Management of Cytomegalovirus (CMV)

I. Background
   a. Definitions
      i. CMV Infection: evidence of CMV viral replication in the blood via polymerase chain reaction (PCR) with the absence of organ-specific signs and symptoms
      ii. CMV Disease: evidence of CMV viral replication in the blood via PCR with the presence of organ-specific signs and symptoms (end-organ damage)
   b. Incidence
      i. Risk of reactivation in D+/R- is ~20-30% and in R+ is ~60-80% (regardless of donor CMV status)

II. Prevention of CMV Exposure
   a. Establish CMV status pre-admission for donor and recipient
      i. Blood CMV IgG should be completed as part of the infectious disease markers during pre-transplant evaluation.
   b. CMV sero-status and blood products
      i. Sero-negative recipients with a sero-negative donor should receive CMV negative blood products only.
      ii. All other patients should receive CMV safe blood products.
      iii. Any CMV seronegative recipient of a CMV seronegative allograft who subsequently exhibits CMV viremia or disease should be reported to the blood bank as a possible case of transfusion-transmitted CMV for case investigation and reporting.

III. CMV Surveillance
   a. Autologous:
      i. Routine CMV DNA PCR screening is NOT necessary unless patient meets one or more of the following criteria below. If necessary, start CMV DNA PCR screening twice weekly on a Monday or Thursday that is closest to day 0 until discharge, then at each clinic visit until day +60.
         1. Total body irradiation
         2. Alemtuzumab, fludarabine or cladribine treatment within 6 months of transplant
         3. History of CMV reactivation
      ii. CMV may also be checked if uncontrolled fevers with no identifiable source.
   b. Allogeneic: Start testing CMV DNA PCR on the Monday or Thursday that is closest to day 0.
      i. Day 0 to +99
         1. Test twice weekly (every Monday/Thursday) while inpatient.
         2. May decrease surveillance to weekly or every clinic visit if outpatient and clinically stable per MD.
ii. Day +100 to +365  
   1. If high risk for late CMV reactivation: at each clinic visit (max 2x/week)  
   2. If low risk for late CMV reactivation: only if signs or symptoms of CMV  

iii. If reactivation occurs, increase frequency to at least once weekly until 2-4 weeks after discontinuation of CMV active therapy.

IV. Management of CMV Infection (see appendix A for treatment algorithm)  
Discontinue anti-viral prophylaxis (acyclovir or valacyclovir) when CMV active therapy is initiated and resume anti-viral prophylaxis when CMV active therapy is discontinued.

Table 1. Criteria for Pre-Emptive CMV Treatment*  
<table>
<thead>
<tr>
<th>Day of Transplant</th>
<th>CMV PCR threshold to treat^</th>
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<tbody>
<tr>
<td></td>
<td>&gt;200 IU/mL</td>
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<tr>
<td>Day 0 to +99</td>
<td>Risk factors for early CMV reactivation (unrelated or mismatched donors [including haploidentical or cord transplants], T-cell depletion [e.g., ATG, alemtuzumab], prednisone ≥ 20 mg or equivalent for ≥ 4 weeks, receiving ≥2 immunosuppressive agents, prior CMV reactivation/disease, acute GVHD grade 3-4, CMV seronegative donor, lymphoid malignancy)</td>
</tr>
<tr>
<td>Day +100 to +365</td>
<td>Risk factors for late CMV reactivation (Recurrent reactivations [≥ 2 reactivations post-SCT], mismatched or unrelated donor [including haploidentical or cord transplants], CMV seronegative donor, persistent T-lymphopenia at day 100, history of lymphoid malignancy, ongoing acute or chronic GVHD)</td>
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</tbody>
</table>

* If there is a high level of suspicion for tissue invasive CMV disease, begin treatment regardless of PCR results. Patients with suspected CMV colitis must be admitted for endoscopic examination.  
^ CMV cell-mediated assays may be considered for use of lower threshold  
^ Obtain baseline CMV PCR upon initiation of therapy if > 24 hours since previous CMV PCR result

