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Guideline

American Society for Transplantation and Cellular Therapy Series: #4 - Cytomegalovirus treatment and management of resistant or refractory infections after hematopoietic cell transplantation

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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 Transpl. Infect. Dis. Special Interest Group (TID-SIG) to update its 2009 compendium-style infectious disease guidelines for hematopoietic cell transplantation (HCT). A new approach was employed 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 (FAQ), tables, and figures. Adult and pediatric infectious diseases 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 fourth topic in the series focuses on the management and treatment of cytomegalovirus (CMV) resistant and refractory infections. The diagnosis, definitions of resistant and refractory CMV, risk factors, virological genotypes and treatment algorithms are reviewed.

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BACKGROUND

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 pre-emptive 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, refractory (R/R) CMV infections or disease remain poor. Current challenges are the limited number of available antivirals and their toxicities plus the lack of HCT-specific randomized trials to inform choice of first-line antiviral (s) and treatment duration. Other issues include delays in a timely diagnosis of R/R CMV infection and disease and how best to incorporate immune-based monitoring and alternative therapies into clinical practice. This guideline in the form of frequently asked questions addresses current knowledge and future directions for management of R/R CMV infections.

FAQ1: How are resistant and refractory CMV infections and disease defined?

Refractory CMV infection is an increase by >1 $\log_{10}$ 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 performed 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 <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(s) that decreases the susceptibility to one 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

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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 resistant, refractory CMV infection and disease?

These include haploidentical [5] and T-cell depleted HCT [6], previous exposure to anti-CMV therapy, prolonged exposure to anti-CMV medication in the presence of replicating virus, and prolonged treatment for CMV disease, particularly CMV encephalitis (Table 1) [7–10]. CMV resistance should be suspected when CMV viral load rises after virological suppression and typically occurs in the setting of immunosuppression, persistent or intermittent low level CMV viremia, prolonged, sub-therapeutic exposure to antivirals and lack of immune reconstitution. Refractory CMV infection (24-39%) [11–13] is more common than resistant CMV infection (1.7-14.5%) [5,6,11,14]. CMV resistance is relatively uncommon after conventional T-cell replete HCT (1-5%) [15,16]. 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 tract, followed less frequently by lungs (pneumonia) and, rarely, central nervous system (CNS) disease (retinitis, encephalitis) [2,17,18].

FAQ3: What signs and symptoms occur with resistant, refractory CMV infection and disease and what tests can help with the diagnosis?

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

Table 1
Risk factors for R/R CMV

Risk Factor	
Transplant-related	HLA mismatch
	Haploidentical donor [5]
	Cord blood
	Pediatric HLA-mismatched donor [97]
	T-cell depleted transplant [6]
	CMV seronegative donor
Viral-related	Persistent low level CMV viremia
	High peak level CMV viremia [32]
	Recurrent episodes of CMV [14]
	CMV central nervous system disease [7–9] e.g. retinitis, ventriculitis
Drug-related	Sub-therapeutic exposure to antivirals due to non-adherence, 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 [5,10]
Host-related	Lymphopenia
	Poor immune recovery
	Graft versus host disease

FAQ4: When is the highest risk for developing resistant and refractory CMV infection and disease after HCT?

Resistant CMV typically occurs more than 2-4 months after the onset of CMV infection [6,14]. It is uncommon during the first 6 weeks of HCT in patients not previously exposed to anti-CMV medications [5,19]. The index of suspicion for resistant CMV disease is high in anyone treated appropriately for extended courses as with CMV encephalitis or retinitis where sub-therapeutic antiviral CNS penetration is likely [7,20]. Refractory CMV can occur at any time following HCT in the setting of relevant risk factors [3].

FAQ5: What are the consequences of resistant or refractory CMV infection or disease?

R/R CMV infections may be associated with CMV disease [6, 13,21], prolonged use of antiviral medications [6], CMV-related mortality [6], increased risk of indirect effects of CMV and increased non-relapse related mortality [13]. In T-cell depleted HCT, resistant CMV disease has a mortality rate up to 42% [6]. Despite treatment with 2nd and 3rd line CMV antivirals, poor tolerability of these medications often results in fatal outcomes [22].

DIAGNOSTICS

FAQ6: What diagnostics 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**) [23]. Plasma viral loads $\geq$1000 IU/ml are recommended for genotype testing (**A-III**) [24]. When resistant CMV disease is suspected, we recommend testing the relevant compartment when feasible as mutations may differ between plasma and various body compartments such as vitreous or spinal fluids [7,25-27] (**A-III).**

In the setting of letermovir primary prophylaxis, consultation with an infectious disease specialist is recommended for guidance on resistance testing when 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 prior to recommending a threshold level. Letermovir resistance may emerge even with relatively short duration of prophylaxis [28].

