DukeMedicine
Division of Cellular Therapy

ADULT AND PEDIATRIC BLOOD AND MARROW TRANSPLANT PROGRAM

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DOCUMENT TITLE:
Cytomegalovirus (CMV) Prevention and Treatment

DOCUMENT NOTES:

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APBMT-COMM-016
CYTOMEGALOVIRUS (CMV) PREVENTION AND TREATMENT

1 PURPOSE

1.1 To provide a consistent approach to monitoring, prevention and treatment of cytomegalovirus (CMV) disease and infection in allogeneic and autologous hematopoietic stem cell transplant (HSCT) recipients.

2 INTRODUCTION

2.1 Supportive Data: HSCT recipients (particularly those receiving allografts) are at risk of developing opportunistic infections, including CMV. Risk is dependent on the degree of immunosuppression experienced by the patient.

3 SCOPE AND RESPONSIBILITIES

3.1 This procedure provides a consistent approach to monitoring, prevention and treatment of CMV.

3.2 Attending physicians, advanced practice providers, pharmacists and registered nurses are responsible for ensuring that the blood and marrow transplant patients are monitored and treated, if necessary, for CMV.

4 DEFINITIONS/ACRONYMS

4.1 BMT - Bone Marrow Transplant

4.2 CMV - Cytomegalovirus

4.3 CrCL - Creatinine Clearance

4.4 DNA - Deoxyribonucleic acid

4.5 GvHD - Graft versus Host Disease

4.6 HLA - Human Leukocyte Antigen

4.7 HSCT - Hematopoietic stem cell transplant

4.8 Ig - Immune Globulin

4.9 IVIG - Intravenous Immune Globulin

4.10 IV - Intravenous

4.11 PCR - Polymerase Chain Reaction

4.12 VL -Viral Load

5 MATERIALS

5.1 N/A

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6 EQUIPMENT

6.1 N/A

7 SAFETY

7.1 N/A

8 PROCEDURE

8.1 NOTE: Supplemental documents exist for pediatrics:

The pediatric program follows recommendations for prophylaxis and treatment as outlined in Duke Pediatric Immunocompromised Host Program's supplemental document: APBMT-COMM-016 JA1 *Cytomegalovirus (CMV) Monitoring, Prophylaxis and Management in Pediatric Hematopoietic Stem Cell Transplant Recipients*. Applicable Staff should refer to that document for additional recommendations.

8.2 Monitoring

8.2.1 CMV immune screen will be performed prior to transplantation (IgG/IgM) for donor and recipient.

8.2.2 CMV DNA (PCR) panel will be obtained:

8.2.2.1 If the recipient is less than (<) 6 months of age.

8.2.2.2 If the recipient has had a dose of IVIG in the previous 3 months regardless of age.

8.2.3 All allogeneic stem cell recipients will be monitored weekly for the presence of CMV infection (CMV-DNA by PCR) beginning during the first week post-transplant and continuing through a minimum of Day +100 or discharge home; intermittent monitoring will be done indefinitely for those receiving ongoing immunosuppression and for those with chronic GVHD.

8.3 Pediatrics Only: Indication for Prophylaxis (prevention of CMV infection and disease in patients at risk)

8.3.1 Pediatric recipients of myeloablative and non-myeloablative allogeneic stem cell transplants who are immune screen-positive or whose donors are immune screen-positive will receive prophylaxis for CMV. Patients with neuroblastoma undergoing autologous BMT who also are CMV seropositive will receive CMV prophylaxis because of the higher risk of CMV disease in patients treated with intensive chemotherapy prior to transplantation therapy.

8.3.2 Prophylactic therapy entails the administration of anti-CMV therapy to pediatric patients who do not have evidence of CMV infection or disease (e.g. the patient is CMV-DNA negative and does not have positive cultures or symptoms of CMV disease).

8.3.3 Prophylaxis is administered to pediatric patients with acyclovir (250mg/m2 per dose IV every 12 hours or adjusted for renal function)

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and beginning on day +0 and continuing until a minimum of day +100 or until CD4 immune function recovers.

8.4 Adults

8.4.1 Indication for prophylaxis (prevention of CMV infection and disease in patients at risk)

8.4.2 Adult allogeneic HCT recipients >/= 18 years of age who are CMV-seropositive. Use in CMV-seropositive donor/CMV-seronegative recipients to be considered on a case-by-case basis at the HCT providers' discretion.