a. Criteria for Foscarnet Therapy  
   i. Alternative treatment should be considered for patients who have borderline graft function.  
   ii. Foscarnet is an alternative for patients who fail to tolerate ganciclovir. Use the same duration of treatment (based on CMV PCR levels) recommended for patients receiving valganciclovir or ganciclovir.  
   iii. Dosing for foscarnet is based on creatinine clearance per kg (ml/min/kg). Some patients with a serum creatinine within the normal range may still require dose adjustments. Consult clinical pharmacist and/or Infectious Diseases (ID) to confirm dosing.  
   iv. Foscarnet should be substituted for ganciclovir/valganciclovir when:  
       1. ANC less than 1500/µL x1 day w/ GCSF or <1000/µL x 2 days, due to risk of worsening neutropenia with prolonged ganciclovir/valganciclovir administration  
          a. Ganciclovir can be re-challenged when ANC >/= 1000/µL x2 consecutive days.  
       2. Platelet count <30x10⁹/L or transfusion dependent  
       3. Ganciclovir/valganciclovir treatment failure defined -as stable/increasing CMV viral load after > 2 weeks of ganciclovir treatment with adequate dosing and administration
v. In the event of toxicity attributable to foscarnet, the decision to return to ganciclovir should be individualized based on risk vs. benefit.

V. Management of CMV Disease (see appendix B for treatment algorithm)
   a. Incidence and Risk Factors
      i. CMV disease affecting the gastrointestinal tract and lungs are the most common manifestations of CMV end organ disease.
      ii. Incidence of CMV disease is < 5%.
   b. Diagnosis
      i. CMV disease is diagnosed with evidence of CMV infection with attributable signs/symptoms (fever, malaise, leukopenia, diarrhea, and/or bone marrow suppression).
      ii. Diagnostic methods to test for CMV in specimens include PCR, cytology, rapid cultures and immunohistochemistry.
   c. Intravenous Immune-Globulin (IVIG)
      i. IVIG has been studied in combination with standard of care in CMV disease; however, data are conflicting
      ii. IVIG may be considered in addition to therapy for CMV disease in consultation with ID.
      iii. There is no clear advantage of CMV-specific IgG (i.e. Cytogam) over IVIG. Due to cost, CMV specific IgG (i.e. Cytogam) may only be used in rare circumstances in consultation with ID.

VI. Management of resistant CMV (see appendix C for treatment algorithm)
   a. Risk factors for CMV resistance
      i. Host factors
         1. Recurrent CMV infection, previous antiviral CMV therapy, poor compliance, active GVHD, inadequate absorption and bioavailability of antiviral CMV drug therapy, suboptimal therapy, variable antiviral CMV drug clearance, T-cell depletion, Haploidentical/allogeneic/cord SCT, delayed immune reconstitution, CMV-seropositive recipient, congenital immunodeficiency syndromes
      ii. Viral factors
         1. Significant increase in CMV viral load (> 0.5-1 log increase e.g. 500 → 5,000) or failure of viral load to decrease after > 14 days of treatment with adequate dosing
         2. Failure of CMV viral load to decrease despite appropriate therapy
         3. Rise in CMV viral load after decline while receiving appropriate therapy
         4. Prolonged low-level CMV infection
         5. High CMV viral loads
   b. Suspicion of CMV resistance
      i. CMV drug resistance may be suspected if CMV viral load is significantly increasing or not improving after > 14 days of appropriate therapy in drug-naive patients OR if there is evidence of worsening or new CMV disease with > 6 weeks of appropriate therapy. The following measures should be taken:
         1. Consult ID
         2. Reduce immunosuppression if possible
         3. Send blood sample for CMV antiviral resistance sequencing
         4. Consider switching/modifying anti-CMV therapy
   c. (+) UL97 mutation (see appendix C)
   d. (+) UL54 mutation (see appendix D)
VII. **Drug Appendix (see appendix D)**

References:

A. Management of CMV Infection

**If viral load > 10,000
initiate therapy with intravenous agent (if not already done so)

CMV PCR in serum meets threshold to treat based on patient characteristics (see Table 1)

CMV PCR in serum does NOT meet threshold to treat

Induction Therapy*

**Valganciclovir 900 mg PO q12h OR
valganciclovir 5mg/kg IV q12h (if patient has poor oral intake, uncontrolled gut GVHD or severe diarrhea) OR foscarnet 90mg/kg IV q12h (see section IV to determine if patient meets foscarnet criteria). Adjust treatment according to patient's renal function. Continue induction treatment until TWO consecutive <137 CMV PCRs

Increase frequency to at least once weekly until discontinuation of CMV active therapy.

