



Guideline

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



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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.

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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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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 \geq 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
Letemovir	Terminase complex (UL56,51,89)	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 letemovir 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/m²/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/mm³) [103]
2. CMV infection before day 100 [22,35,103]
3. GVHD requiring high-dose prednisone (≥ 0.5 mg/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 ≥ 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: ●●●.

REFERENCES

- Pirofski LA, Casadevall A. The damage-response framework as a tool for the physician-scientist to understand the pathogenesis of infectious diseases. *J Infect Dis*. 2018;218(suppl_1):S7–S11.
- Carpenter PA, Papanicolaou GA, Chemaly RF, Boeckh M, Savani BN. American Society for Transplantation and Cellular Therapy Infectious Diseases Guidelines: preface to the series. *Transplant Cell Ther*. 2021;27:103–104.
- Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. *Clin Infect Dis*. 2017;64:87–91.
- Goodrum F, Caviness K, Zagallo P. Human cytomegalovirus persistence. *Cell Microbiol*. 2012;14:644–655.
- Marty FM, Ljungman P, Chemaly RF, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. *N Engl J Med*. 2017;377:2433–2444.
- Marty FM, Winston DJ, Chemaly RF. A randomized, double-blind, placebo-controlled phase 3 trial of oral brincidofovir for cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2019;25:369–381.
- Green ML, Leisenring W, Stachel D, et al. Efficacy of a viral load-based, risk-adapted, preemptive treatment strategy for prevention of cytomegalovirus disease after hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2012;18:1687–1699.
- Green ML, Leisenring W, Xie H, et al. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of preemptive therapy: a retrospective cohort study. *Lancet Haematol*. 2016;3(3):e119–e127.
- Teira P, Battiwalla M, Ramanathan M. Early cytomegalovirus reactivation remains associated with increased transplant-related mortality in the current era: a CIBMTR analysis. *Blood*. 2016;127:2427–2438.
- Ljungman P, Schmitt M, Marty FM. A mortality analysis of letermovir prophylaxis for cytomegalovirus (CMV) in CMV-seropositive recipients of allogeneic hematopoietic cell transplantation. *Clin Infect Dis*. 2020;70:1525–1533.
- Elmaagacli AH, Koldehoff M. Cytomegalovirus replication reduces the relapse incidence in patients with acute myeloid leukemia. *Blood*. 2016;128:456–459.
- Green ML, Leisenring WM, Xie H. CMV reactivation after allogeneic HCT and relapse risk: evidence for early protection in acute myeloid leukemia. *Blood*. 2013;122:1316–1324.
- Ramanathan M, Teira P, Battiwalla M. Impact of early CMV reactivation in cord blood stem cell recipients in the current era. *Bone Marrow Transplant*. 2016;51:1113–1120.
- Takenaka K, Nishida T, Asano-Mori Y. Cytomegalovirus reactivation after allogeneic hematopoietic stem cell transplantation is associated with a reduced risk of relapse in patients with acute myeloid leukemia who survived to day 100 after transplantation: the Japan Society for Hematopoietic Cell Transplantation Transplantation-related Complication Working Group. *Biol Blood Marrow Transplant*. 2015;21:2008–2016.
- Yokoyama H, Takenaka K, Nishida T. Favorable effect of cytomegalovirus reactivation on outcomes in cord blood transplant and its differences among disease risk or type. *Biol Blood Marrow Transplant*. 2020;26:1363–1370.
- Goldsmith SR, Abid MB, Auletta JJ. Post-transplant cyclophosphamide (PTCy) is associated with increased cytomegalovirus infection: A CIBMTR Analysis. *Blood*. 2021;137(23):3291–3305.
- Lindsay J, Othman J, Kerridge I. Cytomegalovirus (CMV) management in allogeneic hematopoietic cell transplantation: Pre-transplant predictors of survival, reactivation, and spontaneous clearance. *Transpl Infect Dis*. 2021;23(3):e13548.
- George B, Pati N, Gilroy N. Pre-transplant cytomegalovirus (CMV) serostatus remains the most important determinant of CMV reactivation after

- allogeneic hematopoietic stem cell transplantation in the era of surveillance and preemptive therapy. *Transpl Infect Dis*. 2010;12:322–329.
19. Navarro D, Fernandez-Ruiz M, Aguado JM, Sandonis V, Perez-Romero P. Going beyond serology for stratifying the risk of CMV infection in transplant recipients. *Rev Med Virol*. 2019;29(1):e2017.
 20. Dowd JB, Aiello AE, Alley DE. Socioeconomic disparities in the seroprevalence of cytomegalovirus infection in the US population: NHANES III. *Epidemiol Infect*. 2009;137:58–65.
 21. Fowler KB, Ross SA, Shimamura M, et al. Racial and ethnic differences in the prevalence of congenital cytomegalovirus infection. *J Pediatr*. 2018;200:196–201 e1.
 22. Nakamae H, Kirby KA, Sandmaier BM, et al. Effect of conditioning regimen intensity on CMV infection in allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2009;15:694–703.
 23. Pergam SA, Xie H, Sandhu R, et al. Efficiency and risk factors for CMV transmission in seronegative hematopoietic stem cell recipients. *Biol Blood Marrow Transplant*. 2012;18:1391–1400.
 24. Ljungman P, Brand R, Hoek J, et al. Donor cytomegalovirus status influences the outcome of allogeneic stem cell transplant: a study by the European group for blood and marrow transplantation. *Clin Infect Dis*. 2014;59:473–481.
