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Guideline

American Society for Transplantation and Cellular Therapy Series: #3—Prevention of Cytomegalovirus Infection and Disease After Hematopoietic Cell Transplantation

Morgan Hakki[1,*,†], Samuel L. Aitken[2,†], Lara Danziger-Isakov[3,†], Marian G. Michaels[4,†], Paul A. Carpenter[5,†], Roy F. Chemaly[6,†], Genovefa A. Papanicolaou[7,†], Michael Boeckh[5,8,†], Francisco M. Marty[9,†]

[1] *Division of Infectious Diseases, Department of Medicine, Oregon Health and Science University, Portland, Oregon*
[2] *Division of Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[3] *Division of Infectious Disease, Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, Ohio*
[4] *Division of Pediatric Infectious Diseases, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh and the University of Pittsburgh, Pittsburgh, Pennsylvania*
[5] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[6] *Department of Infectious Diseases, Infection Control, & Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[7] *Infectious Disease Service, Memorial Sloan Kettering Cancer Center, New York, New York*
[8] *Vaccine and Infectious Disease Divisions, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[9] *Division of Infectious Diseases, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, Massachusetts*

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A B S T R A C T

The Practice Guidelines Committee of the American Society for Transplantation and Cellular Therapy partnered with its Transplant Infectious Disease Special Interest Group to update its 2009 compendium-style infectious diseases guidelines for the care of hematopoietic cell transplant (HCT) recipients. A new approach was taken with the goal of better serving clinical providers by publishing each standalone topic in the infectious disease series as a concise format of frequently asked questions (FAQ), tables, and figures. Adult and pediatric infectious disease and HCT content experts developed and answered FAQs. Topics were finalized with harmonized recommendations that were made by assigning an A through E strength of recommendation paired with a level of supporting evidence graded I through III. The third topic in the series focuses on the prevention of cytomegalovirus infection and disease in HCT recipients by reviewing prophylaxis and preemptive therapy approaches; key definitions, relevant risk factors, and diagnostic monitoring considerations are also reviewed.

Cytomegalovirus (CMV) infection may be latent or active. In the context of immunosuppression associated with hematopoietic cell transplantation (HCT), latent CMV may reactivate to cause an active infection that may progress rapidly to clinical, life-threatening CMV disease, characterized by organ-specific tissue damage by replicating CMV [1]. This guideline is provided in the form of frequently asked questions (FAQ) focusing on the prevention of clinical infection, including prophylaxis and preemptive therapy triggered by CMV DNAemia. The final section reviews unmet needs and future directions. Key recommendations are accompanied in the text by grading in parentheses. For grading of strength of recommendation (A through E) and quality of supporting evidence (level I-III), refer to Appendix 1 [2].

FAQ1: WHAT IS CMV ACTIVE INFECTION AND HOW IS IT ASSESSED?

Definitions of CMV infection and disease in transplant recipients have been published [3]. Briefly, infection with CMV, as with all herpesviruses, may be active or latent. In the context of the HCT recipient, the term "CMV infection" is typically used to describe active infection (viral replication) as determined by the detection of CMV nucleic acid (DNA or RNA) by polymerase chain reaction (PCR), detection of pp65 antigen, or culture. The term "CMV viremia" is commonly used to describe active infection, but because most PCR assays currently used measure CMV DNA fragments, technically CMV DNAemia may be a more appropriate term.

Latent infection is classically defined as the maintenance of replication-competent viral genomes in the absence of active viral replication [4]. It is typically assessed by the detection of CMV-specific immunoglobulin G (IgG). Patients with evidence of prior exposure to CMV by IgG measurement are classified as CMV seropositive [3]. CMV reactivation describes active

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*Correspondence and reprint requests: Morgan Hakki, Oregon Health and Science University, Division of Infectious Diseases, 3181 SW Sam Jackson Park Road, L457, Portland, OR 97239.
E-mail address: hakki@ohsu.edu (M. Hakki).
† All authors contributed equally.

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infection from previously latent virus and is typically applied to seropositive recipients to be distinguished from primary infection, which indicates active infection in a seronegative recipient.

FAQ2: WHAT ARE THE CONSEQUENCES OF CMV INFECTION?

CMV infection is often asymptomatic when diagnosed in the setting of frequent post-HCT surveillance. In the absence of preemptive therapy (PET), infection may lead to clinical CMV disease. CMV pneumonia was the most common clinical disease manifestation in the preantiviral era and before PET was adopted. In the PET era, gastrointestinal disease has become the most common presentation of CMV disease [5-8], perhaps because, compared to pneumonia, there may be relatively poor correlation between CMV DNAemia and gastrointestinal disease in some patients [7]. CMV disease can also affect any organ including the liver, retina, and central nervous system.

Even in the era of PET and absence of CMV disease, CMV infection has been associated with increased nonrelapse mortality after HCT [8,9], suggesting negative indirect effects of CMV infection or its treatment. Negative indirect effects of CMV may also be suggested by the mortality benefit unrelated to CMV disease observed with letermovir prophylaxis in its phase 3 trial [5,10]. Further efforts are required to define these indirect effects and determine their impact on post-HCT outcomes.