Maintenance Therapy*

Valganciclovir 900 mg PO q24h OR
ganciclovir 5mg/kg IV q24h (if patient has poor oral intake, uncontrolled gut GVHD or severe diarrhea) OR foscarnet 90mg/kg IV q24h (see section IV to determine if patient meets foscarnet criteria). Adjust treatment according to patient's renal function. Continue maintenance therapy until at least one “NOT DETECTED” PCR (minimum 14 days of maintenance therapy).
B. Management of CMV Disease

**Suspicion of CMV disease (ID consult required)**

- **Consider**
  - Neurology consult
  - Encephalitis: fever, AMS, seizures with (+) CMV in spinal fluid

- **Consider**
  - Ophthalmology consult
  - Retinitis: fluffy, yellow-white lesions +/- intraretinal hemorrhage, visual changes with (+) CMV in lacrimal fluid

- **Consider**
  - Pulmonology consult
  - Pneumonia: fever, cough, SOB, abnormal CXR/CT with (+) CMV in BAL or lung biopsy

- **Consider**
  - GI Consult
  - Colitis: fever, abdominal pain, diarrhea, GI bleed, gastritis, pancreatitis, esophagitis, N/V.

- **Hepatitis**
  - fever, abnormal LFTs with (+) CMV in liver biopsy

**Induction Therapy**

Ganciclovir 5mg/kg IV q12h OR foscarnet 90mg/kg IV q12h (see section IV to determine if patient meets foscarnet criteria). Adjust treatment according to patient's renal function. Continue induction treatment for a minimum of 2 weeks, until 2 consecutive < 137 PCRs (if CMV viremia was evident) AND at least 7 days after localized signs/symptoms have resolved (patient must meet all criteria in order to de-escalate to maintenance therapy). May switch to oral valganciclovir 900 mg po q12h if symptoms are improved, adequate oral intake/no evidence of malabsorption. In patients with CNS involvement, may consider increasing ganciclovir to 7.5 mg/kg IV q12h and using combination therapy.

**Maintenance Therapy**

Ganciclovir 5mg/kg IV q24h OR foscarnet 90mg/kg IV q24h (see section IV to determine if patient meets foscarnet criteria). Adjust treatment according to patient's renal function. Continue maintenance treatment until at least one “NOT DETECTED” PCR (minimum 14 days of therapy) if CMV viremia was evident. May switch to oral valganciclovir 900 mg po q12h if symptoms are improved, adequate oral intake/no evidence of malabsorption.
C. Management of Resistant CMV [(+) UL97 Mutation(s)]

(+) UL97 Mutation(s)

> 5-fold ganciclovir EC50 (i.e. M460V, H530Q, A594V, L595S, C603W, L595F)

Foscarnet 90 mg/kg IV q12h
If no response or serious toxicities, consider one or a combination of investigational agents

≤ 5-fold ganciclovir EC50 (M460I, C592G, L595W) AND no evidence of CMV disease

Increase ganciclovir dose ~2x standard dose (7.5-10mg/kg IV q12h or corresponding dose per renal function) while supporting with G-CSF to keep WBC > 4.5
OR
consider foscarnet 90mg/kg IV q12h
C. (continued). Management of Resistant CMV [(+) UL54 Mutation(s)]

1. Ganciclovir-foscarnet cross resistance
   - Switch therapy to cidofovir 5mg/kg once weekly (concomitantly with probenecid and hydration [dosing per drug appendix])
   - *Consider alternate or experimental therapy if no response or serious toxicities

2. Ganciclovir-cidofovir cross-resistance
   - Foscarnet 90 mg/kg IV q12h
   - *Consider alternate or experimental therapy if no response or serious toxicities

3. Ganciclovir-cidofovir-foscarnet cross-resistance
   - Foscarnet 90 mg/kg IV q12h
   - Add high-dose ganciclovir 2x standard dose (10mg/kg IV q12h or corresponding dose per renal function)
   - Consider alternate or experimental therapy if no response or serious toxicities
   - *Consider alternate or experimental therapy if no response or serious toxicities

4. Foscarnet Resistance
   - Ganciclovir 5mg/kg IV q12h
   - *Consider alternate or experimental therapy if no response or serious toxicities
## D. Drug Appendix