 25. Nichols WG, Corey L, Gooley T, Davis C, Boeckh M. High risk of death due to bacterial and fungal infection among cytomegalovirus (CMV)-seronegative recipients of stem cell transplants from seropositive donors: evidence for indirect effects of primary CMV infection. *J Infect Dis*. 2002;185:273–282.
 26. Blajchman MA, Goldman M, Freedman JJ, Sher GD. Proceedings of a consensus conference: prevention of post-transfusion CMV in the era of universal leukoreduction. *Transfus Med Rev*. 2001;15:1–20.
 27. Bowden R, Cays M, Schoch G, et al. Comparison of filtered blood (FB) to seronegative blood products (SB) for prevention of cytomegalovirus (CMV) infection after marrow transplant. *Blood*. 1995;86:3598–3603.
 28. Ljungman P, Larsson K, Kumlien G, et al. Leukocyte depleted, unscreened blood products give a low risk for CMV infection and disease in CMV seronegative allogeneic stem cell transplant recipients with seronegative stem cell donors. *Scand J Infect Dis*. 2002;34:347–350.
 29. Nichols WG, Price TH, Gooley T, Corey L, Boeckh M. Transfusion-transmitted cytomegalovirus infection after receipt of leukoreduced blood products. *Blood*. 2003;101:4195–4200.
 30. Ratko TA, Cummings JP, Oberman HA, et al. Evidence-based recommendations for the use of WBC-reduced cellular blood components. *Transfusion*. 2001;41:1310–1319.
 31. Kerkhoffs JL, van Putten WL, Novotny VM, et al. Clinical effectiveness of leukoreduced, pooled donor platelet concentrates, stored in plasma or additive solution with and without pathogen reduction. *Br J Haematol*. 2010;150:209–217.
 32. van Rhenen D, Gulliksson H, Cazenave JP, et al. Transfusion of pooled buffy coat platelet components prepared with photochemical pathogen inactivation treatment: the euroSPRITE trial. *Blood*. 2003;101:2426–2433.
 33. Zhou W, Longmate J, Lacey SF, et al. Impact of donor CMV-status on viral infection and reconstitution of multi-function CMV-specific T-cells in CMV-positive transplant recipients. *Blood*. 2009;113:6465–6476.
 34. Ljungman P, Perez-Bercoff L, Jonsson J, et al. Risk factors for the development of cytomegalovirus disease after allogeneic stem cell transplantation. *Haematologica*. 2006;91:78–83.
 35. Ozdemir E, Saliba R, Champlin R, et al. Risk factors associated with late cytomegalovirus reactivation after allogeneic stem cell transplantation for hematological malignancies. *Bone Marrow Transplant*. 2007;40:125–136.
 36. Mikulska M, Raiola AM, Bruzzi P, et al. CMV infection after transplant from cord blood compared to other alternative donors: the importance of donor-negative CMV serostatus. *Biol Blood Marrow Transplant*. 2012;18:92–99.
 37. Kollman C, Spellman SR, Zhang MJ, et al. The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy. *Blood*. 2016;127:260–267.
 38. Shaw BE, Logan BR, Spellman SR, et al. Development of an unrelated donor selection score predictive of survival after HCT: donor age matters most. *Biol Blood Marrow Transplant*. 2018;24:1049–1056.
 39. Bowden RA, Fisher LD, Rogers K, Cays M, Meyers JD. Cytomegalovirus (CMV)-specific intravenous immunoglobulin for the prevention of primary CMV infection and disease after marrow transplant. *J Infect Dis*. 1991;164:483–487.
 40. Ruutu T, Ljungman P, Brinck L, et al. No prevention of cytomegalovirus infection by anti-cytomegalovirus hyperimmune globulin in seronegative bone marrow transplant recipients. The Nordic BMT Group. *Bone Marrow Transplant*. 1997;19:233–236.
 41. Bowden RA, Sayers M, Flournoy N, et al. Cytomegalovirus immune globulin and seronegative blood products to prevent primary cytomegalovirus infection after marrow transplantation. *N Engl J Med*. 1986;314:1006–1010.
 42. Boeckh M, Gallez-Hawkins GM, Myerson D, Zaia JA, Bowden RA. Plasma polymerase chain reaction for cytomegalovirus DNA after allogeneic marrow transplantation: comparison with polymerase chain reaction using peripheral blood leukocytes, pp65 antigenemia, and viral culture. *Transplantation*. 1997;64:108–113.
 43. Gimeno C, Solano C, Latorre JC, et al. Quantification of DNA in plasma by an automated real-time PCR assay (cytomegalovirus PCR kit) for surveillance of active cytomegalovirus infection and guidance of preemptive therapy for allogeneic hematopoietic stem cell transplant recipients. *J Clin Microbiol*. 2008;46:3311–3318.
 44. Ksouri H, Eljed H, Greco A, et al. Analysis of cytomegalovirus (CMV) viremia using the pp65 antigenemia assay, the amplicor CMV test, and a semi-quantitative polymerase chain reaction test after allogeneic marrow transplantation. *Transpl Infect Dis*. 2007;9:16–21.
 45. Nitsche A, Oswald O, Steuer N, et al. Quantitative real-time PCR compared with pp65 antigen detection for cytomegalovirus (CMV) in 1122 blood specimens from 77 patients after allogeneic stem cell transplantation: which test better predicts CMV disease development? *Clin Chem*. 2003;49:1683–1685.
