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American Society of Transplantation and Cellular Therapy Series, #4: Cytomegalovirus Treatment and Management of Resistant or Refractory Infections after Hematopoietic Cell Transplantation

Q2 Michelle K. Yong[1,2,3,*], Terri Lynn Shigle[4], Yae-Jean Kim[5], Paul A. Carpenter[6], Roy F. Chemaly[7], Genovefa A. Papanicolaou[8]

[1] Department of Infectious Diseases, Peter MacCallum Cancer Center, Melbourne, Victoria, Australia
[2] Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Victoria, Australia
[3] Department of Infectious Diseases, Royal Melbourne Hospital, Melbourne, Victoria, Australia
[4] Division of Pharmacy, The University of MD Anderson Cancer Center, Houston, Texas
[5] Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[6] Clinical Research Division, Fred Hutchinson Cancer Research Centre, Seattle, Washington
[7] Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas
[8] Infectious Diseases Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York

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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 (ASTCT) partnered with its Transplant Infectious Disease Special Interest Group (TID-SIG) to update its 2009 compendium-style infectious disease guidelines for hematopoietic cell transplantation (HCT). A new approach was taken, with the goal of better serving clinical providers by publishing each standalone topic in the infectious diseases series as a concise format of frequently asked questions (FAQs), tables, and figures. Adult and pediatric infectious diseases and HCT content experts developed and answered these 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 fourth topic in the series focuses on the management and treatment of cytomegalovirus (CMV)-resistant/refractory (R/R) infections. The diagnosis, definitions of R/R CMV, risk factors, virologic genotypes, and treatment algorithms are reviewed.

INTRODUCTION

Cytomegalovirus (CMV) is the most common clinically significant viral infection after hematopoietic cell transplantation (HCT). Early detection of active CMV infection by sensitive molecular assays and preemptive therapy has mitigated the risk of CMV disease. In addition, CMV prevention with letermovir has reduced the incidence of CMV infections [1-3], yet the outcomes of resistant or refractory (R/R) CMV infection and disease remain poor. Current challenges include the limited number of available antivirals and their toxicities, as well as the lack of HCT-specific randomized trials to inform the choice of first-line antivirals and the duration of treatment. Other issues include delays in the timely diagnosis of R/R CMV infection and disease and indecision on how best to incorporate immune-based monitoring and alternative therapies into clinical practice. This guideline, in the form of frequently asked questions (FAQs), addresses current knowledge of and future directions for the management of R/R CMV infections.

*Corresponding author: Dr Michelle Yong, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, VIC 3000 Australia
E-mail address: Michelle.Yong@petermac.org (M.K. Yong).

FAQ1: HOW ARE R/R CMV INFECTION AND DISEASE DEFINED?

Refractory CMV infection is defined as a >1 $\log_{10}$ increase in CMV DNA levels in blood or plasma after at least 2 weeks of an appropriately dosed anti-CMV medication [4]. CMV DNA levels should be measured using the same assay and processed in the same laboratory [4]. Probable refractory CMV infection is defined as persistent CMV DNA in the blood or plasma at the same level or a <1 $\log_{10}$ increase after at least 2 weeks of an appropriately dosed anti-CMV medication [4]. Resistant CMV infection is defined as the presence of a known viral genetic mutation that decreases the susceptibility to 1 or more anti-CMV medications [4]. Refractory CMV disease is defined as the worsening of clinical signs and symptoms and/or progression to CMV end-organ disease after at least 2 weeks of appropriately dosed anti-CMV medication [4]. CMV disease is more frequent in the context of R/R CMV infection, but not all R/R CMV infections are associated with CMV disease [3,5].

FAQ2: WHAT ARE THE RISK FACTORS FOR R/R CMV INFECTION AND DISEASE?

These include haploidentical [5] and T cell-depleted HCT [6], previous exposure to anti-CMV therapy, prolonged

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exposure to anti-CMV medication in the presence of replicating virus, and prolonged treatment for CMV disease, particularly CMV encephalitis (Table 1) [7]. CMV resistance should be suspected when CMV viral load rises after virologic suppression; it typically occurs in the setting of immunosuppression; persistent or intermittent low-level CMV viremia; prolonged, subtherapeutic exposure to antivirals; and lack of immune reconstitution. Refractory CMV infection (24% to 39%) [8-10] is more common than resistant CMV infection (1.7% to 14.5%) [5,6,8,11]. CMV resistance is relatively uncommon after conventional T cell-replete HCT (1% to 5%) [12,13]. Risk factors for CMV disease and R/R CMV infection are similar, including prolonged CMV replication in the setting of poor immune status. The most frequent site of CMV disease is the gastrointestinal (GI) tract, followed less frequently by lungs (pneumonia) and, rarely, central nervous system (CNS) disease (retinitis, encephalitis) [2,14,15].