The association of CMV reactivation with reduced risk of relapse of hematologic malignancies after HCT remains controversial [11-15], with two large CIBMTR studies failing to demonstrate a protective effect [9,16]. Regardless, any putative beneficial effect of CMV infection against relapse is likely negated by the increase in nonrelapse and overall mortality [8,9,12,14,17].

FAQ3: WHAT ARE RISK FACTORS FOR CMV ACTIVE INFECTION AND DISEASE AFTER ALLOGENEIC HCT?

The major risk factors are listed in Table 1. Pretransplantation recipient CMV serostatus remains the most important predictor of CMV infection after allogeneic HCT [18]. All patients and donors should be tested for CMV-specific IgG before HCT (A-II). Interpretation of positive serology in a child under the age of 12 months is complicated by the potential presence of maternal transplacental antibody; urine or saliva PCR for CMV can assist in identifying those truly positive before transplantation. Insufficient data exist to recommend other immune-based assays for the pre-HCT determination of CMV latent infection status [19].

Table 1
Risk Factors for CMV Infection and Disease After Allogeneic HCT

Risk Factor	Reference(s)
CMV seropositive recipient	[9,18,23,150-154]
Acute GVHD	[18,34,101,152,155,156]
Prednisone use ≥ 1 mg/kg/day (or equivalent)	[154,157,158]
T-cell depletion (including alemtuzumab or ATG exposure)	[18,114,153,154,159-164]
Haploidentical donor*	[159,165-172]
Cord blood transplant	[36,81,173]
Mismatched or unrelated donor	[101,151,158]
Lymphopenia	[103,174,175]
Older age	[14,151,158,176]
Post-HCT cyclophosphamide	[16]

* Risk may vary depending on whether transplant is performed using a T cell depleted or T cell–replete graft [171,177], but more studies are required.

Racial and socioeconomic disparities in CMV seroprevalence and in the prevalence of congenital CMV infection in the United States have been described [20,21]. Among HCT recipients, one study found non-Caucasian recipient race to be a risk factor for higher-grade CMV infection (CMV pp65 antigenemia > 10 cells/200,000 peripheral blood leukocytes or CMV DNA > 1000 copies/mL of plasma) [22]. The basis for this finding remains unclear, and confounding transplant-related variables likely play contributory roles. Additional studies are needed to further define what is likely a complex association of these factors with CMV infection after HCT.

FAQ4: WHAT NONPHARMACOLOGIC STRATEGIES MAY PREVENT CMV INFECTION IN HCT RECIPIENTS?

For the CMV seronegative HCT recipient, a CMV seronegative donor is preferred when possible (A-II) to reduce the risk of primary CMV infection via transmission of CMV in the allograft [9,18,23] and the risk of nonrelapse mortality [24,25]. Blood products from seronegative donors or leukoreduction are acceptable methods to reduce the risk of transfusion-transmitted infection (A-I) [26-30]. Pathogen-reduced platelets represents another acceptable method of reducing the risk of infection transmission in platelet product (A-I) [31,32].

Primary community-acquired infection in the seronegative HCT recipient remains a longer-term risk. CMV is shed intermittently from the oropharynx and genitourinary tract. Aside from common practice of good hand hygiene, particularly when changing diapers or in contact with toddlers and young children, specific recommendations to reduce the risk of community-acquired CMV infection from these sources cannot be made.

If the recipient is CMV seropositive, the use of a CMV-seronegative donor for T-cell replete HCT has been associated with several negative effects compared to a seropositive donor, including impaired CMV-specific immune reconstitution, higher CMV viral load, increased risk of recurrent CMV reactivations, late CMV infection, and risk of disease [24,33-36]. In addition, decreased overall survival among CMV D−/R+ HCT compared to CMV D+/R+ HCT has been observed when an unrelated donor and myeloablative conditioning are used [24]. However, other studies in unrelated donor HCT have indicated that HLA matching and donor age are the most important predictors of survival [37,38]. Therefore, for the CMV seropositive recipient, a CMV seropositive donor may be considered if multiple donors with similar HLA match and within 10 years of age are available (B-II).

The prophylactic use of intravenous immunoglobulin– or CMV-enriched IgG is not recommended because of a lack of benefit [39-41] (E-I). Vaccination and adoptive immunotherapy are discussed in a later section of the guidelines.

FAQ5: HOW DO PROPHYLACTIC AND PREEMPTIVE CMV PREVENTATIVE STRATEGIES DIFFER?

All centers performing allogeneic HCT should have PET and prophylaxis strategies in place (A-I), and they should be viewed as complementary, not mutually exclusive. Prophylaxis denotes the administration of CMV-active antivirals to those at risk for infection but in the absence of active CMV infection. "*Primary*" prophylaxis is implemented before onset of infection whereas "*secondary*" prophylaxis follows completion of PET or therapy for disease once DNAemia has cleared for the purpose of preventing recurrent infection.