 46. Yakushiji K, Gondo H, Kamezaki K, et al. Monitoring of cytomegalovirus reactivation after allogeneic stem cell transplantation: comparison of an antigenemia assay and quantitative real-time polymerase chain reaction. *Bone Marrow Transplant*. 2002;29:599–606.
 47. Reusser P, Einsele H, Lee J, et al. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. *Blood*. 2002;99:1159–1164.
 48. Kropf D, McCormick D, Erb-Zohar K, et al. Pharmacokinetics and safety of the anti-human cytomegalovirus drug letermovir in subjects with hepatic impairment. *Br J Clin Pharmacol*. 2017;83:2678–2686.
 49. Kropf D, Scheuenpflug J, Erb-Zohar K, et al. Pharmacokinetics and safety of letermovir, a novel anti-human cytomegalovirus drug, in patients with renal impairment. *Br J Clin Pharmacol*. 2017;83:1944–1953.
 50. Kropf D, von Richter O, Stobernack HP, Rubsam-Schaeff H, Zimmermann H. Pharmacokinetics and safety of letermovir coadministered with cyclosporine A or tacrolimus in healthy subjects. *Clin Pharmacol Drug Dev*. 2018;7:9–21.
 51. McCrea JB, Macha S, Adedoyin A, et al. Pharmacokinetic drug-drug interactions between letermovir and the immunosuppressants cyclosporine, tacrolimus, sirolimus, and mycophenolate mofetil. *J Clin Pharmacol*. 2019;59:1331–1339.
 52. Duong A, Sweet A, Jain R, et al. Clinically significant drug interaction: letermovir and voriconazole. *J Antimicrob Chemother*. 2019;75:775–777.
 53. Marshall WL, McCrea JB, Macha S, et al. Pharmacokinetics and tolerability of letermovir coadministered with azole antifungals (posaconazole or voriconazole) in healthy subjects. *J Clin Pharmacol*. 2018;58:897–904.
 54. Terrier J, Zanella MC, Masouridi-Levrat S, et al. Concomitant administration of posaconazole and isavuconazole with letermovir: clinical and pharmacological considerations. *Antimicrob Agents Chemother*. 2021;65(6). e00274-21.
 55. Corp MSD. PREVYMIS: Package Insert and Label Information. 2017.
 56. Anderson A, Raja M, Vazquez N, Morris M, Komanduri K, Camargo J. Clinical “real-world” experience with letermovir for prevention of cytomegalovirus infection in allogeneic hematopoietic cell transplant recipients. *Clin Transplant*. 2020;34(7):e13866.
 57. Derigs P, Radujkovic A, Schubert ML, et al. Letermovir prophylaxis is effective in preventing cytomegalovirus reactivation after allogeneic hematopoietic cell transplantation: single-center real-world data. *Ann Hematol*. 2021;100(8):2087–2093.
 58. Johnsrud JJ, Nguyen IT, Domingo W, Narasimhan B, Efron B, Brown JW. Letermovir prophylaxis decreases burden of cytomegalovirus (CMV) in patients at high risk for CMV disease following hematopoietic cell transplant. *Biol Blood Marrow Transplant*. 2020;26:1963–1970.
 59. Lin A, Flynn J, DeRespiris L, et al. Letermovir for prevention of cytomegalovirus reactivation in haploidentical and mismatched adult donor allogeneic hematopoietic cell transplantation with post-transplantation cyclophosphamide for graft-versus-host disease prophylaxis. *Transplant Cell Ther*. 2021;27(1). 85 e1-e6.
 60. Lin A, Maloy M, Su Y, et al. Letermovir for primary and secondary cytomegalovirus prevention in allogeneic hematopoietic cell transplant recipients: real-world experience. *Transpl Infect Dis*. 2019;21(6). e13187.
 61. Mori Y, Jinnouchi F, Takenaka K, et al. Efficacy of prophylactic letermovir for cytomegalovirus reactivation in hematopoietic cell transplantation: a multicenter real-world data. *Bone Marrow Transplant*. 2021;56:853–862.
 62. Sharma P, Gakhar N, MacDonald J, et al. Letermovir prophylaxis through day 100 post transplant is safe and effective compared with alternative CMV prophylaxis strategies following adult cord blood and haploidentical cord blood transplantation. *Bone Marrow Transplant*. 2020;55:780–786.
 63. Cassaniti I, Colombo AA, Bernasconi P, et al. Positive HCMV DNAemia in stem cell recipients undergoing letermovir prophylaxis is expression of abortive infection. *Am J Transplant*. 2021;21:1622–1628.
 64. Robin C, Thiebaut A, Alain S, et al. Letermovir for secondary prophylaxis of cytomegalovirus infection and disease after allogeneic hematopoietic cell transplantation: results from the French Compassionate Program. *Biol Blood Marrow Transplant*. 2020;26:978–984.
 65. Zamora D, Duke ER, Xie H, et al. Cytomegalovirus-specific T-cell reconstitution following letermovir prophylaxis after hematopoietic cell transplantation. *Blood*. 2021;138(1):34–43.

66. Baden LR, Swaminathan S, Angarone M, et al. Prevention and treatment of cancer-related infections, version 2.2016. NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016;14:882–913.
67. Winston DJ, Yeager AM, Chandrasekar PH, Snyderman DR, Petersen FB, Territo MC. Randomized comparison of oral valganciclovir and intravenous ganciclovir for prevention of cytomegalovirus disease after allogeneic bone marrow transplantation. *Clin Infect Dis*. 2003;36:749–758.