FAQ3: WHAT SIGNS AND SYMPTOMS OCCUR WITH R/R CMV INFECTION AND DISEASE, AND WHAT TESTS CAN AID THE DIAGNOSIS?

Signs and symptoms of R/R CMV infection and disease resemble those of wild-type CMV infection or disease and can be similar to those of graft-versus-host disease (GVHD) or other opportunistic infections (Table 2). Pursuing a biopsy to confirm CMV GI is recommended (A-II). When feasible, local fluid sampling (eg, bronchoalveolar lavage [BAL] fluid, cerebrospinal fluid [CSF], vitreous fluid) with dedicated resistance testing should be sent to inform the choice of antiviral agent **(B-III)** [7].

FAQ4: WHEN ARE PATIENTS AT GREATEST RISK FOR DEVELOPING R/R CMV INFECTION AND DISEASE AFTER HCT?

Resistant CMV typically occurs more than 2 to 4 months after the onset of CMV infection [6,11]. It is uncommon during the first 6 weeks post-HCT in patients not previously exposed to anti-CMV medications [5,16]. The index of suspicion for resistant CMV disease is high in anyone treated appropriately for extended courses, as with CMV encephalitis or retinitis, where subtherapeutic antiviral CNS penetration is likely [7,17]. Refractory CMV can occur at any time following HCT in the setting of relevant risk factors [3].

Table 1
Risk Factors for R/R CMV Infection or Disease

Category	Risk Factors
Transplant-related	HLA mismatch
	Haploidentical donor [5]
	Cord blood
	Pediatric HLA-mismatched donor [93]
	T cell-depleted transplant [6]
	CMV-seronegative donor
Viral-related	Persistent low-level CMV viremia
	High peak level CMV viremia [28]
	Recurrent episodes of CMV [11]
	CMV CNS disease (eg, retinitis, ventriculitis) [7,109, 110]
Drug-related	Subtherapeutic exposure to antivirals due to nonadherence, dose interruption, and/or adjustments due to renal impairment or dose- limiting toxicity
	Prolonged exposure to anti-CMV drugs in the presence of replicating virus [5,111]
Host-related	Lymphopenia
	Poor immune recovery
	GVHD

FAQ5: WHAT ARE THE CONSEQUENCES OF R/R CMV INFECTION OR DISEASE?

R/R CMV infections may be associated with CMV disease [6,10,18], prolonged use of antiviral medications [6], CMV-related mortality [6], increased risk of indirect effects of CMV, and increased nonrelapse mortality [10]. In T cell-depleted HCT, resistant CMV disease has a mortality rate of up to 42% [6]. Despite treatment with second- and third- line CMV antivirals, poor tolerability of these medications often results in fatal outcomes [19].

DIAGNOSTICS

FAQ6: What diagnostic tests are available to confirm resistant CMV?

Genotype assays are commonly used to confirm the presence of resistance-associated mutations (Table 3), and testing is recommended when CMV viral loads fail to decline by >1 $\log_{10}$ after more than 2 weeks of appropriately dosed antivirals (**A-III**). A plasma viral load ≥1000 IU/mL is recommended for genotype testing (**A-III**) [20]. When resistant CMV disease is suspected, we recommend testing the relevant compartment when feasible, because mutations may differ between plasma and various body compartments, such as vitreous fluids and CSF [7,21-23] (**A-III).**

In the setting of letermovir primary prophylaxis, consultation with an infectious disease specialist is recommended for guidance on resistance testing in the presence of CMV DNAemia <1000 IU/mL (**B-III**). Not all detectable low level DNAemia "blips" will be associated with detectable resistance mutations, but further data is required before a threshold level can be recommended. Letermovir resistance may emerge even with a relatively short duration of prophylaxis [24].

FAQ7: What is the clinical significance of quantitative CMV PCR testing of BAL specimens?

There is currently no established BAL viral load cutoff to diagnose CMV pneumonia. A low viral load may indicate asymptomatic pulmonary shedding, but the absence of CMV DNA from a BAL specimen is a good negative predictor of CMV pneumonia [25]. A high quantitative viral load in the context of compatible clinical picture and the right host may correlate with CMV pneumonia. Overall, quantitative BAL CMV PCR testing is recommended to help diagnose suspected CMV pneumonia (**A-II**) [25], but the opinion of an expert infectious diseases specialist is advised.

FAQ8: What is the clinical significance of a biopsy specimen that is negative for CMV viral inclusions or immunohistochemistry but positive for CMV by PCR?

