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Guideline

American Society for Transplantation and Cellular Therapy Series #11: Updated Cytomegalovirus Guidelines in Hematopoietic Cell Transplant and Cellular Therapy Recipients

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A B S T R A C T

The Practice Guidelines Committee of the American Society of Transplantation and Cellular Therapy partnered with the society's Transplant Infectious Diseases Special Interest Group to update its previous infectious disease guidelines for the prevention and management of cytomegalovirus (CMV) infection and disease following hematopoietic cell transplantation (HCT). The two updates, published in 2021, focused on the prevention and management of CMV infection, respectively, including refractory and resistant CMV infections. To best serve clinical providers, each standalone topic in the infectious diseases series has been published in a concise format of frequently asked questions (FAQs). Adult and pediatric infectious diseases and HCT content experts developed the FAQs and the answers; recommendations were graded according to their strength (A-E) and the level of the supporting evidence (I-III). Several advances in CMV prevention and management since 2021 warranted an update to the original third and fourth topics in the series.

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This eleventh topic in the series focuses on new antiviral treatments for CMV, expanded indications of existing antiviral therapy for the prevention of CMV, and the treatment of CMV in special populations such as CAR T-cell therapy recipients and pediatric transplant recipients.

INTRODUCTION

The Practice Guidelines Committee of the American Society for Transplantation and Cellular Therapy partnered with the society's Transplant Infectious Disease Special Interest Group to develop 2 guidelines published in 2021 to assist transplant providers in preventing and managing CMV following HCT [2,3]. New data have recently emerged regarding antiviral agents and cellular therapy that subsequently impact the prevention and management of CMV following HCT. We propose updated guidelines to address some changes in our prior recommendations, such as CMV serology prior to transplant, the duration of prophylaxis for CMV infection with letermovir in adult and pediatric HCT recipients and the management of initial CMV and refractory and/or resistant (R/R) CMV infections with the newly approved antiviral agent maribavir. In addition, we discuss future areas of interest regarding CMV following chimeric antigen receptor (CAR) T-cell therapy, the use of cell-mediated immunity (CMI) to guide CMV therapy, and new CMV therapies being evaluated. No updates were made regarding the epidemiology of CMV, risk factors for CMV, management of a CMV-seropositive donor and CMV-negative recipient, and CMV surveillance following HCT. To best serve clinical providers, each topic is presented as a frequently asked question (FAQ). These recommendations were graded according to their strength (A-E) and the level of the supporting evidence (I-III) [1]. Consensus was attained by an expert panel of adult and pediatric infectious diseases experts, infectious diseases pharmacists and HCT content experts.

FAQ1. What antivirals Have Been Recently Approved for Treatment of CMV Infection or for Prophylaxis?

Since our original guidelines on CMV infection [2,3] were published, maribavir has been approved by the United States Food and Drug Administration (US-FDA) and recommended for the treatment of post-transplant R/R CMV infection or disease [4] in adult and pediatric (12 years or older and weighing at least 35 kg) transplant recipients *(A-I)*. In a phase 3 trial comparing the efficacy of maribavir with an investigator-assigned therapy in transplant recipients with R/R CMV infection and/or disease after transplant, maribavir was shown to have significantly greater viral clearance by week 8 that was maintained up to week 20 [4].

Maribavir should not be used in certain cases. Notably, maribavir and (val)ganciclovir, due to their mechanisms of action, are antagonistic and should not be used in combination [5] *(E-III)*. Also, maribavir has poor central nervous system penetration and should not be used in cases of suspected or confirmed CMV retinitis or encephalitis [6] *(E-III)*.

The US-FDA−approved indication for letermovir has been expanded to include prophylaxis for CMV infection for the first 200 days after HCT in patients at high risk of CMV infection (see *FAQ4*) and the use of its new dosage formulation, oral pellets, in pediatric HCT recipients (see *FAQ10* and *FAQ11*). Importantly, acyclovir-based prophylaxis for herpes simplex virus and herpes zoster virus is recommended for HCT recipients when needed due to the lack of in vitro activity of maribavir and letermovir against these 2 viruses *(A-I)*. Table 1 summarizes all anti-CMV agents currently approved by the US-FDA.

FAQ2. What are Potential Pitfalls in the Interpretation of Pre-HCT CMV Serology?