68. Goodrich JM, Bowden RA, Fisher L, Keller C, Schoch G, Meyers JD. Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. *Ann Intern Med*. 1993;118:173–178.
69. Winston DJ, Ho WG, Bartoni K, et al. Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients. Results of a placebo-controlled, double-blind trial. *Ann Intern Med*. 1993;118:179–184.
70. Boeckh M, Bowden RA, Gooley T, Myerson D, Corey L. Successful modification of a pp65 antigenemia-based early treatment strategy for prevention of cytomegalovirus disease in allogeneic marrow transplant recipients. *Blood*. 1999;93:1781–1782.
71. Pollack M, Heugel J, Xie H, et al. An international comparison of current strategies to prevent herpesvirus and fungal infections in hematopoietic cell transplant recipients. *Biol Blood Marrow Transplant*. 2011;17:664–673.
72. Bacigalupo A, Tedone E, Van Lint MT, et al. CMV prophylaxis with foscarnet in allogeneic bone marrow transplant recipients at high risk of developing CMV infections. *Bone Marrow Transplant*. 1994;13:783–788.
73. Bregante S, Bertelson S, Tedone E, et al. Foscarnet prophylaxis of cytomegalovirus infections in patients undergoing allogeneic bone marrow transplantation (BMT): a dose-finding study. *Bone Marrow Transplant*. 2000;26:23–29.
74. Reusser P, Gambertoglio JG, Lilleby K, Meyers JD. Phase I-II trial of foscarnet for prevention of cytomegalovirus infection in autologous and allogeneic marrow transplant recipients. *J Infect Dis*. 1992;166:473–479.
75. Bontant T, Sedlacek P, Balducci A, et al. Survey of CMV management in pediatric allogeneic HSCT programs, on behalf of the inborn errors, infectious diseases and pediatric diseases working parties of EBMT. *Bone Marrow Transplant*. 2014;49:276–279.
76. Fisher BT, Boge CLK, Dvorak C. A survey of pediatric bone marrow transplant centers regarding local cytomegalovirus prophylaxis management practices and interest in a future randomized trial. *ID Week Vol*. 2018;5. San Francisco, CA, USA: Open Forum Infectious Diseases S546–S547.
77. Meyers JD, Reed EC, Shepp DH, et al. Acyclovir for prevention of cytomegalovirus infection and disease after allogeneic marrow transplantation. *N Engl J Med*. 1988;318:70–75.
78. Prentice HG, Gluckman E, Powles RL, et al. Impact of long-term acyclovir on cytomegalovirus infection and survival after allogeneic bone marrow transplantation. European Acyclovir for CMV Prophylaxis Study Group. *Lancet*. 1994;343(8900):749–753.
79. Ljungman P, de La Camara R, Milpied N, et al. Randomized study of valganciclovir as prophylaxis against cytomegalovirus reactivation in recipients of allogeneic bone marrow transplants. *Blood*. 2002;99:3050–3056.
80. Chen K, Cheng MP, Hammond SP, Einsele H, Marty FM. Antiviral prophylaxis for cytomegalovirus infection in allogeneic hematopoietic cell transplantation. *Blood Adv*. 2018;2:2159–2175.
81. Milano F, Pergam SA, Xie H, et al. Intensive strategy to prevent CMV disease in seropositive umbilical cord blood transplant recipients. *Blood*. 2011;118:5689–5696.
82. Hill JA, Pergam SA, Cox E, et al. A modified intensive strategy to prevent cytomegalovirus disease in seropositive umbilical cord blood transplantation recipients. *Biol Blood Marrow Transplant*. 2018;24:2094–2100.
83. Allen CE, Marsh R, Dawson P, et al. Reduced-intensity conditioning for hematopoietic cell transplant for HLH and primary immune deficiencies. *Blood*. 2018;132:1438–1451.
84. Guilcher GMT, Truong TH, Saraf SL, Joseph JJ, Rondelli D, Hsieh MM. Curative therapies: allogeneic hematopoietic cell transplantation from matched related donors using myeloablative, reduced intensity, and nonmyeloablative conditioning in sickle cell disease. *Semin Hematol*. 2018;55:87–93.
85. Solano C, Gimenez E, Pinana JL, et al. Preemptive antiviral therapy for CMV infection in allogeneic stem cell transplant recipients guided by the viral doubling time in the blood. *Bone Marrow Transplant*. 2016;51:718–721.
86. Muñoz-Cobo B, Solano C, Costa E, et al. Dynamics of cytomegalovirus (CMV) plasma DNAemia in initial and recurrent episodes of active CMV infection in the allogeneic stem cell transplantation setting: implications for designing preemptive antiviral therapy strategies. *Biol Blood Marrow Transplant*. 2011;17:1602–1611.
87. Emery VC, Griffiths PD. Prediction of cytomegalovirus load and resistance patterns after antiviral chemotherapy. *Proc Natl Acad Sci U S A*. 2000;97:8039–8044.
88. Ayala E, Greene J, Sandin R, et al. Valganciclovir is safe and effective as pre-emptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2006;37:851–856.
89. Busca A, de Fabritiis P, Ghisetti V, et al. Oral valganciclovir as preemptive therapy for cytomegalovirus infection post allogeneic stem cell transplantation. *Transpl Infect Dis*. 2007;9:102–107.