Detectable CMV DNA in biopsy specimens is frequently observed in gastric and colonic tissue biopsy specimens and may represent specimen DNA contamination from blood. In the absence of corresponding histologic evidence, the presence of CMV DNA does not currently meet the criteria for proven CMV disease but is a criterion for possible disease in the context of compatible clinical presentation [26].

TREATMENT OF R/R CMV

FAQ9: How is anti-CMV therapy selected for treating R/R CMV infection?

We recommend that treatment of R/R CMV infection be provided in consultation with an infectious disease specialist

Table 2
Symptoms of and Diagnostic Approaches for CMV Infection and Disease

System	Site	Common Symptoms	Diagnostic Procedure	Specimen Type	Findings	Response to Treatment	Comment
Hematologic	Blood	Asymptomatic or fever, cytopenias,lethargy	Quantitative PCR, genotyping (see Table 3)	Whole blood or plasma	See Table 3	Serial blood viral load	High risk of CMV disease
Gastrointestinal	Colitis/ileitis	Diarrhea, abdominal pain, nausea and vomiting, anorexia, lower GI bleeding	Colonoscopy, sigmoidoscopy	Tissue	Macroscopic findings: presence of mucosal lesions Histology: viral inclusion bodies IHC: CMV stain positive	Symptom resolution, serial blood viral load if present	May occur in the absence of viremia
	Gastritis	Upper abdominal pain, nausea and vomiting, anorexia	Gastroscopy	Tissue	Histology: viral inclusion bodies IHC: CMV stain positive		
	Esophagitis	Retrosternal pain, Reflux, dysphagia, Odynophagia, nausea and vomiting	Gastroscopy	Tissue	Histology: viral inclusion bodies IHC: CMV stain positive		
	Hepatitis	Nausea and vomiting, anorexia, upper abdominal pain, abnormal LFTs	Liver biopsy	Liver tissue	Histology: viral inclusion bodies IHC: CMV stain positive	Symptom resolution, serial blood viral load	
Respiratory	Pneumonitis	Lung infiltrates, Fever, dyspnea, Hemoptysis	Bronchoscopy	Lung tissue BAL	Histology: viral inclusion bodies IHC: CMV stain positive BAL CMV: viral load high plus pulmonary infiltrates; possible CMV pneumonitis	Serial lung imaging, serial blood viral load	
CNS	Retinitis	Visual disturbance (blurred vision, scotomata, photopsia), vision loss, ocular pain. May be asymptomatic if peripheral retina is involved	Fundoscopy +/- anterior chamber paracentesis Genotyping as appropriate	Anterior chamber fluid Vitreous fluid	Retinal findings: areas of retinal whitening (necrosis); progressive opacity at the border of a lesion (centrifugal spread), distribution along the vascular arcades, Intra-retinal hemorrhage, vascular sheathing Fluid: detectable and quantitative CMV DNA level Histology: viral inclusion bodies IHC: CMV stain positive	Serial fundoscopy, symptom resolution, serial blood viral load (but may be absent)	High-risk R/R CMV, ophthalmology consult (early), early retinal photos
	Encephalitis	Headache, seizure, impaired cognition, memory disturbance, speech disturbance, focal neurologic symptoms	Lumbar puncture; brain MRI	CSF	Brain MRI: diffuse signal and/or temporal lobe abnormalities CSF: lymphocytic pleocytosis, elevated protein Fluid: detectable CMV DNA and quantitative level	Serial MRI, serial CSF viral load, serial blood viral load (may be absent)	High mortality, high-risk R/R CMV
	Ventriculitis	Headache, fever, impaired cognition, seizure	Lumbar puncture; brain MRI	CSF	Brain MRI: periventricular subependymal abnormalities CSF: lymphocytic pleocytosis, elevated protein Fluid: detectable CMV DNA and quantitative level	Serial MRI, serial CSF viral load, serial blood viral load (may be absent)	High mortality High risk R/R CMV

IHC indicates immunohistochemistry; LFTs, liver function tests; MRI, magnetic resonance imaging.
Note that all these symptoms also can apply to R/R CMV.

Table 3
Diagnostic Testing for CMV Resistance

Diagnostic Method	Comments
Genotype for known mutations associated with phenotypic resistance [112]	Genotypic assays most frequently performed on UL97, UL54, and UL56 Rapid turnaround time Performed directly on clinical specimens such as blood, fluid, CSF, and tissue Ideally requires a plasma CMV viral load ≥1000 IU/mL for testing [20] Send for genotype for viral load breakthrough while on letermovir, but consult ID specialist when viral load is <1000 IU/mL* Resistant subpopulations at low frequencies (<25%) might not be detected Detects only established resistance mutations
Phenotype plaque reduction assays [113] (research setting)	Not readily available clinically Labor-intensive (months) Poor reproducibility
Whole genome sequencing [114,115] (research setting)	Not readily available clinically Performed directly in blood, fluid, or tissue Detects uncommon mutations

* Identification of UL56 letermovir resistance requires a minimum viral load of 100 IU/mL [116].