The CMV serostatus of the recipient is the strongest predictor of CMV infection post HCT [7−12]. HCT candidates should have CMV serology performed prior to conditioning regimen for transplantation (*A-I*). Accurate determination of recipient CMV serostatus is important for donor selection, CMV surveillance, and CMV prevention. Recent data showed that testing CMV serology after treatment of hematologic malignancies and prior to HCT may demonstrate either a false positive or false negative results due to passive transfer of CMV antibodies with blood products or loss of CMV antibodies due to therapies with B-cell depleting agents, respectively [13,14]. Checking CMV serology close to the diagnosis of hematologic malignancy is preferred for accurate

Table 1
Agents for the Treatment or Prevention of CMV Infection and Disease in Hematopoietic Cell Transplant Recipients

Agent	CMV Target	Route	Dose Per Treatment Indication[*]			Major Toxic Effects[‡]	Metabolism/ Transport Effects	Significant Drug Interactions	CMV Genes Involved in Resistance	Activity Against Other Herpes Viruses
			Prophylaxis	Induction[†]	Maintenance[†,§]					
Ganciclovir	DNA polymerase (UL54)	IV	NA	5 mg/kg bid	5 mg/kg/day	Cytopenias	Substrate: OAT1, OAT3	Maribavir[‖]	*UL97, UL54*	HSV1&2, HZV, HHV-6
Valganciclovir	UL54	Oral	NA	900 mg bid or 7 × BSA × GFR[¶] bid[#]	900 mg/day or 7 × BSA ×[¶] GFR/ day[#]	Same as ganciclovir	Substrate: OAT1, OAT3	Tenofovir, maribavir[‖]	*UL97, UL54*	HSV1&2, HZV, HHV-6
Foscarnet	UL54	IV	NA	90 mg/kg q 12 hrs or 60 mg/kg q 8 hours	90 mg/kg/day	Nephrotoxicity, electrolytes, wasting	None	None	*UL54*	HSV1&2, HZV, HHV-6
Cidofovir	UL54	IV	NA	5 mg/kg/week	5 mg/kg every other week	Nephrotoxicity, neutropenia, headache, uveitis/iritis, diarrhea, ocular hypotony	Substrate: OAT1, OAT3 Inhibitor: MPRP2	Tenofovir	*UL54*	HSV1&2, HZV, HHV-6
Letermovir	Terminase complex (UL 56/51/ 89)	IV, oral	480 mg/day[**]	NA	NA	Nausea	Inhibitor/inducer/ substrate: CYP3A4 Inducer: CYP2C9, 2C19 Inhibitor/substrate: P-gp	Cyclosporine, voriconazole, tacrolimus, sirolimus, statins, ergot alkaloids	*UL56*[††]	No
Maribavir	UL97 kinase	Oral	NA	400 mg bid[‡‡]	NA	Dysgeusia	Inhibitor/substrate: CYP3A4 Inhibitor: CYP3A4 Inhibitor: P-gp, BCRP	Cyclosporine, tacrolimus, sirolimus, (val)ganciclovir[‖]	*UL97*[§§]	No

Bid indicates twice daily; BSA, body surface area; GFR, glomerular filtration rate; HHV-6, human herpesvirus-6; hrs, hours; HSV, herpes simplex virus; IV, intravenous; NA, not approved (or not typically used for); q, every; HZV, herpes zoster virus.

[*] Agents may 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 a full listing of toxic effects, please refer to the Summary of Product Characteristics for each agent if available. The listed toxic effects exclude overlapping toxic effects with medications commonly used after HCT.

[§] Dosing may also be used for secondary prophylaxis.

[‖] Antagonistic mechanisms of action; these agents should not be used in combination.

[¶] Dose for adults $\geq$ 18 years old weighing $>$ 40 kg.

[#] Dose for pediatric patients $<$ 18 years old, up to a maximum of 900 mg per dose.

[**] Approved only for primary prophylaxis in adult and pediatric patients $\geq$ 6 months of age weighing $\geq$ 6 kg. Reduce dose to 240 mg/day if co-administered with cyclosporine. Dose is the same for primary and secondary prophylaxis. Pediatric dosing information is listed in Table 3.

[††] Mutations in *UL51* and *UL89* conferring reduced susceptibility to letermovir have been described *in vitro* but not in clinical use, to date [27].

[‡‡] Approved only for treatment of resistant/refractory CMV infection in adults and pediatric patients $\geq$ 12 years old who weigh $\geq$ 35 kg [36].

[§§] Mutations in *UL27* conferring reduced susceptibility to maribavir have been described in vitro and in a single instance in a clinical trial [2].

determination of the recipient CMV serostatus but it is often not feasible as most patients may have been treated prior to referral for HCT. In addition, when CMV serology is checked more than once pre-HCT, discordant results may occur and should be interpreted with caution. For example, the result of the first test obtained closer to the diagnosis of the hematologic malignancy and ideally prior to treatment initiation, is likely to reflect the recipient's proper CMV serostatus.

Testing CMV viral load by PCR prior to HCT is recommended in general as it may complement CMV risk stratification post transplantation [15] (*B-III*). Pre-emptive therapy prior to transplant should be determined on a case-by-case (*CIII*). On the other hand, insufficient data is available for routine PCR testing in CMV seronegative recipients.