PET denotes the routine surveillance for active CMV infection in plasma or whole blood and initiation of antiviral treatment triggered by exceeding a threshold viral load. PET relies on sensitive and rapid detection methods so that treatment

begins early and prevents the development of disease. Because of superior sensitivity, particularly during leukopenia, along with better quantitative performance characteristics, we recommend quantitative PCR (qPCR) over pp65 antigen detection for surveillance of active CMV infection (A-II) [42-46].

PET always begins with "*induction*" dosing (Table 2) and generally is continued until clearance of DNAemia or a substantial decline in the viral load. During PET, "*maintenance*" dosing (Table 2) may be implemented once the viral load decreases on induction therapy [7,47] to continue treatment of DNAemia while reducing the risk of toxicity (discussed in FAQ17), although this practice will vary across centers and will also depend on patient-specific characteristics. Historically, "*maintenance*" therapy has also been used to describe continued treatment at reduced dosing following clearance of DNAemia to prevent recurrent infection, but we feel "*secondary prophylaxis*" is a better term for this latter clinical practice scenario and will refer to it as such throughout these guidelines.

All patients with CMV DNAemia should be assessed for evidence of clinical CMV disease since in general PET management (FAQ17) will differ from management of disease (discussed in separate guideline). We do not recommend preventative strategies that are permissive for CMV reactivation such as PET over prophylaxis for the purpose of reducing the risk of underlying disease relapse (E-II).

FAQ6: WHAT ANTIVIRALS ARE RECOMMENDED FOR CMV PROPHYLAXIS OR TREATMENT?

Refer to Table 2. Only letermovir and ganciclovir have been approved by the United States Food and Drug Administration (US-FDA) for use in HCT recipients for CMV-related indications. Valganciclovir, foscarnet, and cidofovir have been approved for CMV-related indications in solid organ transplant recipients and persons with acquired immunodeficiency syndrome. Additionally, none of these agents are approved for use in children. However, their off-label uses in adults and children described in this guideline are supported by decades-worth of accumulated clinical experience and published data. The role of high dose acyclovir and valacyclovir is discussed in FAQ12.

FAQ7: WHAT IS THE RECOMMENDED CHEMOPREVENTION STRATEGY IN CMV SEROPOSITIVE ADULT ALLOGENEIC HCT RECIPIENTS?

Letermovir was approved by the US Food and Drug Administration and the European Medicines Agency for primary CMV prophylaxis in adult CMV seropositive allogeneic HCT recipients in 2017 based on the results of a directly relevant phase 3 randomized clinical trial [5]. We recommend letermovir prophylaxis for adult CMV seropositive allogeneic HCT recipients, to begin no later than 28 days after HCT and continuing through day 100 (A-I). Based on clinical evidence to date and weighing other issues such as cost, some centers may choose to target higher-risk HCT recipients as defined in the phase 3 clinical trial [5] for letermovir prophylaxis (see also FAQ12). CMV DNA qPCR should be assessed before initiating letermovir prophylaxis (A-II) [5]. If quantifiable CMV DNAemia is detected, PET should be considered as discussed below (FAQ15). Letermovir should be used with caution in persons with Child-Pugh class C (severe) hepatic impairment (C-III), and insufficient data exist to guide dose adjustments in persons with creatinine clearance <10 mL/min [48,49].

Currently, letermovir is not approved for children (age <18 years). A phase 2b open-label study of letermovir prophylaxis in pediatric HCT recipients is underway (NCT03940586), with data anticipated in a graded fashion for those 12 to 18 years and subsequently those under the age of 12 years.

FAQ8: WHAT DRUG-DRUG INTERACTIONS REQUIRE ATTENTION DURING LETERMOVIR PROPHYLAXIS?

Letermovir increases exposure to tacrolimus, sirolimus, and cyclosporine [50,51] and reduces voriconazole exposure [52,53]. Therapeutic drug monitoring and dose adjustment of these agents should be performed when co-administered with letermovir (A-II) [50-53]. Letermovir does not significantly alter posaconazole or isavuconazole levels [53,54].

Because of a drug/drug interaction that is mediated by the organic anion transporters OATP1B1 and OATP1B3, the dose of letermovir for patients receiving cyclosporine is 240 mg/d [5,50,51,55]. Other than cyclosporine, no recommendations can be made at this time regarding routine dose adjustment of letermovir when coadministered with interacting medications (D-II). Letermovir is contraindicated in persons receiving ergot alkaloids, and we recommend pharmacy consultation for patients receiving statins plus cyclosporine (A-II) [55].

FAQ9: SHOULD PATIENTS BE MONITORED FOR ACTIVE CMV INFECTION WHILE RECEIVING LETERMOVIR PROPHYLAXIS?