(**A-III**). Antiviral selection is individualized (Table 4) based on a combination of known or suspected resistance genotype mutations (Table 5), previous drug exposure, and an acceptable toxicity profile. On clinical suspicion of CMV resistance, we recommend switching drug class, confirming genotypic resistance mutations, and reducing immunosuppression if feasible (**A-II**) [27]. Ganciclovir is the medication most commonly affected by CMV resistance due to UL97 phosphotransferase mutations [28]. If high-level UL97 resistance mutations are detected (>5-fold increase in ganciclovir IC_{50}), we recommend a switch to foscarnet (**B-III**). However, certain low-level UL97 resistance mutations (eg, M460I, C592G, L595W) are usually manageable with higher-dose ganciclovir (7.5 to 10 mg/kg every 12 hours) (**B-III**) [27]. Preemptive filgrastim therapy may mitigate myelosuppression from high-dose ganciclovir dosing (**B-I**) [29].

Mutations involving the UL54 polymerase may indicate foscarnet resistance or cross-resistance to ganciclovir, foscarnet, and cidofovir [28]. Management depends on the mutations detected, and treatment options are limited (Table 4). When possible, special access or clinical trials for investigational antiviral agents should be sought (**C-II**). Maribavir and third-party adoptive CMV T cells (FAQ19) have shown benefit in R/R CMV [30,31].

In a recent randomized trial, maribavir was found to be more effective and safer than investigator-assigned treatment for R/R CMV (viral clearance at 8 weeks, 55.7% versus 23.9%; $P < .001$) [30]. Maribavir is yet to receive Food and Drug Administration (FDA)/European Medicines Agency (EMA) approval and is available only through an early access program.

There are insufficient available data to recommend using letermovir monotherapy in R/R CMV infection owing to a concern for a low threshold for rapidly developing resistance mutations, particularly when treating CNS disease (**D-III**) [32]. Limited data suggest that therapy with letermovir alone or in combination may achieve virologic suppression if the viral load is <1000 IU/mL, but results have been mixed when letermovir was initiated at higher viral loads [32,33]. Further studies on combination therapy or alternative letermovir dosing are needed to support a recommendation. New resistance mutations are being identified with increasing use of letermovir [24,34-37] and maribavir [38].

Developing a standardized approach is challenging, given that individual host factors in conjunction with antiviral resistance affect outcomes and current treatment options are limited. Current guidelines are based largely on retrospective cohort studies and expert opinion [27,28].

Table 4
Recommended Guide to the Use of Approved and Investigational Anti-CMV Agents in Resistant/ Refractory CMV [27]

Resistance Genotype (see Table 5)	Recommendations
UL97 mutations with high-level resistance to ganciclovir	Switch to foscarnet as first-line option Switch to cidofovir as second-line option If unacceptable drug toxicity occurs, seek special access or trial participation for investigational agents*
UL97 mutations with low-level resistance to ganciclovir (M460I, C592G, L595W)	High-dose ganciclovir dosing, 7.5-10 mg/kg every 12 h as tolerated if CMV disease not present Switch to foscarnet or cidofovir as the next option If unacceptable drug toxicity occurs, seek special access or trial participation for investigational agents*
UL54 mutations conferring resistance to foscarnet and ganciclovir (± UL97 mutations)	Switch to cidofovir as first-line option Consider adding alternative agents such as leflunomide, artesunate Seek special access or trial participation for investigational agents*, including third-party CMV T cells
UL54 mutations conferring resistance to ganciclovir and cidofovir only	Continue foscarnet as first-line option May consider adding adjunct agents such as leflunomide, artesunate Seek special access or trial participation for investigational agents*, including third-party CMV T cells
UL54 mutations conferring resistance to foscarnet only	Stop foscarnet and start ganciclovir standard dose, 5 mg/kg every 12 h May consider adding adjunct therapy, such as leflunomide or artesunate
UL54 mutations conferring resistance to ganciclovir, foscarnet, and cidofovir	Continue foscarnet and add high-dose ganciclovir, 7.5-10 mg/kg every 12 h as tolerated Consider G-CSF support with high-dose ganciclovir use Consider adding alternative agents, such as leflunomide or artesunate Maribavir through early access or trial participation for investigational agents*,† including third-party CMV T cells
UL56, UL89, or UL51 conferring resistance to letermovir	Switch to ganciclovir or foscarnet as first-line option
Refractory CMV without known resistant mutations	Optimize dosing of current ganciclovir as appropriate Switch to foscarnet as next-line option Maribavir through early access or trial participation for investigational agents*,†

* Investigational agents: maribavir, filociclovir, third-party adoptive CMV T -cells.