8.4.3 Autologous HCT recipients >/=18 years of age who are CMV-seropositive and undergoing transplantation on the scleroderma protocol. Use in this group is not universal and should only be considered on a case-by-case basis at the HCT providers' discretion.

8.5 Letermovir utilization in Pediatrics and Adults

8.5.1 Letermovir is an antiviral that is FDA approved for the prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV seropositive recipients following allogeneic hematopoietic cell transplant (HCT). Dosing is initiated on day +5 through day +100 for prophylaxis. Initiation can be delayed up to day +28. Duration beyond day +100 to be considered on a case-by-case basis at the HCT providers' discretion.

8.5.1.1 Autologous HCT recipients >/=18 years of age who are CMV-seropositive and undergoing transplantation: Note that in some patient groups (i.e. Scleroderma Protocol) may not be universal and should considered on a case-by-case basis at the HCT providers' discretion.

8.5.1.2 Adult Dosing:

8.5.1.2.1 Letermovir 480 mg PO/IV daily.

8.5.1.2.2 Dose should be reduced to 240 mg PO/IV daily in patients receiving concomitant cyclosporine.

8.5.1.3 Pediatric Dosing: Multiple publications support the use of letermovir in children as young as 5 years old.

8.5.1.3.1 Letermivir 5mg/kg daily.

8.5.1.3.2 Dose is adjusted for administration with cyclosporine.

8.5.1.3.3 Utilization in pediatrics requires ID approval.

8.5.1.4 Patients should have a documented plasma quantitative CMV PCR value < 260 IU/mL within 7 days prior to the first dose of letermovir.

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8.6 Indication for Preemptive Treatment (prevention of CMV disease in patients with active CMV infection)

8.6.1 CMV Preemptive Therapy Protocol

8.6.1.1 CMV DNA results by real-time PCR. Monitor weekly CMV starting on day 0 until day +100 in all allogeneic HCT recipients.

8.6.1.2 HCT recipients are further stratified into a “high risk” or “low risk” category based on additional transplant-related factors.

8.6.1.2.1 High Risk Recipients:

•Haploidentical, umbilical cord blood or mismatched (≤ HLA 7/8) adult donor transplant recipients

•Allogeneic HCT recipients requiring the use of anti-thymocyte globulin or alemtuzumab

•HCT requiring ex-vivo T-cell depletion

•HCT recipients with moderate to severe graft- versus-host disease (GVHD) ≥ 0.5 mg/kg/day of prednisone or prednisone equivalent

8.6.1.2.2 Low risk recipients:

•All HCT recipients that do not meet “high risk” criteria

8.6.1.3 CMV DNA: less than (<) 260 IU/mL

8.6.1.3.1 No action

8.6.1.3.2 Repeat test within one week

8.6.1.4 CMV DNA: greater than (>) 260 IU/mL in high-risk recipients

8.6.1.4.1 Initiate induction therapy

8.6.1.5 CMV DNA greater than (>) 900 IU/mL in low-risk recipients

8.6.1.5.1 Initiate induction therapy

8.6.2 Induction Therapy - for patients with normal renal function

8.6.2.1 Ganciclovir 5 mg/kg IV twice daily (preferred therapy)

8.6.2.2 Foscarnet 90 mg/kg IV twice daily (alternative therapy; reserved for patients with cytopenias)

8.6.2.3 Valganciclovir 900 mg PO BID if CMV viral load is < 60,000 IU/mL. Not considered appropriate for CMV disease.

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8.6.3 Induction Therapy Duration

8.6.3.1 CMV disease (proven or probable): Continue for at least 3 weeks and resolution of symptoms and until CMV DNA is undetectable or ≤ 260 IU/mL on two separate occasions one week apart.

8.6.3.2 CMV infection: Continue for at least 2 weeks and until CMV DNA is undetectable or ≤ 260 IU/mL on two separate occasions one week apart.

8.6.3.3 If CMV DNA is not undetectable after 3 weeks of induction, consider alternative therapy and send CMV genotype testing for drug resistance. In addition, consider transplant ID consult for resistant or refractory CMV management.

8.6.4 Maintenance Therapy – for patients with normal renal function

8.6.4.1 Ganciclovir 5 mg/kg IV daily

8.6.4.2 Foscarnet 90 mg/kg IV daily

8.6.4.3 Valganciclovir

8.6.4.3.1 Adult dosing: 900 mg orally daily

8.6.4.3.2 Pediatric dosing: 13 mg/kg orally daily (max 900 mg).

8.6.5 Maintenance Therapy Duration

8.6.5.1 Continue for a minimum of 2 weeks.

8.6.5.2 If the CMV DNA rises for two consecutive weeks on maintenance therapy, re-induce.

8.6.5.3 If the CMV viral load remains stable or increases 2 weeks after re-induction, consider alternative therapy and send CMV genotype testing for drug resistance.