90. van der Heiden PL, Kalpoe JS, Barge RM, Willemze R, Kroes AC, Schippers EF. Oral valganciclovir as pre-emptive therapy has similar efficacy on cytomegalovirus DNA load reduction as intravenous ganciclovir in allogeneic stem cell transplantation recipients. *Bone Marrow Transplant*. 2006;37:693–698.
91. Einsele H, Reusser P, Bornhauser M, et al. Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. *Blood*. 2006;107:3002–3008.
92. Salzberger B, Bowden RA, Hackman RC, Davis C, Boeckh M. Neutropenia in allogeneic marrow transplant recipients receiving ganciclovir for prevention of cytomegalovirus disease: risk factors and outcome. *Blood*. 1997;90:2502–2508.
93. Chakrabarti S, Collingham KE, Osman H, Fegan CD, Milligan DW. Cidofovir as primary pre-emptive therapy for post-transplant cytomegalovirus infections. *Bone Marrow Transplant*. 2001;28:879–881.
94. Kiehl MG, Basara N. Cidofovir for cytomegalovirus-preemptive therapy in stem cell transplant recipients. *Blood*. 2001;98:1626. author reply 1628.
95. Ljungman P, Deliliers GL, Platzbecker U, et al. Cidofovir for cytomegalovirus infection and disease in allogeneic stem cell transplant recipients. The Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Blood*. 2001;97:388–392.
96. Einsele H, Ehninger G, Hebart H, et al. Polymerase chain reaction monitoring reduces the incidence of cytomegalovirus disease and the duration and side effects of antiviral therapy after bone marrow transplantation. *Blood*. 1995;86:2815–2820.
97. Chemaly RF, Chou S, Einsele H, et al. Definitions of resistant and refractory cytomegalovirus infection and disease in transplant recipients for use in clinical trials. *Clin Infect Dis*. 2019;68:1420–1426.
98. Robin C, Hemery F, Dindorf C, et al. Economic burden of preemptive treatment of CMV infection after allogeneic stem cell transplantation: a retrospective study of 208 consecutive patients. *BMC Infect Dis*. 2017;17:747.
99. Servais S, Dumontier N, Biard L, et al. Response to antiviral therapy in haematopoietic stem cell transplant recipients with cytomegalovirus (CMV) reactivation according to the donor CMV serological status. *Clin Microbiol Infect*. 2016;22. 289 e1–7.
100. Boeckh M, Nichols WG, Chemaly RF, et al. Valganciclovir for the prevention of complications of late cytomegalovirus infection after allogeneic hematopoietic cell transplantation: a randomized trial. *Ann Intern Med*. 2015;162:1–10.
101. Einsele H, Hebart H, Kauffmann-Schneider C, et al. Risk factors for treatment failures in patients receiving PCR-based preemptive therapy for CMV infection. *Bone Marrow Transplant*. 2000;25:757–763.
102. Peggs KS, Preiser W, Kottaridis PD, et al. Extended routine polymerase chain reaction surveillance and pre-emptive antiviral therapy for cytomegalovirus after allogeneic transplantation. *Br J Haematol*. 2000;111:782–790.
103. Boeckh M, Leisenring W, Riddell SR, et al. Late cytomegalovirus disease and mortality in recipients of allogeneic hematopoietic stem cell transplants: importance of viral load and T-cell immunity. *Blood*. 2003;101:407–414.
104. Fries BC, Riddell SR, Kim HW, et al. Cytomegalovirus disease before hematopoietic cell transplantation as a risk for complications after transplantation. *Biol Blood Marrow Transplant*. 2005;11:136–148.
105. Hammerstrom AE, Lombardi LR, Pingali SR, et al. Prevention of cytomegalovirus reactivation in haploidentical stem cell transplantation. *Biol Blood Marrow Transplant*. 2018;24:353–358.
106. Verma A, Devine S, Morrow M, et al. Low incidence of CMV viremia and disease after allogeneic peripheral blood stem cell transplantation. Role of pretransplant ganciclovir and post-transplant acyclovir. *Bone Marrow Transplant*. 2003;31:813–816.
107. Kline J, Pollyea DA, Stock W, et al. Pre-transplant ganciclovir and post-transplant high-dose valganciclovir reduce CMV infections after alemtuzumab-based conditioning. *Bone Marrow Transplant*. 2006;37:307–310.
108. Bilgrami S, Aslanzadeh J, Feingold JM, et al. Cytomegalovirus viremia, viruria and disease after autologous peripheral blood stem cell transplantation: no need for surveillance. *Bone Marrow Transplant*. 1999;24:69–73.
109. Boeckh M, Stevens-Ayers T, Bowden RA, et al. Cytomegalovirus pp65 antigenemia after autologous marrow and peripheral blood stem cell transplantation. *J Infect Dis*. 1996;174:907–912.
110. Hebart H, Schroder A, Loffler J, et al. Cytomegalovirus monitoring by polymerase chain reaction of whole blood samples from patients undergoing autologous bone marrow or peripheral blood progenitor cell transplantation. *J Infect Dis*. 1997;175:1490–1493.
111. Kim JH, Goulston C, Sanders S, et al. Cytomegalovirus reactivation following autologous peripheral blood stem cell transplantation for multiple myeloma in the era of novel chemotherapeutics and tandem transplantation. *Biol Blood Marrow Transplant*. 2012;18:1753–1758.