† XXXXX

Table 5
Clinically Relevant Mutations Conferring Resistance to Current Antivirals

CMV Gene	Mutation	Ganciclovir/Valganciclovir	Foscarnet	Cidofovir	Letermovir	Maribavir
UL97	*__M460I/V__	R	S	S		
	*__H520Q__	R	S	S		
	*__C592G__	R	S	S		
	*__A594V__/T	R	S	S		
	*__L595S__/F/W	R	S	S		
	*__C603W__/R/S	R	S	S		
	F342Y, V466G, P521L,C480F	R				R
	V353A T409M					R
	L397R H411Y/N					R
UL54	N495K V715M		R			
	D588E E756D		R			
	T700A T838A	R	R			
	L776M L802M	R	R			
	V7811I/L	R	R			
	A809V T8211	R	R			
	D301N K513E	R		R		
	N408D N410K	R		R		
	L516R I512T	R		R		
	F412C P522A/S	R		R		
	D413A L545S	R		R		
	L501I A987G	R		R		
	D588N A834P	R	R	R		
	E756K G841A	R	R	R		
	V812 T813	R	R	R		
UL56	C325F*/Y* C325R*/W*				R	
	V231L V236M				R	
	S229F L257F				R	
	F261L N368D				R	
	E237D R369M				R	
	L354F C347S				R	
UL51	P91S				R†	
UL89	D334E				R	
UL27	R233S A406V					R
	C415 W326R					R

The most common UL97 genetic mutations are in bold type.

Q6 * A more exhaustive list of mutations can be found in Chou S. 2020 [112]. For the increase in drug concentration required to reduce viral growth by 50% (EC50) compared with wild type for each mutation, refer to Lurain NS, Chou S *Clin Microbiol Rev*. 2010 [117].

† Indicates in vitro resistance.

FAQ10: What is the role of antiviral combinations or mechanistic target of rapamycin (mTOR)-based immunosuppression in treating R/R CMV infection and disease?

Combination therapy generally is not recommended, owing to the absence of data on efficacy and the additive risk of nephrotoxicity and myelotoxicity (**D-III**). Case reports and case series have reported variable clinical success in unique circumstances [39,40].

Although the conversion of calcineurin to mTOR inhibitor-based immunosuppression may provide anti-CMV activity [41,42] based on clinical experience observed in solid organ transplant recipients [43,44], this approach is uncommon in HCT and has not been studied.

FAQ11: What is the role of adjunct intravenous immunoglobulin (IVIG) in managing CMV disease or R/R CMV infection?

IVIG use remains controversial, because no mortality benefit has been observed compared with anti-CMV medications alone [45,46]. Evidence for a potential benefit of IVIG in treating CMV pneumonitis is weak (**C-II**) [47], and IVIG is not recommended for CMV GI disease [48] (**D-II**) or R/R CMV (**D-III**). CMV-specific IVIG also is not recommended owing to a lack of clinical benefit **(D-II)** [46,47,49,50].

FAQ12: What is the role of adjunct leflunomide or artesunate therapy in managing R/R CMV infection or disease?

Leflunomide and artesunate are considered optional adjunctive therapies for R/R CMV if access to a clinical trial or early access program is not possible (Table 4) (**C-III**). Leflunomide as a potential anti-CMV therapy in HCT [51,52] has had variable clinical success in limited case reports/series when typically used in combination with other anti-CMV medications [27,53-59]. Artesunate also has demonstrated in vitro anti-CMV activity [60] but has shown limited success [61], as well as failure [59,62,63], in case reports.

FAQ13: What is the recommended treatment duration for R/R CMV infection or disease?

At least 2 to 4 weeks of optimally selected and dosed anti-CMV medication, guided clinically by resolution of disease

symptoms and aimed at achieving undetectable CMV viremia, if present, on at least 2 consecutive assays (**B-II**). Management of CMV retinitis or encephalitis should be guided by infectious disease, ophthalmology, or neurology experts (**A-III**).

FAQ14: What is meant by primary and secondary CMV prophylaxis? What agents can be used as secondary prophylaxis?

Primary prophylaxis refers to the initiation of an antiviral medication such as letermovir before any clinical or laboratory evidence of CMV is present. Secondary CMV prophylaxis, traditionally known as maintenance, involves starting an antiviral medication after successful completion of CMV preemptive or disease treatment to prevent recurrent infection. Secondary prophylaxis should be initiated when the viral load is undetectable or when the load is quantifiable but below the predefined lower limit of detection and when risk factors for recurrent CMV remain, including inadequate CMV-specific immune responses [64], concurrent infection, and/or GVHD requiring further immunosuppression. Ideally, orally administered agents such as valganciclovir or letermovir should be prescribed [1,65] (**B-II**). Owing to insufficient data, letermovir cannot be recommended for secondary prophylaxis in R/R infections. If an oral agent is infeasible, i.v. ganciclovir (**B-II**) or foscarnet can be given, taking the resistance profile into consideration (**C-III**).