8.6.5.3.1 Maribavir is FDA approved for the treatment of adults and pediatric patients 12 years of age and older weighing at least 35 kg with post-transplant cytomegalovirus infection/disease that is refractory to treatment with or without genotypic resistance with ganciclovir, valganciclovir, cidofovir or foscarnet.

8.6.5.3.2 Maribavir 400 mg orally twice daily with or without food. Dosing is the same for adults and pediatrics.

8.6.5.4 CMV DNA testing is recommended weekly after therapy, at least until the viral load is undetectable.

8.6.6 Renal Dosing

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8.6.6.1 For patients with renal impairment, dosing will be determined in consultation with the clinical pharmacist.

8.7 Treatment of CMV Pneumonitis or Persistent Viremia

8.7.1 Consider one of the following to specific antiviral therapy (IVIG or Cytogam®):

8.7.1.1 Intravenous immune globulin (IVIG) 500 mg/kg (round dose to nearest 5 g) IV daily x 4 days, then every 48 hours x 12 additional doses, then weekly for 4 weeks (or other appropriate dose/schedule as prescribed).

8.7.1.2 Cytomegalovirus hyperimmune globulin (CMV-Ig; Cytogam®) 100 mg/kg IV 3x per week x 21 days, then weekly until no evidence for disease x 2 months or longer in severely immunocompromised patients with ongoing GvHD (or other appropriate dose/schedule as prescribed). Alternative dosing schedule 400 mg/kg IV Days 1, 2, 7, then 200 mg/kg Day 14 +/- Day 21.

8.8 Reportable conditions

8.8.1 Allergy or intolerance to anti-CMV therapy; renal dysfunction, neutropenia, or other adverse effects attributed to anti-CMV therapy.

9 RELATED DOCUMENTS/FORMS

9.1 APBMT-COMM-016 JA1 Cytomegalovirus (CMV) Monitoring, Prophylaxis and Management in Pediatric Hematopoietic Stem Cell Transplant Recipients

10 REFERENCES

10.1 Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients: recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. MMWR 2000; 49 (No. RR-10):11-4, 97.

10.2 Takami A, Mochizuki K, Ito S, Sugimori C, et al. Safety and efficacy of foscarnet for preemptive therapy against cytomegalovirus reactivation after unrelated cord blood transplantation. Transplant Proc 2007 Jan-Feb; 39(1):237-9.

10.3 Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, Wingard J, Young J, Boeckh M. Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients: A Global Perspective. Biol Blood Marrow Transplant 2009; 15: 1143-1238.

10.4 Clinical Pharmacology (current edition) valganciclovir, ganciclovir, foscarnet, IVIG and CMV-IVIG.

10.5 Marty FM Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic cell transplantation. N Engl J Med 2017;377:2433-44.

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10.6 Avery RK, Alain S, Alexander BD, et al. Maribavir for refractory cytomegalovirus infections with or without resistance post-transplant: results from a phase 3 randomized clinical trial. Clin Infect Dis 2021: online ahead of print.

11 REVISION HISTORY

Revision No.	Author	Description of Change(s)
07	MC Author: S. McCollum SME: Kris Mahadeo Erika Summers Goeckerman Elizabeth Eubanks	Document has been heavily revised for content to include current medication and dosing regimens and therefore should be treated by the reader as a new document.

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Author

Name/Signature	Title	Date	Meaning/Reason
Sally McCollum (MOORE171)		23 Jun 2025, 04:39:45 PM	Approved

Management

Name/Signature	Title	Date	Meaning/Reason
Jennifer Frith (JLF29)		25 Jun 2025, 07:02:28 AM	Approved

Medical Director

Name/Signature	Title	Date	Meaning/Reason
Kris Mahadeo (KM193)		25 Jun 2025, 08:48:29 AM	Approved
Stefanie Sarantopoulos (SS595)	Professor of Medicine	25 Jun 2025, 05:19:24 PM	Approved

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Name/Signature	Title	Date	Meaning/Reason
Bing Shen (BS76)	Associate Director, Quality Assurance	25 Jun 2025, 07:30:13 PM	Approved

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