112. Mengarelli A, Annibaldi O, Pimpinelli F, et al. Prospective surveillance vs clinically driven approach for CMV reactivation after autologous stem cell transplant. *J Infect*. 2016;72:265–268.
113. Rossini F, Terruzzi E, Cammarota S, et al. Cytomegalovirus infection after autologous stem cell transplantation: incidence and outcome in a group of patients undergoing a surveillance program. *Transpl Infect Dis*. 2005;7(3–4):122–125.

114. Holmberg LA, Boeckh M, Hooper H, et al. Increased incidence of cytomegalovirus disease after autologous CD34-selected peripheral blood stem cell transplantation. *Blood*. 1999;94:4029–4035.
115. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. *N Engl J Med*. 2018;378:35–47.
116. Styczynski J, Tridello G, Xhaard A, et al. Use of letermovir in off-label indications: Infectious Diseases Working Party of European Society of Blood and Marrow Transplantation retrospective study. *Bone Marrow Transplant*. 2021;56:1171–1179.
117. Chiereghin A, Belotti T, Borgatti EC, et al. Off-label use of letermovir as pre-emptive anti-cytomegalovirus therapy in a pediatric allogeneic peripheral blood stem cell transplant. *Infect Drug Resist*. 2021;14:1185–1190.
118. Kilgore JT, Becken B, Varga MG, et al. Use of letermovir for salvage therapy for resistant cytomegalovirus in a pediatric hematopoietic stem cell transplant recipient. *J Pediatric Infect Dis Soc*. 2020;9:486–489.
119. Strenger V, Sperl D, Kubesch K, et al. Letermovir in paediatric HSCT recipients. *J Antimicrob Chemother*. 2019;74:2820–2821.
120. Adler SP, Lewis N, Conlon A, et al. Phase 1 clinical trial of a conditionally replication-defective human cytomegalovirus (CMV) vaccine in CMV-seronegative subjects. *J Infect Dis*. 2019;220:411–419.
121. Maertens J, Cordonnier C, Jaksch P, et al. Maribavir for preemptive treatment of cytomegalovirus reactivation. *N Engl J Med*. 2019;381:1136–1147.
122. Chou S. Rapid in vitro evolution of human cytomegalovirus UL56 mutations that confer letermovir resistance. *Antimicrob Agents Chemother*. 2015;59:6588–6593.
123. Marty FM, Ljungman PT, Chemaly RF, et al. Outcomes of patients with detectable CMV DNA at randomization in the phase III trial of letermovir for the prevention of CMV infection in allogeneic hematopoietic cell transplantation. *Am J Transplant*. 2020;20:1703–1711.
124. Douglas CM, Barnard R, Holder D, et al. Letermovir resistance analysis in a clinical trial of cytomegalovirus prophylaxis for hematopoietic stem cell transplant recipients. *J Infect Dis*. 2020;221:1117–1126.
125. Egli A, Humar A, Kumar D, et al. State-of-the-art monitoring of cytomegalovirus-specific cell-mediated immunity after organ transplant: a primer for the clinician. *Clin Infect Dis*. 2012;55:1678–1689.
126. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33(9):e13512.
127. Chemaly RF, El Haddad L, Winston DJ, et al. Cytomegalovirus (CMV) cell-mediated immunity and cmv infection after allogeneic hematopoietic cell transplantation: the REACT Study. *Clin Infect Dis*. 2020;71:2365–2374.
128. El Haddad L, Ariza-Heredia E, Shah DP, et al. The ability of a cytomegalovirus ELISPOT assay to predict outcome of low-level CMV reactivation in hematopoietic cell transplant recipients. *J Infect Dis*. 2019;219:898–907.
129. Fleming T, Dunne J, Crowley B, et al. Ex vivo monitoring of human cytomegalovirus-specific CD8(+) T-Cell responses using the QuantiFERON-CMV assay in allogeneic hematopoietic stem cell transplant recipients attending an Irish hospital. *J Med Virol*. 2010;82:433–440.
130. Tey SK, Kennedy GA, Cromer D, et al. Clinical assessment of anti-viral CD8+ T cell immune monitoring using QuantiFERON-CMV(R) assay to identify high risk allogeneic hematopoietic stem cell transplant patients with CMV infection complications. *PLoS One*. 2013;8(10):e74744.
131. Avetisyan G, Aschan J, Hagglund H, Ringden O, Ljungman P. Evaluation of intervention strategy based on CMV-specific immune responses after allogeneic SCT. *Bone Marrow Transplant*. 2007;40:865–869.
132. Navarro D, Amat P, de la Camara R, et al. Efficacy and safety of a preemptive antiviral therapy strategy based on combined virological and immunological monitoring for active cytomegalovirus infection in allogeneic stem cell transplant recipients. *Open Forum Infect Dis*. 2016;3(2):ofw107.
133. Ljungman P, Bermudez A, Logan AC, et al. A randomised, placebo-controlled phase 3 study to evaluate the efficacy and safety of ASP0113, a DNA-based CMV vaccine, in seropositive allogeneic haematopoietic cell transplant recipients. *EclinicalMedicine*. 2021;33: 100787.
134. Liu Y, Freed DC, Li L, et al. A replication-defective human cytomegalovirus vaccine elicits humoral immune responses analogous to those with natural infection. *J Virol*. 2019;93(23): e00747-19.
135. Plotkin SA, Boppana SB. Vaccination against the human cytomegalovirus. *Vaccine*. 2019;37:7437–7442.
136. Wang D, Freed DC, He X, et al. A replication-defective human cytomegalovirus vaccine for prevention of congenital infection. *Sci Transl Med*. 2016;8(362): 362ra145.
