Prophylaxis and management of cytomegalovirus disease (immunocompromised patients)

Primary cytomegalovirus (CMV) infection is often clinically silent or can manifest as a mono-like syndrome (fever for >2 days, fatigue/malaise, elevated transaminases, atypical lymphocytes or leucopenia or thrombocytopenia). The virus then establishes latency primarily in myeloid cells and their precursors in the bone marrow. New infection or reactivation of latent virus in an immunocompromised host (**particularly transplant recipients, or those with poorly controlled HIV infection)** can lead to CMV disease with protean manifestations and multi-organ involvement (bone marrow, GI tract, lungs, liver, kidneys, eyes, CNS). Receipt of depleting antibodies (eg: anti-thymocyte globulin (ATG); alemtuzumab), HLA mismatch between donor and recipient, and graft-versus-host disease or solid organ transplant rejection requiring steroid therapy all significantly increase the risk of CMV disease.

DEFINTIONS

CMV infection (DNAemia)	Virus DNA detection in blood (does not necessarily mean active viral replication)
Clinically significant CMV infection in SOT recipients	**Proven CMV disease** for specific end organs: Presence of appropriate clinical and/or signs **AND** documentation of CMV in relevant tissue (by histopathology or immunohistochemistry) **Possible CMV disease**: Appropriate clinical symptoms and/or signs **AND** high viral DNA in tissue or fluid from relevant organ
Clinically significant CMV infection in HSCT recipients	**Proven/possible CMV disease** (as defined above for SOT recipients), ***OR*** **CMV DNAemia** sufficient to trigger pre-emptive therapy: CMV VL > 150 copies/mL
Refractory CMV infection / disease	**Lack of improvement or worsening** of clinical disease despite >2 weeks of appropriately dosed antiviral therapy ***OR*** **CMV DNAemia increase** (>1 $\log_{10}$) or persistence (≤ 1 log10 increase or decrease) after > 2 weeks of appropriately dosed antiviral therapy
Refractory and Resistant CMV infection/disease	**Lack of improvement or worsening** of clinical disease despite at least 2 weeks of appropriately dosed antiviral therapy AND **presence of mutation** conferring resistance by genotypic testing

**See risk stratification table*

Laboratory tests:

Serologic tests (CMV IgG): useful in pre-transplantation screening of donors and recipients, to guide antiviral prophylaxis (see risk stratification below) – NO ROLE in the diagnosis of CMV disease in immunocompromised patients

CMV detection by qPCR: useful for diagnosis and follow-up of clinically significant infection/disease; should NOT be routinely performed in workup of febrile illnesses in immunocompetent patients (even if critically ill) as the clinical significance of positive results is questionable.

Risk stratification (applies only for transplant recipients

	Donor CMV IgG	Recipient CMV IgG	Risk stratification
Solid organ transplantation	+	-	**High risk**
	+	+	**Intermediate risk**
	-	+	Intermediate risk
	-	-	Low risk
Hematopoietic stem cell transplant	+	-	Intermediate risk
	+	+	**Intermediate risk**
	-	+	**High risk**
	-	-	Low risk

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PHARMACOLOGIC MANAGEMENT

Primary prophylaxis for HSCT *(see risk stratification table)*	**HIGH and INTERMEDIATE RISK:** **Letermovir** 480mg po (or IV if unable to tolerate po) once daily Duration: until day +100 post-transplant (*restart drug if steroids started for GVHD, for the duration of steroid treatment)* *if HSV/VZV seropositive: ADD (val)acyclovir prophylaxis* **LOW risk**: ***no prophylaxis***
Primary prophylaxis for SOT *(see risk stratification table)*	**HIGH and INTERMEDIATE RISK:** **Valganciclovir** 900mg PO once daily OR **ganciclovir** 5mg/kg IV once daily (to start within 10 days of transplantation) Duration: *Kidney recipients: 6 months if high risk; 3 months if intermediate risk* *Liver: 3 months* *Heart: 6 months* *Islet cell / pancreas: 6 months* *If significant leucopenia (ANC < 1), consult ID for consideration of letermovir* **Low risk: *no prophylaxis***
Secondary prophylaxis	**CONSULT ID**
Clinically significant CMV infection	**Valganciclovir**[a] 900 mg PO q12h OR **ganciclovir** 5mg/kg IV q12h if unable to tolerate po or if Gastrointestinal CMV disease **If *severe* disease**: **CONSULT ID** for consideration of IVIG or hyperimmune CMV IgG (Cytogam) *Duration: Until resolution of clinical symptoms AND virologic clearance (based on serial qPCR monitoring) AND > 2 weeks of antiviral treatment*
Refractory/resistant CMV	**CONSULT ID** **Foscarnet**[b] 60 mg/kg IV q8h (or 90 mg/kg q12h) (**non-formulary)** **Maribavir** 400mg po BID **(Non-formulary and medicament d'exception)**

[a]Oral valganciclovir and intravenous ganciclovir are equally effective initial therapy for mild-to-moderate CMV disease.
[b]Complete blood count (with differential), serum creatinine, electrolytes and magnesium should be monitored three time per week at least to assess for potential drug toxicity.
[c]Dosing of antivirals assume normal renal function; adjustments are required if persistently reduced creatinine clearance (caution on risks of under-dosing antivirals based on fluctuating serum creatinine levels; estimates of GFR should be based on steady-state levels; consider using AKIN classification to determine AKI)

Additional Notes:

- A one-log decline in CMV viral load is expected after > 2 weeks of appropriately dosed antiviral therapy. There may be a lag between sending blood test for viral load and the result, so should expect that CMV viral load may increase further before treatment initiation.
- In the setting of leukopenia, changing (val)ganciclovir to another agent is not recommended before the addition of G-CSF (usually started if ANC drop to < 500 per mm^3) or discontinuation of other myelosuppressive therapies. Consult ID if persists.
- Adverse events from ganciclovir include: cytopenias; GI disturbances; CNS symptoms including seizures; safety in pregnancy not established. Consult ID if intolerance.

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