GUIDANCE FOR PREVENTION AND TREATMENT OF CYTOMEGALOVIRUS (CMV)
in Stem Cell Transplant Recipients at
Atrium Health Wake Forest Baptist
Updated: Winter 2025

CMV PREVENTION

1. PRIMARY PROPHYLAXIS

a. Start letermovir between day 0 and day 9 in all CMV R+ patients undergoing allogeneic stem cell transplant.
b. Letermovir dose: 480 mg PO or IV daily (for detailed dosing recommendations, see *Table 3* below)
c. Continue prophylaxis with letermovir until day 200
d. Consider stopping prophylactic letermovir at day 100 for certain patients with lower risk, including the following:
    1. Off all immunosuppressive medications
    2. No prior CMV reactivation requiring treatment
e. If letermovir cannot be used for primary prophylaxis, it is NOT generally recommended to use an alternative agent such as valganciclovir, ganciclovir or foscarnet.

2. SECONDARY PROPHYLAXIS

a. After discontinuation of pre-emptive therapy, consider extending prophylaxis beyond day 200 for patients with one or more of the following risk factors:
    i. Absolute lymphocyte count < 100 cells/µL
    ii. CMV infection prior to day 100
    iii. GVHD requiring steroids equivalent to prednisone 0.5 mg/kg/day or greater
    iv. Absence of CMV-specific T-cell immunity
b. Duration of extended prophylaxis should be customized based on patient-specific factors by the treating clinician

CMV TREATMENT

1. PRE-EMPTIVE THERAPY

a. Monitor all allogeneic stem cell transplant patients with CMV PCR as follows:
    i. Weekly until Day 100
    ii. Every visit (or as clinically indicated) until Day 180
    iii. May continue monitoring beyond Day 180 for patients with GVHD or those remining on immunosuppression (until Day 240 and off immunosuppression)
b. Pre-emptive therapy should be initiated based CMV viral load and the patient factors outlined in *Figure 1*.

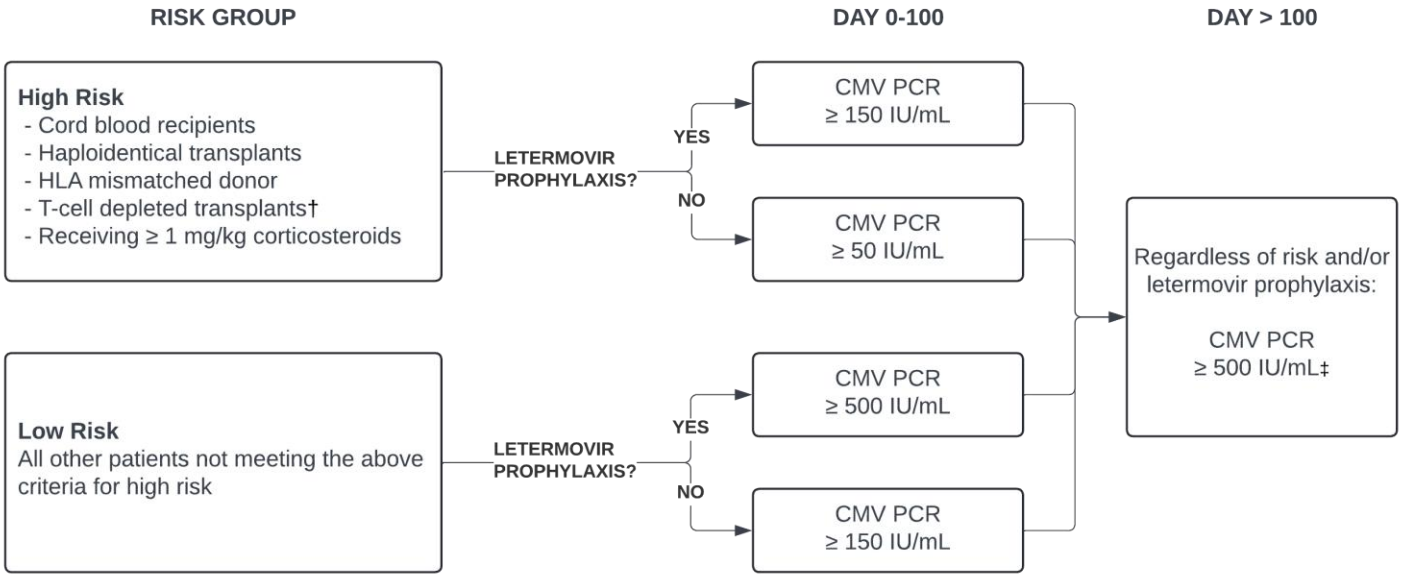

Figure 1. Thresholds for starting pre-emptive therapy based on serial monitoring of CMV PCR. Risk group indicates risk for developing CMV reactivation and/or disease. † *Patients who have received post-transplant cyclophosphamide can be considered as having received a T-cell depleted transplant.* ‡ *Consider that patients on high dose steroids may benefit from pre-emptive therapy at a lower CMV PCR threshold*

2. TREATMENT

a. When initiated, CMV treatment should begin with induction dosing for a minimum of 2 weeks and until the CMV PCR is below the lower limit of quantitation (< 34.5 IU/mL) on 2 weekly laboratory samples
b. Induction should be followed by 2 weeks of maintenance with the same agent

Table 1. Preferred treatment options for CMV viremia and disease. For detailed dosing information based on renal function, refer to *Table 2* below.