Yes—at this time we recommend monitoring during letermovir prophylaxis, with initiation of PET according to institution-specific thresholds (discussed in FAQ15) (A-II). In the phase 3 clinical trial, PET was initiated in 24 patients (7.7%) because of breakthrough DNAemia, 12 (3.7%) of whom were actively receiving letermovir prophylaxis [5]. Subsequent observational studies of letermovir prophylaxis in both high- and lower-risk CMV seropositive HCT recipients have reported rates of clinically-significant CMV infection ranging from 0% to ~20% [56-62]. Variability in patient population and thresholds for initiating PET across these studies limit interpretation. Emerging data suggest that in some cases low-level DNAemia during letermovir prophylaxis may not require discontinuation of prophylaxis and initiation of PET [63,64]. Additional clinical experience is needed to address the optimal approaches to monitoring and managing breakthrough DNAemia during letermovir prophylaxis.

FAQ10: WHAT IS THE APPROPRIATE MONITORING STRATEGY FOLLOWING DISCONTINUATION OF LETERMOVIR PROPHYLAXIS AT DAY 100?

We recommend monitoring through 6 months (Day 180) after HCT with initiation of PET according to institution-specific guidelines (A-II). This is based on the phase 3 clinical trial, where clinically significant CMV infection was observed by week 24 after stopping letermovir prophylaxis at week 14 in ~10% of all patients and in ~20% among those at higher risk for CMV infection [5]. Letermovir prophylaxis may delay CMV-specific cellular immune reconstitution compared to monitoring and PET, perhaps as a result of suppression of reactivation and consequent decreased CMV antigen exposure [65].

FAQ11: DO PATIENTS RECEIVING LETERMOVIR PROPHYLAXIS REQUIRE ACYCLOVIR, VALACYCLOVIR, FOR FAMCICLOVIR FOR HSV AND VZV PROPHYLAXIS?

Yes—Letermovir has no activity against HSV or VZV, and therefore prophylaxis against those herpesviruses is required [66] (A-I).

FAQ12: WHAT IF LETERMOVIR PROPHYLAXIS CANNOT BE USED IN A CMV-SEROPOSITIVE ADULT ALLOGENEIC RECIPIENT BECAUSE OF COST, ACCESS, AGE, OR OTHER ISSUES?

We recommend a monitoring and PET approach for CMV disease prevention (A-I). Primary prophylaxis with an alternative agent such as valganciclovir, ganciclovir, or foscarnet is generally not recommended (D-I).

Table 2
Agents for the Treatment or Prevention of CMV Infection and Disease in HCT Recipients

Agent	CMV target	Route of Administration	Dose per Indication*			Major Toxicities[†,‡]	Significant Drug Interactions	CMV genes involved in resistance	Activity against other herpes viruses
			Treatment[†]						
			Prophylaxis	Induction	Maintenance[‖]				
Ganciclovir	DNA polymerase (UL54)	IV	NA[¶]	5 mg/kg bid	5 mg/kg/day	Cytopenias	None	kinase (UL97), UL54	HSV1&2, VZV, HHV-6
Valganciclovir	UL54	Oral	NA[¶]	900 mg bid[#] 7 × BSA × GFR bid[**]	900 mg/day[#] 7 × BSA × GFR/day[**]	Same as ganciclovir	None	UL97, UL54	HSV1&2, VZV, HHV-6
Foscarnet	UL54	IV	NA[¶]	90 mg/kg q 12 hrs or 60 mg/kg q 8 hours	90 mg/kg/day	Nephrotoxicity, electrolyte wasting, gastrointestinal	None	UL54	HSV1&2, VZV, HHV-6
Cidofovir	UL54	IV	NA[¶]	5 mg/kg/week	5 mg/kg every other week	Nephrotoxicity, neutropenia, headache, uveitis/iritis, diarrhea, ocular hypotony	None	UL54	HSV1&2, VZV, HHV-6
Letermovir	Terminase complex (UL 56,51,89)	IV, oral	480 mg/day[††,§§]	NA[¶]	NA[¶]	Nausea	Cyclosporine, voriconazole, tacrolimus, sirolimus, statins, ergot alkaloids	UL56[‖‖]	No

BSA, body surface area; GFR, glomerular filtration rate; BID, twice daily; q, every; NA, not applicable; mg, milligram; kg, kilogram

* All agents require dose adjustment in the setting of renal dysfunction. Loading doses of ganciclovir and valganciclovir should be administered even in patients with renal impairment. Consultation with Pharmacy is recommended.

† Preemptive therapy or therapy for disease.

‡ For full listing of toxicities, please refer to the Summary of Product Characteristics (SPC) for each agent if available.

§ Excludes overlapping toxicities with medications commonly used after HCT.

‖ Dosing may also be used for secondary prophylaxis.

¶ NA = the agent is not approved for, or typically used for, the indication.

Dose for adults ≥ 18 years of age weighing >40 kg.

** Dose for pediatric patients <18 years of age, up to maximum 900 mg per dose.

†† Approved only for primary prophylaxis in adult CMV seropositive HCT recipients; not approved for pediatric patients.‡‡Reduce dose to 240 mg/day if coadministered with cyclosporine.

§§ Dose is same for primary and secondary prophylaxis.

‖‖ Mutations in UL51 and UL89 conferring reduced susceptibility to letermovir have been described in vitro but not in clinical use to date.