FAQ3. Is There a Role for Maribavir in Preemptive Therapy (PET) for CMV Infection?

Currently, maribavir is not approved by the US-FDA as a first-line PET for CMV. In a randomized trial of maribavir (400 mg twice daily) versus valganciclovir (900 mg twice daily) for 8 weeks in HCT recipients experiencing a first episode of CMV infection requiring preemptive therapy, maribavir failed to reach the strict 7% noninferiority margin for CMV DNAemia clearance [16]. Resistance to maribavir developed more frequently and faster but later than resistance to valganciclovir during the 8-week period, and patients who developed maribavir resistance were treated successfully with other antivirals [17]. We do not recommend maribavir as a first-line agent for preemptive therapy for HCT recipients who are able to receive (val)ganciclovir or foscarnet *(D-III)*. However, maribavir could be considered in place of foscarnet or (val) ganciclovir for preemptive therapy in patients who developed toxic effects from, or intolerance to, (val)ganciclovir or foscarnet, or had renal impairment or myelosuppression prior to initiating CMV directed therapy *(C-III)*. Factors associated with potential suboptimal responses to maribavir, such as acute graft-versus-host disease, a high CMV viral load ($\geq$ 9100 IU/mL), the use of T-cell depletion, and a CMV D+/R- serostatus [16] should be considered prior to PET, and an infectious diseases consultation is advised *(B-II)*.

FAQ4. What is the Role of Letermovir for Prophylaxis for CMV Infection More Than 100 Days After HCT?

We recommend extending letermovir primary prophylaxis through day 200 after HCT for high-risk HCT recipients, including patients who received allografts from a mismatched or haploidentical donor, umbilical cord transplant, underwent T-cell depletion, or received systemic prednisone at a dosage higher than 1 mg/kg/day within 6 weeks of day 100 after HCT, based on the results of a recent phase 3 randomized placebo-controlled clinical trial [18] *(B-I)*. In this trial, CMV-seropositive HCT recipients receiving letermovir prophylaxis without clinically significant CMV infection (CS-CMVi) during the first 100 posttransplant days but who remained at high risk for later CMV events were randomized to continue receiving letermovir until day 200 or receive placebo [18]. HCT recipients who received letermovir had a significantly lower incidence of CS-CMVi by day 200 than those who received placebo; rates of CMV disease and mortality were similar in both arms. By week 48 following HCT, the incidence of CS-CMVi was similar in both arms.

If letermovir therapy cannot be extended more than 100 days after the transplant, we recommend continued CMV surveillance and initiation of preemptive therapy when appropriate [2] *(A-II)* or consideration of valganciclovir prophylaxis [19] *(C-II)*. Based on currently published data, extending the duration of letermovir prophylaxis beyond 200 days after HCT is not generally recommended *(D-III)*.

FAQ5. What is the Role of Letermovir for Secondary Prophylaxis After an Episode of CMV Infection?

Secondary prophylaxis for CMV infection, as previously defined, is the use of an antiviral agent to prevent recurrent CMV infection after treatment of CMV viremia or end organ disease [20]. Published data regarding secondary prophylaxis with letermovir in HCT recipients are limited to small retrospective studies [21−23]. The incidence of CS-CMVi in patients receiving secondary letermovir prophylaxis has ranged from 0% to 11% [21−24]. In a recent prospective observational study, the incidence of breakthrough CS-CMVi within 14 weeks of letermovir secondary prophylaxis was 11%; all events occurred among patients who underwent ex vivo T-cell−depleted HCT [9]. Thus, we recommend secondary prophylaxis in HCT recipients successfully treated for CS-CMVi who are at highrisk for recurrence even though the optimal duration of secondary prophylaxis with letermovir has not yet been determined *(C-II)*. Secondary prophylaxis with letermovir should not be initiated until the CMV viral load is low or undetectable owing to letermovir's low genetic barrier to resistance [21,25−27] *(C-II)*.

FAQ6. How do we define CS-CMVi, low-level CMV DNAemia, and CMV DNA blips, and what are the key considerations for management of low-level CMV DNAemia or CMV DNA blips while patients are receiving letermovir prophylaxis?

CS-CMVi is often defined by the initiation of antiviral preemptive therapy based on local institutional prespecified CMV viral load thresholds and/or by the occurrence of tissue invasive disease [12]; CMV viral loads below these thresholds are considered low-level DNAemia. CMV DNA blips are defined by an isolated positive polymerase chain reaction (PCR) test result preceded and followed by a negative or below the level of detection of the PCR test result, usually drawn 3 to 7 days apart based on the risk assessment of patients for CMV infections [28]. Solitary CMV DNA blips or intermittent low-level CMV DNAemia may occur in patients receiving letermovir prophylaxis; however, such findings may represent a false positive result due to assay variability or indicate transient low-level viral replication or a degradation of free-floating viral DNA (theoretically supported by the mechanism of action of letermovir) [29,30]. Left untreated, many of these cases of CMV DNA blips or intermittent low-level CMV DNAemia revert to undetectable levels [31,32]; as such, withholding PET and continuing letermovir may be appropriate *(C-II)*.

