).</td></tr>
<tr><td>Antimicrobial Prophylaxis Considerations</td><td>1. Viral prophylaxis: acyclovir or valacyclovir (should be administered concomitantly as letermovir does NOT have activity against herpes simplex virus or varicella zoster virus).
2. Fungal prophylaxis:
a. Posaconazole is the preferred antifungal agent due to lack of drug interactions. Isavuconazole can be considered as an alternative prophylactic therapy on a case-by-case basis.
b. If voriconazole use is deemed necessary, please consider the following:
i. Letermovir has been shown to cause a decrease in voriconazole concentrations.
ii. Voriconazole dosing should be as follows: 6 mg/kg PO/IV Q12h x 2 doses followed by 4 mg/kg PO/IV Q12h. thereafter.
iii. Voriconazole trough levels should be obtained on day 5 of therapy and adjusted to maintain trough concentrations greater than 1.0 mcg/mL.
c. Micafungin is the preferred antifungal agent if non-azole therapy is required due to drug interactions, hepatic abnormalities or other azole intolerability issues.</td></tr>
<tr><td>Monitoring on Therapy</td><td>1) Weekly quantitative plasma CMV PCR
2) Baseline EKG
3) A CMV genotype should be ordered in any patient who develops clinically significant CMV infection (as defined above) while on letermovir prophylaxis. The plasma CMV quantitative PCR should be ≥ 500 IU/mL to perform this test.
[The CMV genotype should be ordered as “GEN CODE COMMERCIAL LAB-BLOOD”. Fields should be completed as follows: 1) Test name: CMV Resistance - Letermovir, 2) Performing lab: Viracor Eurofins and 3) Test code: 30722.]</td></tr>
<tr><td>Monitoring after Cessation of Therapy</td><td>Quantitative plasma CMV PCR should be performed a minimum of every two-weeks for at least 10-weeks following cessation of letermovir prophylaxis. Thereafter plasma CMV PCR monitoring frequency can be adjusted by providers based on patients’ overall risk for clinically significant CMV.</td></tr>
<tr><td>Adverse Effects[1]</td><td>Adverse effects demonstrated in at least 10% of letermovir subjects and at a frequency at least 2% greater than placebo:
<table>
<tr><th>Adverse Effect</th><th>Letermovir 480 mg daily (n=373)</th><th>Placebo (n=192)</th></tr>
<tr><td>Diarrhea</td><td>26%</td><td>24.5%</td></tr>
<tr><td>Nausea</td><td>26.5%</td><td>23.4%</td></tr>
<tr><td>Vomiting</td><td>18.5%</td><td>13.5%</td></tr>
<tr><td>Cough</td><td>14.2%</td><td>10.4%</td></tr>
<tr><td>Peripheral edema</td><td>14.5%</td><td>9.4%</td></tr>
<tr><td>Fatigue</td><td>13.4%</td><td>10.9%</td></tr>
<tr><td>Headache</td><td>13.9%</td><td>9.4%</td></tr>
<tr><td>Abdominal Pain</td><td>11.8%</td><td>9.4%</td></tr>
</table>
Cardiac adverse event rate was higher in subjects receiving letermovir compared with placebo (13% vs 6%). The most common cardiac adverse events were tachycardia (4% vs. 2%) and atrial fibrillation (3% vs. 1%).</td></tr>
</table>

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