137. Diamond DJ, La Rosa C, Chiuppesi F, et al. A fifty-year odyssey: prospects for a cytomegalovirus vaccine in transplant and congenital infection. *Expert Rev Vaccines*. 2018;17:889–911.
138. Aldoss I, La Rosa C, Baden LR, et al. Poxvirus vectored cytomegalovirus vaccine to prevent cytomegalovirus viremia in transplant recipients: a phase 2, randomized clinical trial. *Ann Intern Med*. 2020;172:306–316.
139. Nakamura R, La Rosa C, Longmate J, et al. Viraemia, immunogenicity, and survival outcomes of cytomegalovirus chimeric epitope vaccine supplemented with PF03512676 (CMV-PepVax) in allogeneic haematopoietic stem-cell transplantation: randomised phase 1b trial. *Lancet Haematol*. 2016;3(2):e87–e98.
140. Einsele H, Roosnek E, Rufer N, et al. Infusion of cytomegalovirus (CMV)-specific T cells for the treatment of CMV infection not responding to antiviral chemotherapy. *Blood*. 2002;99:3916–3922.
141. Feuchtinger T, Opher K, Bethge WA, et al. Adoptive transfer of pp65-specific T cells for the treatment of chemorefractory cytomegalovirus disease or reactivation after haploidentical and matched unrelated stem cell transplantation. *Blood*. 2010;116:4360–4367.
142. Pei XY, Zhao XY, Chang YJ, et al. Cytomegalovirus-specific T-cell transfer for refractory cytomegalovirus infection after haploidentical stem cell transplantation: the quantitative and qualitative immune recovery for cytomegalovirus. *J Infect Dis*. 2017;216:945–956.
143. Blyth E, Clancy L, Simms R, et al. Donor-derived CMV-specific T cells reduce the requirement for CMV-directed pharmacotherapy after allogeneic stem cell transplantation. *Blood*. 2013;121:3745–3758.
144. Mackinnon S, Thomson K, Verfuert S, Peggs K, Lowdell M. Adoptive cellular therapy for cytomegalovirus infection following allogeneic stem cell transplantation using virus-specific T cells. *Blood Cells Mol Dis*. 2008;40:63–67.
145. Micklethwaite K, Hansen A, Foster A, et al. Ex vivo expansion and prophylactic infusion of CMV-pp65 peptide-specific cytotoxic T-lymphocytes following allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2007;13:707–714.
146. Micklethwaite KP, Clancy L, Sandher U, et al. Prophylactic infusion of cytomegalovirus-specific cytotoxic T lymphocytes stimulated with Ad5F35pp65 gene-modified dendritic cells after allogeneic hemopoietic stem cell transplantation. *Blood*. 2008;112:3974–3981.
147. Peggs KS, Verfuert S, Pizzey A, et al. Adoptive cellular therapy for early cytomegalovirus infection after allogeneic stem-cell transplantation with virus-specific T-cell lines. *Lancet*. 2003;362(9393):1375–1377.
148. Leen AM, Bollard CM, Mendizabal AM, et al. Multicenter study of banked third-party virus-specific T cells to treat severe viral infections after hematopoietic stem cell transplantation. *Blood*. 2013;121:5113–5123.
149. Boeckh M, Corey L. Adoptive immunotherapy of viral infections: should infectious disease embrace cellular immunotherapy? *J Infect Dis*. 2017;216:926–928.
150. Schmidt-Hieber M, Labopin M, Beelen D, et al. CMV serostatus still has an important prognostic impact in de novo acute leukemia patients after allogeneic stem cell transplantation: a report from the Acute Leukemia Working Party of EBMT. *Blood*. 2013;122:3359–3364.
151. Ljungman P, Aschan J, Lewensohn-Fuchs I, et al. Results of different strategies for reducing cytomegalovirus-associated mortality in allogeneic stem cell transplant recipients. *Transplantation*. 1998;66:1330–1334.
152. Osarogiagbon RU, Defor TE, Weisdorf MA, Erice A, Weisdorf DJ. CMV antigenemia following bone marrow transplantation: risk factors and outcomes. *Biol Blood Marrow Transplant*. 2000;6:280–288.
153. George B, Kerridge IH, Gilroy N, et al. A risk score for early cytomegalovirus reactivation after allogeneic stem cell transplantation identifies low-, intermediate-, and high-risk groups: reactivation risk is increased by graft-versus-host disease only in the intermediate-risk group. *Transpl Infect Dis*. 2012;14:141–148.
154. Yoon HS, Lee JH, Choi ES, et al. Cytomegalovirus infection in children who underwent hematopoietic stem cell transplantation at a single center: a retrospective study of the risk factors. *Pediatr Transplant*. 2009;13:898–905.
155. Miller W, Flynn P, McCullough J, et al. Cytomegalovirus infection after bone marrow transplantation: an association with acute graft-v-host disease. *Blood*. 1986;67(4):1162–1167.
156. Cohen L, Yeshurun M, Shpilberg O, Ram R. Risk factors and prognostic scale for cytomegalovirus (CMV) infection in CMV-seropositive patients after allogeneic hematopoietic cell transplantation. *Transpl Infect Dis*. 2015;17:510–517.