FAQ7. What are the Updated Definitions for CMV Infections Including R/R CMV Infections and Disease?

The consensus definitions for CMV infections and disease in transplant recipients, including R/R CMV infections, for use in clinical trials [33] were updated in 2024, and 2 key changes were made. The definitions of refractory and probable refractory CMV infection were combined as follows: CMV DNAemia that increases ($>1 \log_{10}$) or persists ($<1 \log_{10}$ increase or decrease) after at least 2 weeks of antiviral therapy. Probable CMV pneumonitis was defined as CMV DNA levels greater than 1000 IU/mL in bronchoalveolar lavage fluid without co-pathogens; CMV DNA levels less than 500 IU/mL are unlikely to be CMV pneumonitis in most clinical situations [34].

FAQ8. What are the Updated Recommendations for the Management of R/R CMV Infections?

The new treatment paradigm for R/R CMV infections includes maribavir based on results from recent randomized controlled trials [4,35] *(A-I)*. Genotypic testing is recommended when a R/R CMV infection is clinically suspected *(B-II)*, and the antiviral treatment should be modified while awaiting the genotypic testing results *(A-II)*. Genotypic testing should include the assessment of *UL97* mutations associated with (val)ganciclovir resistance; mutations in specific codons in *UL97* associated with only maribavir resistance or with cross-resistance to (val)ganciclovir; *UL54* mutations associated with foscarnet, (val)ganciclovir, and/or cidofovir resistance; and *UL56* or *UL89* mutations associated with letermovir resistance. Table 2 provides guidance on the treatment options for R/R CMV infections based on genotypic testing results.

Repeat genotypic testing is recommended in patients with breakthrough CMV DNAemia after initial successful treatment, as additional mutations can be selected in highly immunosuppressed patients, especially those receiving maribavir, as seen in two phase 3 trials [4,16,36]. For example, resistance to maribavir occurred in 25.6% of patients with R/R CMV infections in the SOLSTICE trial [4].

FAQ9. What is the Burden and Management of CMV Infection in CAR T-Cell Therapy Recipients?

The incidence of CMV DNAemia and CS-CMVi following CAR T-cell therapy has been reported to be as high as 33% and 11%, respectively [37–40]. CMV end-organ disease, including pneumonitis and retinitis, has occurred in approximately 3% of CAR T-cell therapy recipients [37,41]. Additionally, CS-CMVi following CAR T-cell therapy was associated with increased overall and nonrelapse mortality in a few studies [37,42]. Nevertheless, the definitions of CS-CMVi, the patients' underlying conditions, and/or the CAR T-cellular products used were not consistent in these studies.

The American Society of Transplantation and Cellular Therapy's best practice document recommended CMV surveillance in high-risk CAR T-cell recipients for 2 to 6 weeks after cellular infusion [43] *(B-II)*. Although a viral load threshold for the initiation of treatment has not yet been determined, prior studies have reported initiating treatment at viral loads from at least 500 IU/mL or 10,000 IU/mL [37,39,40], extrapolating from local institutional guidelines for allogeneic HCT recipients. The viral load threshold needed to initiate CMV infection treatment may be affected by the type of CAR T-cell therapy, complications after CAR T-cell therapy (eg, immune effector cell−associated neurotoxicity syndrome, cytokine release syndrome), the disease state before CAR T-cell therapy, and clinical concern for CMV end-organ disease [37,39,40,44]. Thus, CMV therapy