FAQ7: What is the clinical significance of quantitative CMV PCR testing of bronchoalveolar lavage (BAL) specimens?

There is currently no established BAL viral load cut-off to diagnose CMV pneumonia. Low viral loads may indicate asymptomatic pulmonary shedding but absence of CMV DNA from a BAL is a good negative predictor for CMV pneumonia [29]. 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**) [29] but expert ID opinion 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 biopsies and may represent specimen DNA contamination from blood. In the absence of corresponding histological evidence, presence of CMV DNA does not currently meet the criteria of proven CMV disease but

Table 2
Symptoms and diagnostic approaches for CMV infection and disease

System	Site	Common symptoms	Diagnostic procedure	Specimen type	Findings	Response to treatment	Comment
Hematological	Blood	Asymptomatic 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, 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 –may be *possible* CMV pneumonitis	Serial lung imaging Serial blood viral load	
Central Nervous System	Retinitis	Visual disturbance (blurred vision, scotomata, photopsia) Visual loss Ocular pain. May be asymptomatic if peripheral retina 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 neurological symptoms	Lumbar puncture MRI Brain	CSF	MRI Brain: diffuse signal and/or temporal lobe abnormalities CSF: lymphocytic pleocytosis, elevated protein Fluid: detectable CMV DNA & 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 MRI Brain	CSF	MRI Brain: periventricular subependymal abnormalities CSF: lymphocytic pleocytosis, elevated protein Fluid: detectable CMV DNA & quantitative level	Serial MRI Serial CSF viral load Serial blood viral load (may be absent)	High mortality High risk R/R CMV

Abbreviations: IHC, immunohistochemistry; CMV, cytomegalovirus; GI, gastrointestinal; LFTs, liver function tests; BAL, broncho-alveolar lavage; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; LP, lumbar puncture; R/R, resistant, refractory; *note that all these symptoms can also apply to R/R

Table 3
Diagnostic testing for CMV resistance

Diagnostic Method	Comments
Genotype for known mutations associated with phenotypic resistance [23]	Genotypic assays on UL97, UL54 and UL56 most commonly performed Rapid turn-around time Performed directly on clinical specimens such as blood, fluid, CSF or tissue Ideally requires plasma CMV viral load ≥1000 IU/mL for testing [24] Send for genotype for viral load breakthrough whilst on letermovir but consult ID specialist when viral load < 1000 IU/mL^ Resistant subpopulations at low frequencies (<25%) may not be detected Detects only established resistance mutations
Phenotype plaque reduction assays [112] (research setting)	Not readily available clinically Labor intensive (months) Poor reproducibility
Whole genome sequencing [113,114] (research setting)	Not readily available clinically Performed directly on blood, fluid or tissue Detects uncommon mutations

^Identification of UL56 letermovir resistance requires a minimum of 100 IU/mL viral load [115]

is a criterion for possible disease in the context of compatible clinical presentation [30].

TREATMENT OF RESISTANT AND REFRACTORY CMV

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

We recommend that treatment of R/R CMV infection be done in consultation with an infectious disease specialist (**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 acceptable toxicity profile. Upon clinical suspicion of CMV resistance, we recommend switching drug class, confirming genotypic resistance mutations and reducing immunosuppression if feasible (**A-II**) [31]. Ganciclovir is the medication most commonly affected by CMV resistance due to UL97 phosphotransferase mutations [32]. If high-level UL97 resistance mutations are detected (>5-fold increase in ganciclovir IC50) we recommend a switch to foscarnet (**B-III**). However, certain low-level UL97 resistance mutations (M460I, C592G, L595W) are usually manageable with higher-dose ganciclovir (7.5-10mg/kg q12h) (**B-III**) [31]. Preemptive use of filgrastim therapy may mitigate myelosuppression from high-dose ganciclovir dosing (**B-I**) [33].

Mutations involving the UL54 polymerase may indicate foscarnet resistance or cross-resistance to ganciclovir, foscarnet and cidofovir [32]. Management depends on the mutations detected and treatment options are limited (Table 4). Where possible, seek special access or clinical trials for investigational antiviral agents (**C-II**). Maribavir and 3rd party adoptive CMV T-cells (FAQ19) have shown benefit in R/R CMV [34,35].

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% vs 23.9%, $p<0.001$) [34]. Maribavir is yet to receive FDA/EMA approval and is only available through an early access program.