FAQ15: Can the same antiviral agent be used as secondary prophylaxis in a patient with prior documented CMV resistance mutations?

It depends on whether a resistance mutation specifically affects the ability of the virus to replicate. For example, canonical mutations in UL97 that confer ganciclovir resistance can persist indefinitely and be selected on reintroduction of the inciting antiviral(s) [66]. Mutations that affect viral replication may not persist, and sometimes the affected anti-CMV agent can be used for secondary prophylaxis after the R/R CMV is controlled (**C-III**).

MANAGEMENT OF SIDE EFFECTS

FAQ16: How do I manage acute kidney injury during therapy with CMV antivirals?

Frequent dose adjustments are often required for (val)ganciclovir, foscarnet, and cidofovir (Supplementary Table S1) and may be necessary for other potentially nephrotoxic medications (eg, calcineurin inhibitors). Acute renal impairment during preemptive CMV therapy within 100 days post-HCT has been observed in 13% of patients on val(ganciclovir) and 34% of those on foscarnet [67]. In resistant CMV, a 51% incidence of renal dysfunction has been reported with foscarnet despite preventive measures such as i.v. hydration [19].

FAQ17: What if treatment-related neutropenia occurs?

Dosage reduction is not recommended in the setting of active CMV infection owing to the risk of developing resistance (**D-III),** but the use of G-CSF [29,68] (**B-I**), switching from val (ganciclovir) to foscarnet, and/or temporary withholding of not immediately essential other myelosuppressive medications are common practices to mitigate or manage myelosuppression. Substitution of concomitant myelosuppressive medications, including mycophenolate mofetil and trimethoprim/sulfamethoxazole, should be considered (**C-III**). Management of neutropenia is frequently needed, given that it has been reported in up to 57% of patients on (val)ganciclovir [69,70] (Supplementary Table S2 [67]).

Risk factors for severe neutropenia, defined as an absolute neutrophil count (ANC) <500, include a high viral load, a low pretreatment ANC, and serum creatinine >2 mg/dL [67,69,70].

FAQ18: What is the role of (val)ganciclovir therapeutic drug monitoring (TDM)?

There is insufficient evidence to recommend routine TDM of (val)ganciclovir (**D-III**), and it is not readily available, at least in the United States [71,72]. Although routine TDM may detect under or overdosing of ganciclovir, trough and peak plasma concentration levels do not correlate with clinical efficacy [73,74], myelotoxicity [74], or a change in the incidence of R/R CMV infections. Further studies are needed to assess the potential utility of TDM in young children or in other clinical settings.

ADOPTIVE CMV T CELL IMMUNOTHERAPY

FAQ19: What is the role of adoptive T cell immunotherapy in R/R CMV management?

Restoration of CMV-specific immunity through the infusion of third-party adoptive CMV-specific T cells (CTLs) is a promising approach and should be considered for managing R/R CMV infections and disease when feasible (**C-II**) [31,75-77]. The safety and efficacy of donor-derived or third-party CMV-specific CTLs has been demonstrated in nonrandomized clinical studies, with clinical and viral response rates of 74% to 93% reported (Supplementary Table S3) [31,75,78]. Major hurdles limiting the broad applicability of CMV-specific CTLs include access, timing, cost, and unknown efficacy in the setting of high-dose steroids, given that >0.5 mg/kg/day prednisolone (or equivalent) was an exclusion criterion in these studies [31,75]. Third-party viral specific T cell banks are currently being established to mitigate access limitations [79,80].

SPECIAL POPULATIONS

FAQ20: What are key considerations for CMV management in children after HCT?

- Children are more likely than adults to be CMV-seronegative at HCT and may have a higher chance of experiencing primary CMV infection than reactivation [81,82].
- Caution is needed when assigning pre-HCT CMV seropositivity in infants, because IgG positivity may represent persistence of passively transferred maternal antibodies [83,84].
- Breast milk from CMV-seropositive mothers commonly tests positive (40%) intermittently for CMV and infects approximately two-thirds of exposed infants around birth, but healthy term infants rarely develop symptomatic disease from this source [85,86]. Breastfeeding recommendations vary among centers that treat patients with severe combined immunodeficiency (SCID), with the most common (48%) recommendation to restrict breastfeeding to CMV-seronegative mothers (**B-III**) [87]. Future large studies proposed by the Primary Immune Deficiency Treatment Consortium in the United States are needed to answer whether this is the best approach [88,89].
- In the era before newborn SCID screening, one study found that 7% of infants with SCID were diagnosed with CMV infection [90]. CMV disease in patients with SCID is often fatal, may require prolonged antiviral treatment, and is associated with a higher risk for developing antiviral resistance [91].