Table 2
Treatment Options for Resistant CMV Infections Based on Genotype Results

Resistance Genotype	Examples of Mutations	Recommendations
UL97 mutations conferring high-level resistance to ganciclovir*	A594V, H520Q, L595S, M460V	• Consider foscarnet or maribavir*
UL97 mutations conferring low-level resistance to ganciclovir*	M460I, C592G, L595W	• Consider maribavir or foscarnet† • Consider high-dose ganciclovir (dosing 7.5 mg/kg−10 mg/kg for 12 hours) as tolerated if CMV end-organ disease is not suspected
UL97 mutations conferring resistance to maribavir	T409M, H411Y, G343A, C480F	• Consider (val)ganciclovir if no mutations conferring cross-resistance are detected (eg, *UL97* mutations T409M and H411Y) • Consider foscarnet if the detected mutations confer cross-resistance to (val)ganciclovir (eg, *UL97* mutations C480F and F342Y)
UL54 mutations conferring resistance only to foscarnet	N495K, V715M, D588E	• Consider ganciclovir or maribavir
UL54 mutations conferring resistance to foscarnet and ganciclovir (with or without *UL97* mutations)	L776M, L802M, V787L	• Consider maribavir • Seek special access or trial participation for investigational agents or adjunct agents‡
UL54 mutations conferring resistance only to ganciclovir and cidofovir	D301N, K313E, K313N, N408D, N408K, I512T	• Consider foscarnet or maribavir • Seek special access or trial participation for investigational agents or adjunct agents‡
UL54 mutations conferring resistance to ganciclovir, foscarnet, and cidofovir	D588N, A834P, E756K	• Consider maribavir • Seek special access or trial participation for investigational agents or adjunct agents‡
UL56, *UL89*, and *UL51* mutations conferring resistance to letermovir	S229F, E237D, E237G	• Antiviral therapy with ganciclovir or foscarnet is appropriate if CS-CMVi is suspected, as no cross-resistance is expected with these 2 agents
Refractory CMV infection without known resistant mutations		• Optimize dosing of current antiviral therapy. Use an alternative antiviral agent if available • Reduce immunosuppression if feasible§ • Consider alternative immunosuppressive agents such as mTor inhibitors • Seek special access or trial participation for investigational agents or adjunct agents‡

CS-CMVi indicates clinically significant cytomegalovirus infection; CMV, cytomegalovirus; HSV, herpes simplex virus; mTOR, mammalian target of rapamycin.

* High- and low-level CMV resistance to ganciclovir is defined as mutations that confer 5-15x or 2-5x change in EC50 respectively.

† Consider reducing high CMV viral load prior to commencing maribavir if feasible. Maribavir does not have activity against herpes simplex nor herpes zoster viruses. Add appropriate prophylaxis as needed. Avoid maribavir for CMV retinitis or encephalitis.

‡ Investigational agents or special access agents can include third-party adoptive CMV T cells or intravenous brincidofovir. Additional adjunct therapies may include artesunate or leflunamide.

§ Reduction in immunosuppression can be considered in all scenarios regardless of resistance genotype, but in cases of refractory CMV, reduction of immunosuppression may play an important role, as host factors are potentially the primary drivers of the ongoing infection.

after CAR T-cell therapy should be delivered on a case-by-case basis *(B-III)*.

No primary prophylaxis treatment is currently recommended to prevent CMV infection in CAR T-cell therapy recipients *(D-III)*. Letermovir has been used for secondary prophylaxis in a limited number of patients following CAR T-cell therapy with no reports of recurrent CMV infection [45]. However, whether letermovir prophylaxis is associated with an overall survival benefit, as seen in HCT recipients, is unknown. To determine the survival benefit, as well as the efficacy, of letermovir for primary prophylaxis following CAR T-cell therapy, a National Cancer Institute–supported interventional trial (NCT06575374) is planned in patients with underlying lymphoma.

FAQ10. What is the Role of Primary Prophylaxis for CMV Infection in Pediatric Allogeneic HCT Recipients?

Given the safety profile of letermovir compared with (val)ganciclovir or foscarnet, we recommend letermovir prophylaxis for pediatric CMV-seropositive allogeneic HCT recipients, *(A-II)*. In pediatric CMV-seropositive patients in whom letermovir prophylaxis cannot be used, primary prophylaxis with (val)ganciclovir [19], or even high-dose acyclovir or valacyclovir [46], should be considered in select patients at high risk for CMV infections, such as cord blood transplant recipients, as described in previous guidelines [47,48] *(C-III)*. In the absence of primary prophylaxis, a pre-emptive strategy is recommended [47,48] *(A-II)*. Following US-FDA approval, letermovir's labeling was updated to include its new dosage formulation, oral pellets, and its use in pediatric HCT recipients 6 months or older who weigh at least 6 kg. These updates are supported by pharmacokinetic and safety data from a phase 2b multicenter open-label single-arm study that evaluated letermovir use in 63 children aged 2 months to less than 18 years [49–51]. Although this study did not assess efficacy of letermovir, it demonstrated that appropriate drug levels seen in adults were also attained in children, leading to US-FDA approval for the use of letermovir in pediatric HCT. Additionally, prior to its FDA approval, multiple retrospective single-center studies on letermovir for primary prophylaxis in pediatric HCT patients [52–56] showed that letermovir was safe in children and had a low incidence of CMV end-organ disease following prophylaxis.