There is insufficient data to recommend using letermovir monotherapy in R/R CMV infection due to concern about a low threshold for rapidly developing resistance mutations particularly when treating CNS disease (**D-III**) [36]. Limited data suggests that therapy with letermovir alone or in combination may achieve virologic suppression if viral load < 1000 IU/mL; but results were mixed when letermovir was initiated at higher viral loads [36,37]. Further studies on combination therapy or alternative letermovir dosing are needed to support recommendation. New resistance mutations are being

Table 4
Recommended guide to use of approved and investigational anti-CMV agents in resistant refractory CMV (El Chaer, Chemaly 2017 [31].

Resistance genotype (refer to Table 5)	Recommendations
1. 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: seek special access or trial participation for investigational agents*
2. UL97 mutations with LOW Level resistance to ganciclovir (M460I, C592G, L595W)	High-dose ganciclovir dosing 7.5mg-10mg/kg q12h as tolerated if CMV disease not present Switch to foscarnet or cidofovir as next option If unacceptable drug toxicity: seek special access or trial participation for investigational agents*
3. UL54 mutations conferring resistance to foscarnet and ganciclovir (± UL97 mutations)	Switch to cidofovir as first-line option And consider adding alternative agents such as leflunomide, artesunate Seek special access or trial participation for investigational agents* including 3rd party CMV T-cells
4. 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 3rd party CMV T-cells
5. UL54 mutations conferring resistance to foscarnet only	Stop foscarnet and start ganciclovir standard dose 5mg/kg q12h May consider adding adjunct therapies such as leflunomide, artesunate
6. UL54 mutations conferring resistance to ganciclovir, foscarnet and cidofovir	Continue foscarnet and ADD high-dose ganciclovir 7.5-10mg/kg q12h 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 3rd party CMV T-cells
7. UL56, UL89, UL51 conferring resistance to letermovir	Switch to ganciclovir or foscarnet as first-line option
8. 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, 3rd party adoptive CMV T-cells

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

For Increase in drug concentration required to reduce viral growth 50% (EC50) compared with wild type for each mutation refer to Lurain NS, Chou S *Clin Microbiol Rev*. 2010 [116].
[^] A more exhaustive list of mutations can be found at Chou S. 2020 [23]
* Bold Indicates the most common UL97 genetic mutations
~ Indicates in-vitro resistance

identified with increasing use of letermovir [28,38-41] and maribavir [42].

Developing a standardized approach is challenging as 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 [31,32].

FAQ10: What is the role of antiviral combinations or mTOR based immunosuppression in treating R/R CMV infection and disease?

Combination therapy is generally not recommended due 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 [43,44].

Although conversion of calcineurin to mTOR inhibitor-based immunosuppression may provide anti-CMV activity [45,46] based on clinical experience observed in solid organ transplant recipients [47,48], 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 for R/R CMV infection?

IVIG use remains controversial because no mortality benefit has been observed when compared to anti-CMV medications alone [49,50]. Evidence for a potential benefit of IVIG in treating CMV pneumonitis is weak (**C-II**) [51] and not recommended for CMV gastrointestinal disease [52] (**D-II**) or R/R CMV (**D-III**). CMV specific IVIG is also not recommended due to lack of clinical benefit **(D-II)** [50,51,53,54].

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

Leflunomide or 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 [55,56], has had variable clinical success in limited case reports/series when typically used in combination with other anti-CMV medications [31,57-63]. Artesunate which also demonstrated in-vitro anti-CMV activity [64], has limited success in case reports [65] as well as failure [63,66,67].

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

At least 2-4 weeks of optimally selected and dosed anti-CMV medication, guided clinically by resolution of disease symptoms and aiming to achieve undetectable CMV viremia, if present, for at least two 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 like letermovir before any clinical or laboratory evidence of CMV. Secondary CMV prophylaxis, traditionally known as maintenance, refers to starting an antiviral medication after successful completion of CMV pre-emptive or disease treatment in order to prevent recurrent infection. *Secondary prophylaxis* should be commenced when viral loads are undetectable or when quantifiable but below the pre-defined lower limit of detection and when risk factors for recurrent CMV remain, including inadequate CMV-specific immune responses [68], concurrent infection and/or GVHD requiring further immunosuppression. Ideally, orally administered agents like valganciclovir or letermovir should be prescribed [1,69] (**B-II**). Due to insufficient data, letermovir cannot be recommended yet for secondary prophylaxis in R/R infections. If an oral agent is unfeasible, intravenous 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 upon reintroduction of the inciting antiviral(s) [70]. 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, cidofovir (Supplementary Table 1) and may be necessary for other potentially nephrotoxic medications (e.g. calcineurin inhibitors). Acute renal impairment during pre-emptively CMV therapy within 100 days after HCT has been observed in 13% of patients on val(ganciclovir) and 34% on foscarnet [71]. In resistant CMV, a 51% incidence of renal dysfunction has been reported with foscarnet despite preventative measures such as IV hydration [22].