- Diagnosing CMV disease in young children is challenging, because they may not express organ-specific symptoms such as headache with CMV encephalitis, vision loss with CMV retinitis, or chest or abdominal pain with CMV esophagitis or enterocolitis. Careful observation and broad diagnostic evaluation are necessary to diagnose CMV disease in an irritable child with possible signs and symptoms.
- In children of all ages, the recommendations for CMV monitoring and treatment should be followed [92]. Data are limited, but one study reported that approximately 4% of children developed antiviral resistance after 2 months of prolonged antiviral therapy [93]. Because antiviral resistant mutations can occur in patients of any age, management of R/R CMV infection should follow the algorithm for all ages. Ganciclovir TDM may be considered in young children post-HCT (**C-III**). Although letermovir prophylaxis is available for adults, it has not been approved for children age <18 years. A clinical trial in pediatric patients ranging from neonates to adolescents (<18 years) is currently underway to evaluate pharmacokinetics (ClinicalTrials.gov identifier NCT03940586).

FAQ21: What are the main differences in CMV management for recipients of T cell- depleted, cord blood, or haploidentical donor allografts?

There is a lack donor-derived CMV-specific T cells in recipients of T cell-depleted grafts owing to deliberate removal of viral-specific T cells and in recipients of cord blood grafts via inherent T cell naivety [5,6]. Recipients of haploidentical HCT are at elevated risk of CMV-related complications, including CMV disease and R/R CMV infection [5,94]. Treatment of CMV is similar to that in patients who receive other graft sources, but we recommend increased clinical vigilance for R/R CMV infection and disease, such as more frequent and longer duration of CMV monitoring and prophylaxis, a lower viral load threshold for initiation of preemptive therapy, and higher clinical suspicion for workup of CMV disease (**A-II**) [94,95].

FAQ22: What is the risk of CMV-related complications after immunotherapy with chimeric antigen receptor-modified T cells (CAR T cell therapy)?

Retrospective studies have reported a low incidence of CMV infections after CAR T cell therapy in which routine CMV monitoring was not used [96-99]. CMV infection contributed to 6% of all infectious events in both the early and late periods following CAR T cell infusion [96]. Larger prospective studies with routine CMV monitoring are needed to evaluate the risk of CMV by underlying disease, prior chemotherapies, type of CAR T cell infusion, and the presence of cytokine release syndrome. Currently, there are insufficient data to recommend routine CMV viral load monitoring and/or CMV prophylaxis in CAR T cell recipients (**D-II**). Active CMV infection diagnosed before CAR T cell infusion should be treated (**B-III**), with consideration given to secondary prophylaxis postinfusion (**C-III**) [100-102].

UNMET NEEDS AND FUTURE DIRECTIONS

FAQ23: What will be the impact of letermovir prophylaxis in the first 100 days post-HCT on timing of R/R CMV and tissue invasive disease?

Previous studies of ganciclovir primary prophylaxis have reported late-onset CMV complications associated with worse patient outcomes [103], perhaps related to delayed diagnosis, less frequent monitoring, and less contact with specialists for post-transplantation care. The use of letermovir has led to less clinically significant CMV viremia during prophylaxis [2]. Risk factors for late CMV reactivation after discontinuation of prophylaxis include GVHD, high dose-corticosteroids, cord blood or T cell-depleted allografts, and mismatched or haploidentical donors [104]. A phase 3 study is currently underway to assess whether these high-risk patients would benefit from extending prophylaxis to 6 months post-HCT (ClinicaTrials.gov identifier NCT03930615). By allowing CMV antigen presentation, letermovir may promote CMV immune reconstitution even without clinically significant viremia [105], unlike ganciclovir, which inhibits DNA replication. R/R CMV and tissue-invasive CMV disease were uncommon in the letermovir clinical trial [2]. Similarly, real-world data have shown an 85% reduction in R/R CMV with the use of primary letermovir prophylaxis [3].

FAQ24: What CMV antivirals are currently in development?