Adult dosing recommendations are appropriate for adolescents aged 12 years to less than 18 years [33], and in this phase 2b study adolescents had a rate of CS-CMVi through week 24 (24%) [33] similar to that of adults (37.5%) [40]. Table 3 lists the dosing recommendations for pediatric HCT recipients. Importantly, pharmacokinetic data suggest letermovir dosage adjustment is needed when switching between oral and intravenous formulations to maintain a similar drug exposure only in children younger than age 12 years who weigh less than 30 kg, when letermovir is not co-administered with cyclosporine (based on the letermovir package insert). An oral pellet formulation in 20 mg and 120 mg strengths has been approved; once available, it will provide ease of administration in patients requiring doses less than 120 mg or those unable to swallow tablets. The oral pellets can be administered by mouth following mixing with soft food or via a nasogastric tube or gastrostomy tube [57]. There have been several reports of manipulating the oral tablet for administration via enteral feeding tubes; however, this administration method is not endorsed by the manufacturer [55,58,59].

FAQ11. What are the Key Considerations for Management of R/R CMV Infection in Pediatric HCT Recipients?

Published data on post-transplant antiviral resistance rates in children are scarce, and these resistance rates range from 4% with prospective monitoring up to 11.5%, as seen in 96 pediatric HCT recipients with T-cell depletion and CMV DNAemia levels greater than or equal to 400 copies/mL after the transplant [60–62]. The US-FDA indication of maribavir for the treatment of post-transplant R/R CMV infection includes pediatric patients 12 years or older who weigh at least 35 kg, mainly on the basis of pharmacokinetic and pharmacodynamic studies and the results of a landmark phase 3 randomized clinical trial (*FAQ1*), although no patients younger than 18 years were enrolled in this study [4,63]. A population pharmacokinetic modeling and simulation study was conducted to support utilizing the adult maribavir dosing for adolescents [63]. For patients 12 years and older who weigh at least 35 kg, standard maribavir dosing for R/R CMV infection was recommended *(A-I)*; for children younger than 12 years, maribavir use can be considered, but further data are required to inform appropriate dosing [64] *(C-III)*. To help determine such appropriate dosing, a phase 3 study of maribavir in pediatric HCT and solid organ transplant recipients is underway (NCT05319353). Since antiviral resistant mutations can occur in patients of any

Table 3
Letermovir Dosing Recommendations for Patients 6 Months to Younger Than 12 Years or Patients 12 Years or Older Who Weigh Less Than 30 kg

	Dose Without Cyclosporine		Dose With Cyclosporine	
Patient Weight	IV	PO	IV	PO
≥30 kg*	480 mg	480 mg	240 mg	240 mg
		1×480 mg tablet; 2×240 mg tablets; 4×120 mg packets of oral pellets		1×240 mg tablet; 2×120 mg packets of oral pellets
15 kg to <30 kg	120 mg†	240 mg	120 mg	120 mg
		1×240 mg tablet; 2×120 mg packets of oral pellets		1×120 mg packet of oral pellets
7.5 kg to <15 kg	60 mg†	120 mg	60 mg	60 mg
		1×120 mg packet of oral pellets		3×20 mg packets of oral pellets
6 kg to <7.5 kg	40 mg†	80 mg	40 mg	40 mg
		4×20 mg packets of oral pellets		2×20 mg packets of oral pellets

IV indicates intravenous; PO, by mouth.
* Letermovir dosing in pediatric patients less than 12 years of age and weighing ≥30 kg is equivalent to dosing for adult and pediatric patients 12 years or older weighing at least 30 kg.
† Dosage adjustment may be necessary for pediatric patients younger than 12 years and weighing less than 30 kg when switching between PO and IV formulations.

age, management of R/R CMV infection should follow the algorithm for all ages *(C-III)*.

FAQ12. What is the Role of CMV CMI Testing in Managing CMV Infections?

The use of CMV CMI testing to guide CMV infection management following HCT in clinical practice appears promising but has yet to be defined. With the scarcity of interventional trials investigating its utility, we currently recommend a case-by-case determination of the usefulness of CMI testing as an adjunct test to guide clinical management, based on available assays and institutional experience *(C-II)*.

CMV CMI is affected by clinical factors, such as the type of transplant, level of immunosuppression, use of corticosteroids, and/or presence of graft-versus-host disease [65−68]. An absent or low CMV CMI has been associated with CS-CMVi [69−71], progression from low-level CMV viremia to CS-CMVi, recurrent CMV infection in HCT recipients [72], and an increase in all-cause mortality [67]. In the largest series of HCT recipients who underwent CMV CMI monitoring using a peptide-based enzyme-linked immunospot for CMV, a low level of CMV CMI was associated with the onset of CS-CMVi within 2 weeks of measurement. Among solid organ transplant recipients, CMV CMI has been used to tailor the duration of prophylaxis in a limited number of cases [73]; however, this finding has yet to be replicated in HCT recipients. To determine the duration of letermovir prophylaxis—which has greatly reduced the overall incidence of CMV infections in HCT recipients [74,75]—a personalized approach with the knowledge of CMV CMI may be helpful. A recent study reported that HCT recipients with high CMV CMI following discontinuation of letermovir prophylaxis around 100 days post-HCT had a significantly lower incidence of late CS-CMV infection [71]. Interestingly, most patients with late CS-CMVi despite having high CMV CMI had a relative increase in their immunosuppression. In addition, testing for CMV CMI may determine whether it is necessary to treat low-level CMV DNAemia and whether secondary prophylaxis for CMV infection is required; interventional trials in HCT recipients are still lacking and are needed to confirm the clinical utility of CMV CMI in these clinical scenarios.