FAQ17: What if treatment-related neutropenia occurs?

Dose reduction is not recommended in the setting of active CMV infection due to the risk of developing resistance (**D-III**) but use of G-CSF [33,72] (**B-I**), switching from val(ganciclovir) to foscarnet, and/or temporary withholding of non-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 [73,74] (Supplementary Table 2 [71]).

Risk factors for severe neutropenia, defined as absolute neutrophil count (ANC) $<$ 500 include a high viral load, a low pre-treatment ANC and serum creatinine $>$2mg/dL [71,73,74].

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

There is insufficient evidence to recommend routine use of (val)ganciclovir TDM (**D-III**) and it is not readily available at least in the US [75,76]. Although routine TDM may detect under or overdosing of ganciclovir, trough and peak plasma concentration levels do not correlate with clinical efficacy [77,78], myelotoxicity [78], or change in the incidence of R/R CMV infections. Further studies are required to assess the potential utility of TDM in young children or in some other clinical settings.

ADOPTIVE CMV T-CELL IMMUNOTHERAPY

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

Restoration of CMV-specific immunity through infusion of 3rd party adoptive CMV-specific T cells (CTLs) is a promising approach and when feasible should be considered for managing R/R CMV infections and disease (**C-II**) [35,79-81]. Safety and efficacy of donor-derived or third party CMV-specific CTLs has been demonstrated in non-randomized clinical studies, achieving 74-93% clinical and viral response (Supplementary Table 3) [35,79,82]. Major hurdles limiting the broad applicability of CMV-specific CTLs include access, timing, cost, and unknown efficacy in the setting of high-dose steroids since $>$0.5mg/kg/day prednisolone (or equivalent) was an exclusion criterion for these studies [35,79]. Third-party viral specific T cell banks are currently being established to mitigate access limitations [83,84].

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 [85,86].
- Caution is needed when assigning pre-HCT CMV-seropositivity in infants because IgG positivity may represent persistence of passively transferred maternal antibodies [87,88].
- 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 [89,90]. Breastfeeding recommendations vary among centers that treat severe combined immunodeficiency deficiency (SCID), with the most common (48%) being to restrict breastfeeding to CMV-seronegative mothers (**B-III**) [91]. Future large studies proposed by the Primary Immune Deficiency Treatment Consortium in

the U.S. are needed to answer whether this is the best approach [92,93].

- In the era before newborn SCID screening one study found that 7% of infants with SCID were diagnosed with CMV infection [94]. 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 [95].
- 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 is necessary to diagnose CMV disease in an irritable child with possible signs and symptoms.
- Children follow the recommendations for all ages for CMV monitoring and treatment [96]. Data are limited but one study reported approximately 4% of children develop antiviral resistance after two months of prolonged antiviral therapy [97]. Since 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 following HCT (**C-III**). While letermovir prophylaxis is available in the adult population, it is not approved in children under 18 years of age. A clinical trial in neonates to adolescents (<18 years) is underway to evaluate pharmacokinetics (NCT03940586).

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

There is a lack donor-derived CMV specific T-cells in recipients of T-cell depleted grafts (via deliberate removal of viral specific T cells) and cord blood grafts via inherent T cell naivety [5,6]. Recipients of haploidentical HCT are at higher risk of CMV complications including CMV disease and R/R CMV infection [5,98]. Treatment of CMV is similar to 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, lower viral load threshold for initiation of pre-emptive therapy, and higher clinical suspicion for work up of CMV disease (**A-II**) [98,99].

FAQ22: What is the risk of CMV-related complications after Chimeric Antigen Receptor-Modified T-cell Immunotherapy (CAR T-cells)?

Retrospective single studies have reported low incidence of CMV infections after CAR-T cell therapy where routine CMV monitoring was not used [100–103]. CMV infection contributed to 6% of all infectious events in both the early and late period following CAR-T cell infusion [100]. 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 presence of cytokine release syndrome (CRS). At present there is 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 post-infusion (**C-III**) [104–106].

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?