In the early post-HCT period, the use of ganciclovir as primary prophylaxis was effective for preventing CMV infection but did not yield a demonstrable survival benefit [67-69]. In addition, among CMV seropositive allogeneic HCT recipients, pp65-antigenemia-guided PET using ganciclovir starting with any antigen detection and continuing through day 100 after HCT was demonstrated to be as effective in preventing CMV disease as ganciclovir prophylaxis administered from engraftment to day 100 [70]. Primary prophylaxis with valganciclovir or ganciclovir is not used commonly today for prevention [71] given the risk of myelosuppression and the improvements in PET with the use of highly sensitive qPCR-based surveillance. Similarly, foscarnet primary prophylaxis in the early post-HCT period is effective in preventing CMV infection and disease but is not recommended or routinely used because of its unfavorable toxicity profile [71-74].

Differing from adult populations, the use of primary prophylaxis with ganciclovir or foscarnet in children is more common [75,76]. Primary prophylaxis with valganciclovir, ganciclovir, or foscarnet may be considered in select pediatric HCT recipients (C-III), but recommendations with regard to the optimal patient population and regimen cannot be made given multiple described regimens without comparative outcome data.

High-dose intravenous acyclovir (1500 mg/m^2/d in patients with normal renal function) and valacyclovir (8 grams/day with normal renal function) primary prophylaxis reduces the risk of CMV active infection but not disease [67,77-80]. This strategy, coupled with CMV monitoring and PET, has been used in certain high-risk populations such as cord-blood and haploidentical HCT recipients [62,81,82]. Based on currently available data, we cannot recommend the routine use of high-dose acyclovir or valacyclovir prophylaxis alone for CMV prevention (E-II), and use of these agents for prophylaxis should always be accompanied by a CMV monitoring and PET strategy (A-I).

FAQ13: IN WHICH OTHER ALLOGENEIC HCT RECIPIENT POPULATIONS SHOULD THE MONITORING AND PET APPROACH BE USED?

All CMV D+/R− HCT recipients should be monitored and PET used because of the risk for transmission of CMV from donor to recipient via the stem cell product [9,18,23] (A-I). In contrast, the risk of CMV infection in CMV D−/R− HCT is relatively low [9,18], and no randomized trial has evaluated prevention strategies in the D−/R− setting. One single-center study that used monitoring and PET in CMV D−/R− HCT recipients demonstrated effectiveness in preventing CMV disease resulting from transfusion-transmitted CMV infection, with the incidence of infection being 3% [29]. Taking these points together, it is unclear whether CMV monitoring is a cost-effective preventative strategy for D−/R− recipients but may be considered in those with significant post-HCT transfusion requirements (C-II).

FAQ 14: WHEN SHOULD MONITORING FOR CMV BEGIN AND HOW OFTEN SHOULD IT BE PERFORMED?

Monitoring should be performed once per week beginning either at the time of transplant or in the second week after HCT and continued until day 100 after HCT (or longer as discussed in FAQ20) (A-II) [5-7,9,47]. In CMV seropositive patients undergoing HCT for nonmalignant disorders who receive T-cell–depleting agents (ATG, alemtuzumab) weeks before admission as a GVHD prophylaxis strategy, monitoring should begin at the time of admission [83,84] (C-II). A monitoring strategy in seropositive cord blood recipients involving twice weekly testing has been described [81,82] but insufficient evidence exists to assign a recommendation to this strategy, especially with the use of letermovir primary prophylaxis in this population.

FAQ15: WHEN SHOULD PET BE INITIATED?

There is no validated, universal quantitative viral load threshold for initiating PET. Thresholds may vary across institutions and according to underlying CMV risk characteristics of the patient. Thresholds for initiating PET that have been successful in preventing CMV disease in recent phase 3 clinical trials include 300 to 1000 copies/mL (~274-909 IU/mL) for low-risk patients and ~150 copies/mL (137 IU/mL) for high-risk patients [5,6]. We recommend that each institution determine quantitative viral load thresholds that account for patient risk category and center-specific data [7] (A-II). The dynamics of viral load may predict and guide the need for initiation of PET [85-87], but additional data are required before this strategy can be recommended for routine use.

FAQ16: WHAT IS THE FIRST-LINE AGENT FOR PREEMPTIVE THERAPY AND WHAT PRECAUTIONS ARE ADVISED?

Oral valganciclovir or intravenous (IV) ganciclovir are recommended over foscarnet in most situations (B-II). Because of ease of administration and clinical equivalence to IV ganciclovir, valganciclovir is often preferred [88-90]. Valganciclovir is not recommended if barriers to oral administration or absorption of an orally-administered medication exist such as severe gastrointestinal graft-versus-host disease (D-II).

Neutropenia is a frequent complication of valganciclovir and ganciclovir therapy in HCT recipients [91,92] and absolute neutrophil counts should be regularly assessed (A-III). Avoiding or switching concomitant myelosuppressive medications such as mycophenolate mofetil or trimethoprim/sulfamethoxazole should be considered. During PET, dose reductions of valganciclovir and ganciclovir in the setting of neutropenia are generally not recommended unless criteria for changing to maintenance dosing as described below in FAQ17 are met (D-III). Instead, granulocyte colony-stimulating factor (G-CSF) support should be considered or foscarnet should be substituted until absolute neutrophil count recovery.