The current limitations of CMI testing include a lack of standardization, challenging access to commercially available assays, poor concordance across assays [68,76], a lack of validated cutoffs defining low or high CMV CMI (especially in the setting of prophylaxis for CMV infection), and the dynamic changes over time of the risk for CMV infection requiring serial monitoring [77]. Future interventional trials addressing these limitations are needed to better determine the clinical utility of CMV CMI testing in HCT recipients in varying circumstances.

FAQ13. What New Antiviral Agents and Vaccines for CMV Infection are Currently in Development?

Despite the ongoing need for safe and effective antiviral agents, limited compounds have been evaluated for the treatment of CMV infection in immunocompromised patients. Brincidofovir (a lipid conjugate of cidofovir) is active against CMV and has minimal organ toxicity, such as nephrotoxicity or myelotoxicity [78]. However, the development of an oral formulation of brincidofovir was halted due to dose-limiting gastrointestinal toxic effects observed in a randomized phase 3 trial of prophylaxis for CMV infection in allogenic HCT recipients [79]. The intravenous formulation of brincidofovir is being evaluated in a phase 2 open-label dose-escalation trial for the treatment of adenovirus infection in immunocompromised patients; the protocol was recently amended to include patients with CMV infection reactivation (NCT04706923). At the highest dosing level studied, 90% of patients have achieved adenovirus viremia clearance within 4 weeks of therapy [80].

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 [81]. Phase 2 clinical trials have been conducted for other vaccine candidates, including a replication-deficient viral vector (Triplex) [82] and a chimeric peptide-based vaccine [83]. The replication-deficient viral vector reduced the risk of a CMV event (defined as CMV DNAemia >1250 IU/mL, end-organ disease, or CMV DNAemia requiring antiviral therapy) by half in the first 100 days after HCT [82], whereas the chimeric peptide-based vaccine (PepVax) was highly immunogenic but did not meet its primary efficacy endpoint in the prevention of CMV infection and disease [83]. A phase 2 clinical trial of mRNA-1647 [84], an mRNA-based vaccine candidate, in CMV-seropositive allogenic HCT recipients is now enrolling (NCT05683457). Several other vaccine candidates are under evaluation [85−88].

FAQ14. What is the Role of Combination Therapy With New Antiviral Agents for the Treatment of CMV Infection?

The introduction of safe oral antiviral agents such as letermovir and maribavir has increased the possibility of combination therapy for the treatment for CMV infection. Some combination therapies may achieve faster viral clearance, manage difficult to treat CMV infections (including R/R CMV infection), and possibly reduce the risk of developing resistance in the setting of active replication [89,90]. Combination therapy with intravenous ganciclovir and foscarnet has been used previously, but their cumulative toxic effects were excessive [91].

Limited data exist on letermovir and (val)ganciclovir combination therapy for resistant CMV infections [92−95]. An ongoing single-center clinical trial is currently being conducted to better study this combination therapy (NCT06334497).

Options for combination therapy with maribavir are limited to foscarnet and letermovir owing to maribavir’s antagonism with (val)ganciclovir [96−98]. In vitro studies showed the additive interaction of maribavir with foscarnet, cidofovir, and letermovir [99]. However, clinical experience with such combination therapy is limited [100]. A short course of combination therapy with foscarnet and maribavir followed by maribavir monotherapy could be considered (potentially enhance the reduction of high or persistent CMV viral loads) in some patients with complicated R/R CMV infections *(C-III)* [98], and an infectious diseases consultation is highly recommended (*A-I*).

SUMMARY

In these updated guidelines for the prevention and management of CMV, we recommend maribavir for the treatment of R/R CMV, extending letermovir as primary prophylaxis up to 200 days after HCT in high-risk patients, and employing letermovir for secondary prophylaxis in specific circumstances. We discussed practice considerations surrounding low level CMV viremia and CMV viral blips while on CMV prophylaxis. Lastly, we included recommendations regarding testing for CMV cellular mediated immunity and for special patient populations such as CAR T cell therapy and pediatric HCT recipients. Our recommendations are summarized in Table 4.