	Treatment Selection
Pre-engraftment[§]	Foscarnet
Post-engraftment[†]	Ganciclovir *or* Valganciclovir (if no issues with GI absorption)
Treatment Resistant OR Refractory	Maribavir[‡]

[§] For patients not likely to tolerate foscarnet (e.g. poor renal function, electrolyte disturbances, heart failure or volume overload), maribavir may be considered as an alternative to foscarnet prior to engraftment.
[†] Engraftment is defined as ANC > 500 cells/µL for 3 days. For patients who develop leukopenia and/or neutropenia on treatment, consider switching therapy to IV foscarnet.
[‡] Should be reserved for patients with CMV PCR ≤ 50,000 IU/mL, but may be considered when CMV PCR ≤ 100,000 IU/mL; see below for details on specific genotypic resistance mutations and indications for maribavir

3. RESISTANT & REFRACTORY (R/R) TREATMENT

a. CMV genotype testing should be considered for the following:
   i. CMV Viral load fails to decline by > 1 $\log_{10}$ after more than 2 weeks of appropriately dosed antiviral therapy
   ii. Plasma viral load ≥ 1000 IU/mL
b. For suspected CMV resistance, it is recommended to switch drug class, test for genotypic resistance mutations and reduce immunosuppression as much as possible. See *Table 2* below for more detailed management of resistant/refractory CMV.
c. Treatment of R/R CMV should continue for at least 2-4 weeks and be guided by resolution of symptoms in addition to achieving undetectable CMV DNA on 2 separate assays.

Table 2. Recommended use of anti-CMV agents for resistant/refractory CMV

Use of maribavir for resistant/refractory CMV	
Maribavir should be considered the preferred therapy for patients with EITHER refractory CMV OR resistance documented by one or more genotypic mutations. In patients for whom maribavir is not accessible or not clinically appropriate, see the ASTCT recommendations below.	
Genotype Result(s)	**Management**
UL97 mutation[†] *High-level resistance to ganciclovir*	First line: foscarnet Second line: cidofovir
UL97 mutation *Low-level resistance to ganciclovir*	First line: high-dose ganciclovir (7.5-10 mg/kg q12h) Second line: foscarnet OR cidofovir
UL54 mutation *Foscarnet/Ganciclovir resistance*	First line: cidofovir (can consider adding adjunctive agents such as leflunomide, artesunate or clinical trial)
UL54 mutation *Ganciclovir/Cidofovir resistance*	First line: foscarnet (can consider adding adjunctive agents such as leflunomide, artesunate or clinical trial)
UL54 mutation *Foscarnet resistance only*	First line: standard-dose ganciclovir (can consider adding adjunctive agents such as leflunomide, artesunate or clinical trial)
UL54 mutation *Ganciclovir, Foscarnet AND Cidofovir resistance*	First line: foscarnet PLUS high-dose ganciclovir (7.5-10 mg/kg q12h) as tolerated – can consider G-CSF support. (can consider adding adjunctive agents such as leflunomide, artesunate or clinical trial)
UL56, UL89, UL51 mutations *Letermovir resistance*	First line: ganciclovir or foscarnet
Refractory CMV without know resistance mutations	Optimize dosing of ganciclovir; can consider switch from ganciclovir to foscarnet.