Foscarnet is recommended as an alternative initial antiviral for pre-engraftment CMV DNAemia or other situations where valganciclovir/ganciclovir use may be undesirable such as early post-engraftment, concomitant cytopenias, or patient intolerance (A-I) [47]. Renal function and electrolytes should be monitored frequently during foscarnet therapy. Cidofovir should be considered a third-line agent due to a high incidence of renal toxicity and reports of variable efficacy [93-95] (C-II). Regardless of the agent chosen, PET should be initiated at induction dosing (Table 2), with dose adjustment as needed for renal dysfunction.

FAQ17: HOW LONG SHOULD PET BE CONTINUED?

Although variation in practice exists [71], PET should generally be continued at induction dosing for 2 weeks and until DNAemia clearance (B-II) [7,47,96]. Alternatively, if the viral load is declining after 1 to 2 weeks of induction therapy, a change to maintenance dosing (Table 2) can be considered and continued until clearance of DNAemia (B-II) [7,47].

FAQ18: WHAT IF THE VIRAL LOAD INCREASED WHILE RECEIVING PET?

A similar or increased ($\leq$1 $\log_{10}$) viral load during the first 14 days of induction-dose PET is common [97], especially in patients with acute GVHD being treated with systemic

glucocorticoids or those who received T-cell–depleted grafts. In treatment naïve patients, the likelihood of resistance is low, and typically no change is needed (B-II). The diagnosis and management of refractory or resistant infection is outside the scope of this document and is discussed in a separate guideline.

FAQ19: HOW SHOULD PATIENTS BE MANAGED FOLLOWING DISCONTINUATION OF PET?

HCT recipients treated with a first course of PET remain at risk of recurrent DNAemia necessitating additional PET [96,98,99]. Therefore, after discontinuation of PET, secondary prophylaxis with valganciclovir 900 mg daily (with normal renal function) or letermovir at the same dosing as primary prophylaxis, or monitoring and PET, are recommended [64,96,100] (A-II). If a monitoring and PET strategy is implemented, reinitiation of PET with recurrent DNAemia is recommended according to institution-defined viral load thresholds. Typically, the same agent used in the first course of PET can be used for a second course of preemptive therapy [47,96,99,101] (B-II).

FAQ20: WHICH PATIENTS SHOULD CONTINUE A CHEMOPREVENTION STRATEGY CONTINUE BEYOND DAY 100 AFTER HCT?

As discussed in FAQ10, we recommend monitoring for infection through 6 months (day 180) after HCT in patients who receive letermovir prophylaxis through day 100. In addition, we recommend continued monitoring and initiation of PET, or consideration of valganciclovir or letermovir prophylaxis [64,100,102], for patients with at least 1 of the following risk factors for CMV infection after day 100 (A-II):

1. Lymphopenia ($<$100 lymphocytes/mm^3) [103]
2. CMV infection before day 100 [22,35,103]
3. GVHD requiring high-dose prednisone ($\geq$0.5mg/kg/d) or equivalent [22,35,101,103]
4. Absence of CMV-specific T-cell immunity (if measured) [103]

On the basis of current data, we cannot make a recommendation with regard to the duration of preventative strategies after day 100 in patients meeting these criteria, and this may vary according to individual patient characteristics.

FAQ21: WHAT IS THE OPTIMAL PREVENTION APPROACH IN PATIENTS WITH CMV DISEASE BEFORE HCT?

CMV disease before HCT is rare but has been associated with early recurrence of CMV disease after HCT and poor outcomes [104]. In general, HCT should be delayed to adequately treat CMV disease (B-III). An aggressive approach to secondary prevention has been suggested, including post-HCT foscarnet or ganciclovir prophylaxis, or PET using more frequent monitoring than standard (i.e., twice weekly) [104]. The contemporary practice of using letermovir prophylaxis in CMV seropositive HCT recipients may supplant these strategies. However, in patients with pre-HCT CMV disease who are unable to receive letermovir prophylaxis after HCT, the approaches described above may be considered (C-III), although the optimal approach in this setting remains undefined.

FAQ22: IS THERE A ROLE FOR PROPHYLAXIS IMMEDIATELY BEFORE ALLOGENEIC HCT?

Pre-HCT prophylaxis is generally not recommended (D-II). Ganciclovir or valganciclovir primary prophylaxis in the immediate pre-HCT period has been used [81,105-107]. However, the benefit of this intervention remains unclear and may vary according to the patient population and post-HCT preventative strategy. A recent study suggested that ganciclovir prophylaxis administered from days −8 to −2 in seropositive cord blood transplant recipients did not affect post-HCT outcomes when the same post-HCT prevention strategy was used [82].

FAQ23: WHAT IS THE APPROACH TO CMV PREVENTION IN AUTOLOGOUS HCT RECIPIENTS?