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Table 4
Summary and Grading of Recommendations

Recommendations	Grade
Maribavir and R/R CMV infections (FAQ 1, 3, 7, 8 and 14)	
Maribavir is recommended for the treatment of post-transplant resistant or refractory CMV infection or disease in adult and pediatric (12 years or older and weighing at least 35 kg) transplant recipients	A-I
Maribavir and (val)ganciclovir are antagonistic and should not be used in combination	E-III
Maribavir has poor central nervous system penetration and should not be used in cases of suspected or confirmed CMV retinitis or encephalitis	E-III
Acyclovir-based prophylaxis for herpes simplex virus and herpes zoster virus is recommended during maribavir treatment due to lack of in vitro activity of maribavir against these 2 viruses	A-I
We do not recommend maribavir as a first-line agent for preemptive therapy for HCT recipients who are able to receive (val)ganciclovir or foscarnet. Maribavir could be considered for preemptive therapy in patients who have developed or are at risk of developing toxic effects or intolerance to (val)ganciclovir or foscarnet such as renal impairment or myelosuppression	D-III C-III
If maribavir is used as preemptive therapy for the treatment of CMV in patients with factors associated with suboptimal response, an infectious diseases consultation is advised.	B-II
Genotypic testing is recommended when a refractory or resistant CMV infection is clinically suspected	B-II
When a refractory or resistant CMV infection is clinically suspected, antiviral treatment should be modified while awaiting the testing results	A-II
A short course of combination therapy with foscarnet and maribavir followed by maribavir monotherapy could be considered (potentially enhance the reduction of high or persistent CMV viral loads) in some patients with complicated R/R CMV infections	C-III
CMV screening, prophylaxis and letermovir (FAQ 2, 4, 5, 6, and 13)	
HCT candidates should have CMV serology performed prior to conditioning regimen for transplantation. Ideally, CMV serology should be tested at the time of cancer diagnosis prior to blood or immunoglobulin transfusion, or immunosuppressive therapy.	A-I
CMV DNA qPCR can be checked prior to HCT to further risk stratify patients for CMV reactivation post transplantation.	B-III
We recommend extending letermovir primary prophylaxis through day 200 for high-risk HCT recipients. Acyclovir-based prophylaxis for herpes simplex virus and herpes zoster virus is also recommended while on letermovir due to lack of activity of letermovir against these 2 viruses.	B-I
If letermovir prophylaxis is not extended beyond day 100 for high-risk HCT recipients, we recommend continued CMV surveillance and initiation of preemptive therapy when appropriate.	A-II
If letermovir prophylaxis is not extended beyond day 100 for high-risk HCT recipients, prophylaxis with valganciclovir could be considered	C-II
Extending the duration of letermovir prophylaxis beyond day 200 is not generally recommended	D-III
We recommend secondary prophylaxis with letermovir in HCT recipients at high risk for recurrences when letermovir resistance is not suspected or documented. Secondary prophylaxis should be initiated when the CMV viral load is undetectable or low on consecutive measurements	C-II
Withholding PET and continuing letermovir may be appropriate in cases of intermittent low-level CMV DNAemia (blips) as they may revert to undetectable levels spontaneously	C-II
CAR T cell recipients and CMV (FAQ 9)	
CMV surveillance is recommended in high-risk CAR T-cell therapy recipients for 2 to 6 weeks after cellular infusion	B-II
CMV therapy after CAR T-cell therapy should be delivered on a case-by-case basis	B-III
No prophylaxis is currently recommended to prevent CMV infection in CAR T-cell therapy recipients	D-III
Pediatric HCT recipients and CMV (FAQ 10 and 11)	
We recommend letermovir prophylaxis for pediatric CMV-seropositive allogeneic HCT recipients	A-II
In pediatric CMV-seropositive allogeneic HCT recipients in whom letermovir prophylaxis cannot be used, primary prophylaxis with (val)ganciclovir or high-dose acyclovir or valacyclovir could be considered in patients at high risk for reactivation	C-III

(*continued*)

Table 4 (*Continued*)

Recommendations	Grade
In the absence of primary prophylaxis, pre-emptive strategy is recommended in pediatric CMV-seropositive allogeneic HCT	A-II
For patients 12 years and older who weigh at least 35 kg, standard maribavir dosing for R/R CMV infection is recommended.	A-I
For children younger than 12 years, maribavir can be considered, but further data are needed to inform appropriate dosing	C-III
Management of refractory or resistant CMV infection in children should follow the general recommendations for adult HCT recipients	C-III
Cell mediated immunity for CMV (FAQ 12)	
We currently recommend a case-by-case determination regarding the clinical usefulness of CMI testing using commercially available assays in patients currently receiving or who have received letermovir	C-II

CAR indicates chimeric antigen receptor; CMV, cytomegalovirus; CS-CMVi, clinically significant cytomegalovirus infection; HCT, hematopoietic cell transplant; PET, pre-emptive therapy.

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