Maribavir, a benzimidazole riboside, is active against CMV, including strains resistant to ganciclovir or foscarnet [106]. In a phase 3 randomized trial of maribavir 400 mg orally twice daily versus investigator-assigned therapy for the treatment of R/R CMV, among HCT recipients, 55.9% in the maribavir arm achieved clearance of CMV viremia by week 8, compared with 20.8% in the investigator-assigned therapy arm ($P < .001$) [30]. No new safety concerns were identified among the maribavir-treated patients, who otherwise had a lower rate of renal impairment compared with the foscarnet-treated patients and a lower rates of neutropenia compared with those treated with val(ganciclovir) [30]. Maribavir is an effective and well-tolerated orally administered anti-CMV medication for the treatment of R/R CMV infection but is yet to receive FDA/EMA approval (**B-I**) (this grading may change in the future if FDA approval is granted). Because maribavir does not adequately penetrate the CNS, it should not be used for treatment of CMV encephalitis or retinitis (**D-II**). A low index of suspicion for workup of CNS disease is recommended for patients receiving maribavir.

Filociclovir (cyclopropavir, MBX-400) is another nucleoside analog currently under phase 1b evaluation for CMV and adenovirus activity, including activity against in vitro CMV-resistant viral strains [61,107]. Finally, a single-institution phase 2 study of letermovir use for R/R CMV infections is currently enrolling patients (ClinicalTrials.gov identifier NCT03728426).

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2021.09.010.

APPENDIX 1. GRADING OF STRENGTH OF RECOMMENDATIONS AND LEVEL OF EVIDENCE

FAQs 3 to 8: Diagnostics

Question	Grade*	Supporting References
Should tissue biopsy be performed to confirm CMV GI disease?	A-II	[26]
Should local fluid sampling (CSF, vitreous fluid) with dedicated resistance testing be sent in CMV retinitis or CNS disease?	A-III	[7,21-23]
Resistance testing should be performed when the CMV viral load fails to reduce by >1 log after longer than 2 weeks on appropriately dosed antivirals.	A-III	[4]
To perform genotype resistance testing, a CMV viral load ≥1000 IU/mL is recommended.	A-III	[20]
Assay the quantitative CMV viral load in BAL fluid to aid the diagnosis of CMV pneumonia.	A-III	[25]

FAQs 9 to 15: Treatment of R/R CMV

Question	Grade*	Supporting References
Should consultation with an infectious diseases specialist be sought in the management of R/R CMV?	A-III	
Whenever possible, seek special access or trial participation for maribavir.	C-II	[30]
Should CMV agents be switched while awaiting confirmatory tests of CMV resistance?	A-II	[27]
Should high-dose ganciclovir be used in patients with UL97 mutations conferring low-level ganciclovir resistance?	B-III	[27]
Should third-party or donor-derived adoptive CMV T cells be used to treat R/R CMV?	B-II	[31,75,78]
Should the use of leflunomide or artesunate be considered as adjunct therapy for R/R CMV infection?	C-III	[53-55,57-59,62]
Should combination ganciclovir and foscarnet be used to treat R/R CMV?	D-III	[39,40]
Should adjunct IVIG be used in the management of CMV pneumonia?	C-II	[47]
Should adjunct IVIG be used in the management of CMV GI disease?	D-II	[48]
Should adjunct IVIG be used in the management of R/R CMV infection?	D-III	
Should CMV IVIG be used in the management of CMV pneumonitis?	D-II	[46,47,49,50]
Aim to treat R/R CMV with effective optimally dosed anti-CMV agent for at least 2 to 4 weeks guided by clinical resolution and achievement of undetectable CMV viremia for at least 2 consecutive assays.	B-II	
Management of CMV retinitis should be guided by expert infectious diseases and ophthalmology specialists.	A-III	
Should secondary prophylaxis be used for patients at high risk for recurrent CMV, including R/R CMV infection, ideally with an oral agent?	A-III	[1,65]
Can secondary prophylaxis be given with a previously used agent with documented mutations conferring resistance?	C-III	

FAQs 16 to 18: Management of side effects

Question	Grade*	Supporting References
The valganciclovir dose should be reduced in the setting of active CMV viremia or disease when treatment-related neutropenia occurs.	D-III	
G-CSF should be recommended when treatment-related neutropenia occurs.	B-I	[29]
Substituting concomitant medications that may be contributing to neutropenia, such as mycophenolate mofetil and trimethoprim/sulfamethoxazole, should be considered whenever possible. Therapeutic drug monitoring of (val)ganciclovir should be routinely performed.	B-III D-III	[73,74]

FAQs 19 to 22: Special populations, including pediatric patients and CAR T cell recipients

Question	Grade*	Supporting References
Discontinuation of breastfeeding should be considered in a patient with newly diagnosed SCID.	B-III	[87]
Increased clinical vigilance for R/R CMV infection and disease is recommended for T cell-depleted, cord blood, and haploidentical donor allograft recipients.	A-II	[94]
In CAR T cell recipients, routine CMV monitoring or CMV prophylaxis should be prescribed.	D-II	[96,98,99]
Active CMV infection diagnosed before CAR T cell infusion should be controlled before proceeding with a conditioning regimen.	B-III	

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