Prevention strategies are not required in most cases because autologous recipients are at very low risk for CMV disease (D-II) [108-113]. Recipients of autologous transplants using CD34-selected grafts are at higher risk for CMV infection and disease [114,115] and therefore may benefit from monitoring and PET (C-II).

UNMET NEEDS/FUTURE DIRECTIONS

Addressing the knowledge gap pertaining to the use of novel antiviral agents in children

Pediatric HCT recipients generally experience similar risks for CMV infection, disease, and resistance as do adult HCT recipients. However, there is a lack of safety and efficacy data for novel antiviral agents in pediatric HCT recipients. Letermovir is currently not approved for use in pediatric populations. Anecdotal off-label use of letermovir in pediatric HCT recipients has been reported [116-119], but further data are required. As mentioned in FAQ7, a phase 2b study of letermovir in pediatric HCT recipients is underway. If available, children under the age of 18 should be enrolled in a clinical trial (A-III) until more data are available.

Optimizing prophylactic strategies using letermovir

Further defining efficacy and mortality benefit

Additional study is needed to better define the benefit of letermovir prophylaxis in HCT populations with different CMV risks given its overall favorable impact on mortality as observed in the phase 3 clinical trial [5]. Not all high-risk HCT recipients were equally represented in the phase 3 trial, with haploidentical transplant recipients comprising 14.3% of the total population, cord blood recipients 4%, and ex vivo T-cell–depleted recipients 2.5% [5]. Therefore more data in specific high-risk patients who were relatively underrepresented in the phase 3 clinical trial but for whom the benefit of letermovir prophylaxis appeared greatest are needed [62,120].

Determining the optimal duration of letermovir prophylaxis

In the phase 3 prophylaxis trial, clinically significant CMV infection developed in ~10% of all patients and in ~20% in those at high risk of CMV between week 14, when letermovir was discontinued, and week 24 [5]. An ongoing phase 3 trial will compare 100 versus 200 days of letermovir prophylaxis, with the primary efficacy outcome measure being CMV infection through week 28 after HCT (NCT03930615).

Defining the roles of other agents for PET

Maribavir

A recent phase 2 study suggested noninferiority of maribavir to valganciclovir used as PET in HCT and solid organ transplant recipients with a blood or plasma CMV viral load $\leq$100,000 copies/mL [121]. A phase 3 trial of maribavir 400 mg twice daily versus valganciclovir for the treatment of first episodes of asymptomatic CMV infection in HCT recipients age $\geq$16 years is under way (NCT02927067).

Letermovir

Its use as monotherapy for PET is not currently recommended due to the lack of supporting data and low barrier for development of resistance in vitro [122]. Approximately 31% of patients who had detectable DNAemia at the time of randomization to letermovir in the phase 3 prophylaxis study required discontinuation of letermovir and initiation of standard PET for clinically significant CMV infection [123]. However, the reported incidence of resistance in the phase 3 prophylaxis trial was relatively low [124]. Additional studies are needed to define the role of letermovir for PET.

Defining the role of determining CMV-specific cell-mediated immunity (CMI)

Several methods for assessing CMV-specific T cell responses are available [125]. Among solid organ transplant recipients, these assays have shown potential utility in risk assessment and in guiding the duration of prophylaxis [126]. The use of these assays after allogeneic HCT has demonstrated an association between the development of CMV-specific immunity and protection from infection [127-130]. Small, single center studies have shown that using measures of CMV-specific immunity may help guide preemptive therapy after HCT [128,131,132]. Additional studies are required before this strategy can be recommended.

CMV vaccination strategies

The development of an effective CMV vaccine in transplant recipients has proven to be a challenge, and none is currently available for use. A promising candidate, ASP0113, recently failed to meet primary or secondary endpoints in a placebo-controlled, phase 3 clinical trial in CMV-seropositive HCT recipients [133]. Several other candidate vaccines are being evaluated [120,134-139].

CMV cellular therapies

Adoptive immunotherapy denotes the reconstitution of CMV-specific T-cell responses via the isolation, in vitro propagation, and transfusion of donor T-cells to the recipient. Adoptive immunotherapy has been safely used in HCT recipients as an adjunct to PET and prophylactically, but all in relatively small series [140-147]. The use of partially HLA-matched, banked third-party cells addresses several limitations inherent to the preparation of T cells [148]. Randomized studies are needed to definitively assess the benefit and safety of adoptive immunotherapy for CMV prophylaxis or PET in the HCT recipient [149]. The use of immunotherapy as an adjunct strategy in refractory/resistant CMV infection and disease is discussed in a separate guideline.

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Authorship statement: •••.

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Appendix 1
Grading of Strength of Recommendation and Level of Evidence (Ref – Editorial).