Past studies of ganciclovir primary prophylaxis showed late onset CMV complications associated with worse patient outcomes [107] perhaps due to delayed diagnosis, less frequent monitoring and less contact with specialists for post-transplant care. 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 [108]. A phase 3 study is currently underway to assess if these high-risk patients would benefit from extending prophylaxis to 6 months post-HCT (NCT03930615). By allowing CMV antigen presentation, letermovir may promote CMV immune reconstitution even without clinically significant viremia [109], 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 showed an 85% reduction in R/R CMV with 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 [110]. In a phase 3 randomized trial of maribavir 400 mg orally twice daily versus investigator assigned therapy for the treatment of refractory or resistant CMV, among HCT recipients, 55.9% in the maribavir arm compared with 20.8% in the investigator assigned therapy arm achieved clearance of CMV viremia by week 8 ($p<0.001$) [34]. No new safety concerns were identified among maribavir treated patients who otherwise had lower rates of renal impairment compared to foscarnet and lower rates of neutropenia compared to val(ganciclovir) [34]. 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 work-up of CNS disease is recommended for patients on maribavir.

Filociclovir (cyclopropavir, MBX-400) is another nucleoside analogue under phase 1b evaluation for CMV and adenovirus activity including activity against in-vitro CMV resistant viral strains [64,111]. Finally, a single institution phase 2 study of letermovir use for R/R CMV infections is currently enrolling (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 RECOMMENDATION AND LEVEL OF EVIDENCE

FAQ 3-8 Diagnostics

Question	Grade*	Supporting References
Should tissue biopsy be performed to confirm CMV gastrointestinal disease?	A-II	[30]
Should local fluid sampling (CSF, vitreous fluid) with dedicated resistance testing be sent in CMV retinitis or CNS disease	A-III	[7,25-27]
Resistance testing should be sent when there is a failure of CMV viral load to reduce by > 1 log after more than 2 weeks on appropriately dosed antivirals	A-III	[4]
To perform genotype resistance testing, it is recommended to have a CMV viral load ≥1000 IU/ml	A-III	[24]
Perform a quantitative CMV viral load on bronchoalveolar lavage to aid the diagnosis of CMV pneumonia	A-III	[29]

FAQ 9-15 Treatment of Resistant Refractory CMV

Question	Grade*	Supporting References
Consultation of Infectious Diseases specialists should be sought in the management of R/R CMV?	A-III	
Where possible seek special access or trial participation for maribavir	C-II	[34]
Should CMV agents be switched whilst waiting for confirmatory tests of CMV resistance?	A-II	[31]
Should high dose ganciclovir be used in UL97 mutations conferring low level ganciclovir resistance?	B-III	[31]
Should 3rd party or donor derived adoptive CMV T-cells be used to treat R/R CMV?	B-II	[35,79,81,82,117-122]
Should use of leflunomide or artesunate be considered as adjunctive therapies for R/R CMV infection?	C-III	[57-59,61-63,66]
Should combination ganciclovir and foscarnet be used to treat R/R CMV?	D-III	[43,44]
Should adjunctive IVIG be used in the management of CMV pneumonia?	C-II	[51]
Should adjunctive IVIG be used in the management of CMV gastrointestinal disease?	D-II	[52]
Should adjunctive IVIG be used in the management of resistant, refractory CMV infection?	D-III	
Should CMV IVIG be used in the management of CMV pneumonitis?	D-II	[50,51,53,54]
Aim to treat R/R CMV with effective optimally dosed anti-CMV agent for at least 2-4 weeks guided by clinical resolution and achieving undetectable CMV viremia for at least two consecutive assays	B-II	
Management of CMV retinitis should be guided by expert ID 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	[1,69]
Can secondary prophylaxis be given with a previously used agent with document mutations conferring resistance?	C-III	

(*continued*)

FAQ 16-18 Management of side effects

Question	Grade*	Supporting References
Should valganciclovir be dose reduced in the setting of active CMV viremia or disease when treatment related neutropenia occurs?	D-III	
Should G-CSF colony stimulating factors be recommended when treatment related neutropenia occurs?	B-I	[33]
Consider substituting concomitant medications that may be contributing to neutropenia such as mycophenolate mofetil, trimethoprim/sulfamethoxazole where possible	B-III	
Should therapeutic drug monitoring of (val)ganciclovir be routinely performed	D-III	[77,78]

FAQ 19-22 – Special populations including paediatrics and CAR-T

Question	Grade*	Supporting References
Discontinuation of breastfeeding should be considered in a newly diagnosed patient with SCID	B-III	[91]
Increased clinical vigilance for R/R CMV infection and disease is recommended for T-cell depleted, cord blood or haplo-identical donor allografts	A-II	[98]
In CAR-T cell recipients, should routine CMV monitoring or CMV prophylaxis be prescribed?	D-II	[100,102,103]
Active CMV infection diagnosed pre CAR-T cell infusion should be controlled before proceeding with conditioning regimen	B-III	

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