157. Suarez-Lledo M, Martinez-Cibrian N, Gutierrez-Garcia G, et al. Deleterious effect of steroids on cytomegalovirus infection rate after allogeneic stem cell transplantation depends on pretransplant cytomegalovirus serostatus of donors and recipients. *Biol Blood Marrow Transplant*. 2018;24:2088–2093.
158. Watanabe M, Kanda J, Hishizawa M, Kondo T, Yamashita K, Takaori-Kondo A. Impact of cumulative steroid dose on infectious diseases after allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis*. 2019;21:e13049.
159. Aversa F, Terenzi A, Tabilio A, et al. Full haplotype-mismatched hematopoietic stem-cell transplantation: a phase II study in patients with acute leukemia at high risk of relapse. *J Clin Oncol*. 2005;23:3447–3454.
160. Bacigalupo A, Mordini N, Pitto A, et al. Transplantation of HLA-mismatched CD34+ selected cells in patients with advanced malignancies: severe immunodeficiency and related complications. *Br J Haematol*. 1997;98:760–766.
161. Chakrabarti S, Mackinnon S, Chopra R, et al. High incidence of cytomegalovirus infection after nonmyeloablative stem cell transplantation: potential role of Campath-1H in delaying immune reconstitution. *Blood*. 2002;99:4357–4363.

162. Chakrabarti S, Milligan DW, Brown J, et al. Influence of cytomegalovirus (CMV) sero-positivity on CMV infection, lymphocyte recovery and non-CMV infections following T-cell-depleted allogeneic stem cell transplantation: a comparison between two T-cell depletion regimens. *Bone Marrow Transplant.* 2004;33:197–204.
163. Matsuda Y, Hara J, Osugi Y, et al. Allogeneic peripheral stem cell transplantation using positively selected CD34+ cells from HLA-mismatched donors. *Bone Marrow Transplant.* 1998;21:355–360.
164. Schmidt-Hieber M, Schwarck S, Stroux A, et al. Immune reconstitution and cytomegalovirus infection after allogeneic stem cell transplantation: the important impact of in vivo T cell depletion. *Int J Hematol.* 2010;91:877–885.
165. Baker M, Wang H, Rowley SD, et al. Comparative outcomes after haploidentical or unrelated donor bone marrow or blood stem cell transplantation in adult patients with hematological malignancies. *Biol Blood Marrow Transplant.* 2016;22:2047–2055.
166. Crocchiolo R, Castagna L, Furst S, et al. The patient's CMV serological status affects clinical outcome after T-cell replete haplo-HSCT and post-transplant cyclophosphamide. *Bone Marrow Transplant.* 2016;51:1134–1136.
167. Goldsmith SR, Slade M, DiPersio JF, et al. Cytomegalovirus viremia, disease, and impact on relapse in T-cell replete peripheral blood haploidentical hematopoietic cell transplantation with post-transplant cyclophosphamide. *Haematologica.* 2016;101(11). e465–e8.
168. Raiola AM, Dominietto A, di Grazia C, et al. Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts. *Biol Blood Marrow Transplant.* 2014;20:1573–1579.
169. Raj RV, Hari P, Pasquini M, et al. Impact of haploidentical hematopoietic cell transplantation conditioning intensity on the incidence and severity of post-transplantation viral infections. *Bone Marrow Transplant.* 2016;51:1602–1604.
170. Slade M, Goldsmith S, Romee R, et al. Epidemiology of infections following haploidentical peripheral blood hematopoietic cell transplantation. *Transpl Infect Dis.* 2017;19(1):e12629.
171. Tischer J, Engel N, Fritsch S, et al. Virus infection in HLA-haploidentical hematopoietic stem cell transplantation: incidence in the context of immune recovery in two different transplantation settings. *Ann Hematol.* 2015;94:1677–1688.
172. Lin CH, Su YJ, Hsu CY, Wang PN, Teng CJ. Haploidentical allogeneic hematopoietic stem cell transplantation increases the risk of cytomegalovirus infection in adult patients with acute leukemia. *Transpl Infect Dis.* 2019;21(4):e13096.
173. Walker CM, van Burik JA, De For TE, Weisdorf DJ. Cytomegalovirus infection after allogeneic transplantation: comparison of cord blood with peripheral blood and marrow graft sources. *Biol Blood Marrow Transplant.* 2007;13:1106–1115.
174. Meesing A, Abraham RS, Razonable RR. Clinical correlation of cytomegalovirus infection with CMV-specific CD8+ T-cell immune competence score and lymphocyte subsets in solid organ transplant recipients. *Transplantation.* 2019;103:832–838.
175. Einsele H, Ehninger G, Steidle M, et al. Lymphocytopenia as an unfavorable prognostic factor in patients with cytomegalovirus infection after bone marrow transplantation. *Blood.* 1993;82: 1672–168.
176. Han XY. Epidemiologic analysis of reactivated cytomegalovirus antigenemia in patients with cancer. *J Clin Microbiol.* 2007;45:1126–1132.
177. Ciurea SO, Mulanovich V, Saliba RM, et al. Improved early outcomes using a T cell replete graft compared with T cell depleted haploidentical hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2012;18:1835–1844.
178. Boeckh M, Gooley TA, Myerson D, Cunningham T, Schoch G, Bowden RA. Cytomegalovirus pp65 antigenemia-guided early treatment with ganciclovir versus ganciclovir at engraftment after allogeneic marrow transplantation: a randomized double-blind study. *Blood.* 1996;88:4063–4071.

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 log ₁₀ 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].