Question	Recommendation	Highest Grade*	Supporting References
FAQ2-5			
Should all patients and donors be tested for CMV-specific IgG prior to HCT?	Yes	A-II	[18]
Is a CMV seronegative donor preferred for a CMV seronegative recipient when possible?	Yes	A-II	[9,18,23-25]
Should CMV seronegative blood products or leukoreduction of red cells, and pathogen-reduced platelet products, be used for CMV seronegative recipients?	Yes	A-I	[26-32]
Should a CMV seropositive donor be considered for a CMV seropositive recipient if multiple donors with similar HLA-match and within 10 years of age are available?	Yes	B-II	[24,33-36]
Should IVIG or CMV-enriched IgG be used prophylactically to prevent CMV infection after HCT?	No	E-I	[39-41]
Should all centers performing HCT have preventative CMV strategies in place, including PET and prophylaxis?	Yes	A-I	[5,70,178]
Should routine CMV surveillance for the purposes of PET be by plasma or whole blood quantitative PCR rather than pp65 antigen detection?	Yes	A-II	[42-46]
Should a PET prevention strategy be chosen over prophylaxis for the purpose of reducing the risk of disease relapse after HCT?	No	E-II	[8,9,12,14,17]
FAQ7-10			
Should letermovir primary prophylaxis be used in CMV seropositive adult allogeneic HCT recipients?	Yes	A-I	[5]
Should a plasma or whole blood CMV DNA qPCR be checked to document absence of active infection prior to starting letermovir prophylaxis?	Yes	A-II	[5,123]
When tacrolimus, sirolimus, or voriconazole are co-administered with letermovir, should therapeutic drug monitoring and dose adjustment as needed be performed for these agents?	Yes	A-II	[5,50-53]
Should letermovir be dose-modified in patients also taking tacrolimus, sirolimus, voriconazole, or posaconazole?	No	D-II	[5,50-53]
Should CMV monitoring be performed while receiving letermovir prophylaxis?	Yes	A-II	[5,56-62]
Should CMV monitoring be continued to day 180 post-HCT after stopping letermovir prophylaxis?	Yes	A-II	[5]
FAQ11-14			
Do patients receiving letermovir prophylaxis require acyclovir, valacyclovir, or famciclovir for prevention of HSV and VZV infection?	Yes	A-I	[66]
If letermovir prophylaxis cannot be used in a CMV-seropositive adult recipient, should a CMV monitoring and PET approach be used over (val)ganciclovir or foscarnet primary prophylaxis?	Yes	A-I	[67-70,72-74,96]
Should CMV D+/R- recipients undergo CMV monitoring and PET?	Yes	A-I	[9,18,23]
Should CMV D-/R- recipients undergo CMV monitoring?	Optional	C-II	[29]
Should weekly CMV monitoring begin no later than the second week after HCT?	Yes	A-II	[5-7,9,47]
FAQ15-20			
Should PET be initiated based on institutional determinations of viral load thresholds that account for patient risk category and center-specific data?	Yes	A-II	[7]
Are either oral valganciclovir or IV ganciclovir recommended as first-line PET over foscarnet?	Yes	B-II	[7,47,88-90]
Is foscarnet recommended as second-line PET in settings where valganciclovir/ganciclovir use is undesirable?	Yes	A-I	[47]
Is cidofovir reasonable as third-line PET if barriers to (val)ganciclovir and foscarnet exist?	Yes	C-II	[93-95]
Should PET generally be continued for 2 weeks and until DNAemia clearance?	Yes	B-II	[7,47]
Should one usually hold the course for treatment naïve patients who have a ≤1 log10 increase in DNAemia during the first 14 days of PET?	Yes	B-II	[97]
Should CMV prevention strategies (secondary prophylaxis and monitoring) remain in place after stopping PET?	Yes	A-II	[96,98,99]
Can valganciclovir or letermovir secondary prophylaxis be considered for patients following completion of PET infection but who remain at high-risk for recurrent CMV DNAemia?	Yes	A-II	[64,100]
Should the same agent used in the first course of PET be used for a second course of PET?	Yes	B-II	[47,96,99,101]
FAQ20-23			
Should CMV prevention strategies extend > Day 100 post-HCT for patients at high-risk for late CMV infection?	Yes	A-II	[5,35,100,102,103]
Should pre-HCT antiviral prophylaxis be used?	No	D-II	[82]
	No	D-II	[108-113]

(*continued*)

Appendix 1 (*Continued*)

Question	Recommendation	Highest Grade*	Supporting References
Do CMV seropositive recipients of autologous HCT routinely require CMV prevention strategies?			
Should CMV monitoring and PET be performed in CMV seropositive autologous HCT recipients receiving CD34-selected grafts?	Yes	C-II	[114,115]

NA, not applicable; GI-GVHD, gastrointestinal GVHD; IVIG, intravenous immunoglobulin; PET, preemptive therapy.

* Highest grade = strength of recommendation from "A" should always be offered, "B" should generally be offered, "C" Optional, "D" should generally not be offered, "E" should never be offered; along with quality of evidence supporting the recommendation from "I" (evidence from at least one properly randomized, controlled trial), "II" evidence for at least one well-designed clinical trial without randomization, from cohort or case controlled analytic studies (preferable from more than one center) or from multiple time-series or dramatic results from uncontrolled experiments, and "III" evidence from opinions of respected authorities based on clinical experience, descriptive [1].