[†] Greater than 5-fold increase in ganciclovir IC50

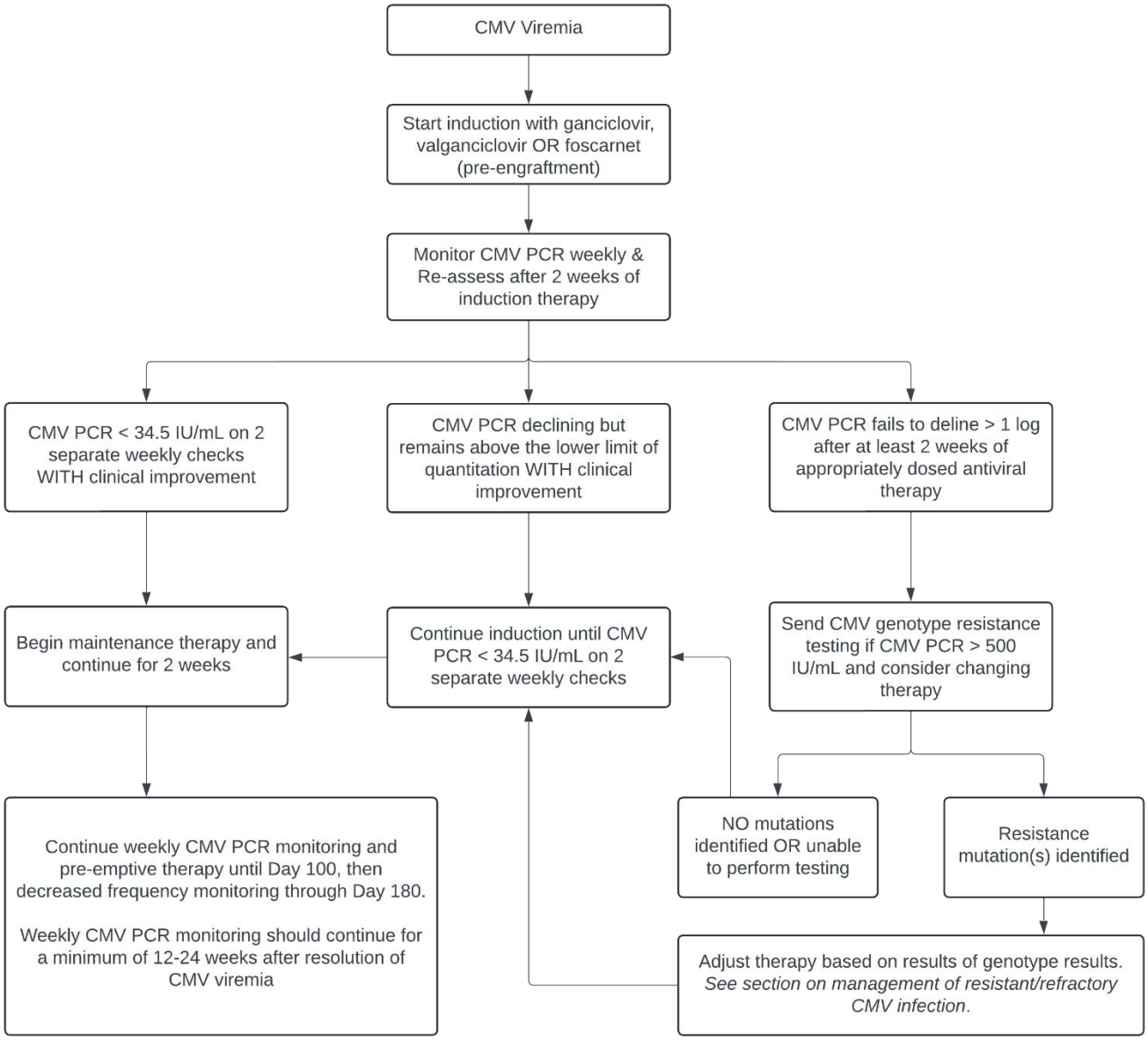

Figure 2. Management of CMV viremia and disease after stem cell transplant.

Table 3. Drug therapies for CMV infection

Prophylaxis				
Drug Name	**Dosing**	**Side effects**	**Important Interactions**	**Notes**
Letermovir	CrCl > 10 mL/min: 480mg IV or PO daily CrCl ≤ 10 mL/min: No data *Caution with IV formulation when CrCl < 50 mL/min*	GI: abdominal pain, nausea, vomiting or diarrhea Thrombocytopenia, headache, peripheral edema	1. Cyclosporine increases concentrations of letermovir and letermovir increases cyclosporine concentrations. Use letermovir 240 mg IV/PO daily when co-administering with cyclosporine. 2. Voriconazole: letermovir may decrease voriconazole concentrations. Monitor serum concentrations of voriconazole. (No interactions described with posaconazole and isavuconazole.)	No activity against HSV/VZV

Treatment					
Drug Name	**Dosing**			**Side effects**	**Notes**
Ganciclovir (IV)	*Renal Function (ml/min)*	*Induction*	*Maintenance*	1.Bone marrow suppression (leukopenia and neutropenia) 2. Nausea, vomiting, diarrhea 3. Confusion, headache	If there is leukopenia or neutropenia, consider foscarnet, and consider G-CSF when feasible
	CrCl >70	5mg/kg q12h	5mg/kg q24h		
	CrCl 50-69	2.5mg/kg q12h	2.5mg/kg q24h		
	CrCl 25-49	2.5mg/kg q 24h	1.25mg/kg q24h		
	CrCl 10-24	1.25mg/kg q24h	0.625mg/kg q24h		
	CrCl<10/HD	1.25mg/kg 3 x week (dose after dialysis)	0.625mg/kg 3 x week (dose after dialysis)		
	CVVHD	2.5mg/kg q24h	1.25 mg/kg q24h		
Drug Name	**Dosing**			**Side effects**	**Notes**
Valganciclovir (PO)	*Renal Function (ml/min)*	*Induction*	*Maintenance*	1.Bone marrow suppression (leukopenia and neutropenia) 2. Nausea, vomiting, diarrhea 3. Confusion, headache	If there is leukopenia or neutropenia, consider foscarnet, and consider G-CSF when feasible
	CrCl ≥ 60	900 mg q12h	900mg q24h		
	CrCl 40-59	450mg q12h	450mg q24h		
	CrCl 25-39	450mg q24h	450mg every 2 days		
	CrCl 10-24	450mg every 2 days	450mg 2 x week		
	CrCl <10 /HD	Use not recommended			