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ORALDOSE -DOSE ADJUSTMENTS -DOSE FORMS</th>
<th>IV DOSE -DOSE ADJUSTMENTS</th>
<th>WARNINGS/PRECAUTIONS</th>
<th>MONITORING</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganciclovir (Cytovene)</td>
<td>Induction: 5mg/kg IV Q12h Maintenance: 5mg/kg IV Q24h</td>
<td>Induction dose</td>
<td>Maintenance dose</td>
<td>Granulocytopenia (neutropenia), anemia, thrombocytopenia, animal studies have shown it to be carcinogenic, teratogenic and inhibition of spermatogenesis</td>
<td>CBC with differential and platelets, renal function</td>
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<tr>
<td></td>
<td>CrCl (mL/min)</td>
<td>50-69</td>
<td>2.5mg/kg IV Q12h</td>
<td>2.5mg/kg IV Q24h</td>
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<td></td>
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<td>25-49</td>
<td>2.5mg/kg IV Q24h</td>
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<td></td>
<td></td>
<td>10-24</td>
<td>1.25mg/kg IV Q24h</td>
<td>0.625mg/kg IV Q24h</td>
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<td></td>
<td>CRRT</td>
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<td>Valganciclovir (Valcyte)</td>
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<td>N/A</td>
<td>N/A</td>
<td>Acute renal failure, blood dyscrasias (dose or therapy limited granulocytopenia, anemia, and/or thrombocytopenia), animal studies have shown ganciclovir to be carcinogenic, teratogenic and inhibition of spermatogenesis</td>
<td>CBC with differential and platelets, renal function</td>
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<td>Maintenance dose</td>
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<tr>
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<td>50-69</td>
<td>450 mg PO Q12h</td>
<td>450 mg PO Q24h</td>
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<tr>
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<td>25-49</td>
<td>450 mg PO Q24h</td>
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<td></td>
<td>10-24</td>
<td>450 mg PO Q48h</td>
<td>450 mg PO 2x/week</td>
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<td></td>
<td>&lt;10 &amp; HD</td>
<td>450 mg PO Q48h &amp; 900mg Q48h</td>
<td>450 mg PO 2x/week &amp; 450mg PO Q48h</td>
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<td>DRUG</td>
<td>ORAL DOSE -DOSE ADJUSTMENTS -DOSAGE FORMS</td>
<td>IV DOSE -DOSE ADJUSTMENTS</td>
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<td>MONITORING</td>
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<tr>
<td><strong>Foscarnet</strong> (Foscavir)</td>
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<td>N/A</td>
<td>Induction: 90mg/kg IV Q12h Maintenance: 90mg/kg IV Q24h</td>
<td>CrCl (mL/min/kg)</td>
<td>Induction dose</td>
<td>Maintenance dose</td>
<td>Adversely affect enamel in teeth, electrolyte imbalances (≥15% of low Ca, Ica, Phos [low or high], Mg, K), hematologic effects (anemia and granulocytopenia), renal impairment (usually reversible), seizures, vascular irritant, genital ulcers</td>
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<td>&gt;1-1.4</td>
<td>70mg/kg IV Q12h</td>
<td>70mg/kg IV Q24h</td>
<td>Electrolytes (K, Mg, Phos, Ca, Ica) 2x/week then qwk during maintenance, renal function, CBC, hydration status</td>
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<td>&gt;0.8-1</td>
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<tr>
<td>&gt;0.6-0.8</td>
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<td>80mg/kg IV Q48h</td>
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<tr>
<td>&gt;0.5-0.6</td>
<td>60mg/kg IV Q24h</td>
<td>60mg/kg IV Q48h</td>
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<tr>
<td>≥0.4-0.5</td>
<td>50mg/kg IV Q24h</td>
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<td>HD</td>
<td>60mg/kg IV 3x/week post-HD</td>
<td>60mg/kg IV 3x/week post-HD</td>
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<td>N/A</td>
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<tr>
<td>N/A</td>
<td>Induction: 5mg/kg IV weekly x2 doses Maintenance: 5mg/kg IV every other week OR 0.5-1mg/kg IV Qweek</td>
<td>Pre-existing renal impairment: Scr &gt; 1.5 mg/dL, CrCl ≤ 55 mL/min, or urine protein ≥ 100 mg/dL (≥ 2+ proteinuria): use is contraindicated. Changes in renal function during therapy: Scr increase by 0.3 to 0.4 mg/dL: reduce dose to 3mg/kg. Scr increases ≥ 0.5 mg/dL or development of ≥3+ proteinuria: discontinue therapy.</td>
<td>Metabolic acidosis (wasting of NaHCO3), nephrotoxicity (dose dependent toxicity), neutropenia, ocular hypotony, possibly carcinogenic and/or teratogenic, and may cause hypospermia</td>
<td>Renal function (within 48 hrs of each dose), LFTs, CBC, intraocular pressure and visual acuity, sign and symptoms of uveitis/iritis</td>
<td>High dose weekly cidofovir should receive concomitant probenecid 2grams PO 3 hrs prior to and 1gram PO 2hrs &amp; 8hrs after infusion (total dose: 4grams). Hydrate with 1 liter of NS IV prior to each infusion, if needed may infuse 1 liter of IV fluids after infusion. Use actual body weight for dosing</td>
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</tbody>
</table>