<table>
<tr><th>Drug Name</th><th colspan="3">Dosing</th><th>Side effects</th><th>Notes</th></tr>
<tr><td rowspan="8">Foscarnet (IV)</td><td>Renal Function (ml/min/kg)</td><td>Induction</td><td>Maintenance</td><td rowspan="8">1.Nephrotoxicity (damage to tubular cells)
2. Hypomagnesemia and hypocalcemia
3. Genital ulcers
4. Seizures</td><td rowspan="8">Administer an IV fluid bolus with each dose to reduce renal injury. May add IV magnesium and calcium before and/or after each dose.</td></tr>
<tr><td>CrCl/kg >1.4</td><td>90mg/kg q12h</td><td>90mg/kg q24h</td></tr>
<tr><td>CrCl/kg >1-1.4</td><td>70 mg/kg q12h</td><td>70 mg/kg q24h</td></tr>
<tr><td>CrCl/kg >0.8-1</td><td>50 mg/kg q12h</td><td>50 mg/kg q24h</td></tr>
<tr><td>CrCl/kg >0.6-0.8</td><td>80 mg/kg q24h</td><td>80 mg/kg q48h</td></tr>
<tr><td>CrCl/kg >0.5-0.6</td><td>60 mg/kg q24h</td><td>60 mg/kg q48h</td></tr>
<tr><td>CrCl/kg ≥0.4-0.5</td><td>50 mg/kg q24h</td><td>50 mg/kg q48h</td></tr>
<tr><td>CrCl/kg <0.4</td><td colspan="2">Use not recommended</td></tr>
<tr><th>Drug Name</th><th colspan="3">Dosing</th><th>Side effects</th><th>Notes</th></tr>
<tr><td>Maribavir (PO)</td><td colspan="3">400 mg BID

Not adjusted for renal dysfunction</td><td>1. nausea, vomiting, diarrhea
2. decreased hemoglobin and platelets
3. taste disturbances
4. increased SCr</td><td>May increase tacrolimus, cyclosporine and sirolimus concentrations</td></tr>
<tr><th>Drug Name</th><th colspan="3">Dosing</th><th>Side effects</th><th>Notes</th></tr>
<tr><td>Cidofovir (IV)</td><td colspan="3">1 mg/kg/dose IV 3 times weekly for 9 doses. Administer with IV hydration and probenecid to reduce the risk for renal injury.

Administer 1 liter bolus of NS before & after cidofovir.
3 hours prior to each dose: Probenecid 2 g PO
1 hour after each dose: Probenecid 1 g PO
8 hours after each dose: Probenecid 1 g PO

Do not administer if CrCl < 55 mL/min</td><td>1. Acute renal failure – monitor creatinine closely & ensure appropriate supportive care
2. Neutropenia
3. Carcinogen/teratogen</td><td>Cidofovir should only be used after exhausting other treatment options in consultation with an infectious diseases specialist.</td></tr>
</table>

DEFINITIONS

Pre-emptive therapy (PET): routine surveillance for active CMV infection in plasma or whole blood and initiation of antiviral treatment triggered by exceeding a threshold viral load.

Primary prophylaxis: initiation of an antiviral medication (e.g. letermovir) before any laboratory or clinical evidence of CMV.

Probable refractory CMV infection: persistent CMV DNA in the blood at the same level or < 1 $\log_{10}$ increase after at least 2 weeks of appropriately dosed anti-CMV therapy.

Refractory CMV infection: increase by > 1 $\log_{10}$ in CMV DNA levels in the blood after at least 2 weeks of appropriately dosed anti-CMV therapy.

Resistant CMV infection: presence of a known viral genetic mutation that decreases the susceptibility to one or more anti-CMV therapies.

Refractory CMV disease: worsening of clinical signs/symptoms and/or progression to CMV end-organ disease after at least 2 weeks of appropriately dosed anti-CMV therapy.

Secondary prophylaxis: initiated following completion of pre-emptive therapy or treatment of CMV disease once CMV DNA has cleared for the purpose or preventing a recurrent infection.

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