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The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation

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INTRODUCTION

We are in the midst of a true modernization of the management of cytomegalovirus (CMV) infection after organ transplantation. Numerous recent advances are the culmination of years of basic and translational research followed by rigorous clinical trials by the transplant community. CMV has always been, and remains, one of the most common opportunistic infections affecting solid organ transplant (SOT) recipients. CMV can lead to serious illness in transplant patients and also impact short- and long-term allograft function through immunomodulatory downstream sequelae. It carries the infamous but befitting title as the "troll of transplantation." However, recent advances, covering the spectrum from understanding host-viral interactions to optimal prevention and treatment strategies, have paved the way for an increasingly scientific and evidence-based approach to CMV. A panel of experts on CMV and SOT recipients convened under the auspices of The Transplantation Society published international consensus guidelines on CMV management in 2010,[1] 2013,[2] and 2018.[3] Topics included diagnostics, immunology, prevention, treatment, resistance, and pediatrics. Given many recent advances in the field, a fourth meeting of experts was convened in June 2024 in Montreal, Canada, to update these guidelines.

As with the last version of the guidelines, the expert panel rated the quality of evidence, on which recommendations are based, by following the Grading of Recommendations Assessment, Development, and Evaluation system, which allows for a systematic weighting of the strength of recommendation (eg, high, moderate, low, very low) and quality of evidence (eg, strong, weak; **Table S1, SDC,** http://links.lww.com/

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TP/D243).[4-10] During the meeting, we used an online polling system to collect votes and gather consensus on various questions.

For consistency, recently updated consensus definitions for CMV infection and disease, developed by the Transplant-Associated Virus Infections Forum,[11] were used as the baseline for the current document as follows:

- CMV infection: evidence of CMV replication regardless of symptoms (differs from latent CMV); "defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen."
- CMV disease: consists of "end-organ disease" and "CMV syndrome" and requires evidence of CMV infection with attributable symptoms.

The document does not address CMV management after hematopoietic stem cell transplantation. As in our prior versions, the term DNAemia is used instead of viremia to reflect the detection of CMV DNA in blood or plasma (whether actively replicating virus or not). For accuracy, the phrases "viral load" or "quantitative nucleic acid amplification testing (QNAT)" are used instead of "polymerase chain reaction (PCR)." Additional definitions appear in Table 1.

DIAGNOSTICS

Pretransplant CMV Laboratory Testing

Pretransplant risk stratification for CMV infection posttransplant is based on the CMV serostatus of the donor (D) and recipient (R). The risk levels are high (D^+/R^-), intermediate (D^+/R^+ or D^-/R^+), and low (D^-/R^-). These categories guide decisions on antiviral prophylaxis, screening, and preemptive therapy.[3,12-14]

A sensitive, CMV-specific IgG serologic test should be used. Tests that detect IgM should be avoided because of reduced specificity.[15-18] If the donor or candidate tests seronegative in advance of the transplant, CMV serology should be repeated immediately before transplant to avoid missing a change in CMV serostatus. If results are equivocal, the higher-risk group should be assumed for posttransplant management. CMV IgG-positive results can be affected by recent transfusions of IVIG and blood products (platelets, plasma, and red blood cells),[19] and a pretransfusion sample should be tested if possible. In seropositive children younger than 12 mo, maternal antibody transfer can cause false-positive results.[19] False-negative results may occur after plasmapheresis or with profound hypogammaglobulinemia.

Not all CMV serology tests are equivalent, and performance of the assays should be documented in comparative studies. Laboratories switching CMV IgG assays should compare the performance characteristics with the previous assay. Discordant results have been reported for 1.0%–2.6% of samples tested by common assays.[15,17]

Cell-mediated immunity (CMI) assays can help determine CMV status in cases of inconclusive, false-negative, or false-positive serology results.[20,21] These assays may also clarify CMV exposure in children younger than 12 mo with passively transferred antibodies, although negative results in young children should be interpreted cautiously due to immature immune responses.[20-22] Pretransplant testing for CMV-specific CMI (CMV-CMI) is generally not useful in donors (especially in deceased donors due to frequent indeterminate results).[23]

There is little role for pretransplant CMV-specific quantitative nucleic acid testing (CMV-QNAT), with exceptions that include candidates on significant immunosuppression and infants under 12 mo with unreliable serology. In these cases, CMV-QNAT of urine or oral samples can detect persistent CMV shedding.[24] A negative CMV-QNAT does not rule out past exposure. False-positive saliva NAT results have been reported in breastfeeding infants with CMV-shedding seropositive mothers, so positive saliva NAT results warrant confirmatory urine NAT testing.[25]

Posttransplant CMV Laboratory Testing

Serial CMV DNA blood testing by CMV-QNAT guides preemptive antiviral treatment and monitors treatment efficacy.[26-32] Both plasma and whole blood CMV-QNAT provide diagnostic and prognostic information, with whole blood generally detecting CMV earlier and in higher quantities per unit volume compared with plasma.[33-38] In comparison with whole blood, persistent plasma CMV DNAemia better predicts ongoing CMV infection.[35,39] Many experts favored the use of plasma over whole blood, although most felt that either specimen type was valid. Probable refractory CMV infection is considered if CMV DNAemia levels remain unchanged or increase after at least 2 wk of appropriate therapy.[40,41] Consistently using a single specimen type (whole blood or plasma) for monitoring is strongly recommended because results on different specimen types are not comparable.[39]

Several commercial reagents and automated platforms are available for CMV-QNAT. Most CMV-QNAT testing in North America is performed using US Food and Drug Administration (FDA)-approved commercial, often fully automated assays (see **Table S2, SDC,** http://links.lww.com/TP/D243), but some laboratories still use laboratory-developed tests. Commercial assays (FDA-approved or Conformité Européenne-marked for diagnostic use) show similar performance characteristics and are preferred over laboratory-developed tests.[42,43] The higher costs of commercial CMV-QNAT assays may be a barrier in resource-limited settings. The CMV antigenemia assay, while specific, is less favored because of its need for same-day processing, laborious nature, observer dependency, and limited sensitivity in leukopenic patients but may still be used where CMV-QNAT is unavailable.[2,44-46]

TABLE 1.

CMV-related definitions used in the guidelines

Term	Definition
Antigenemia	Measuring CMV-specific antigen in peripheral blood leukocytes (eg, pp65 assay)
Viremia	Culture-based detection of infectious CMV
DNAemia	Measuring CMV DNA by QNAT (whole blood and plasma)
CMV-specific IgG	Marker of previous exposure (positive serology does not define "active infection")
Surveillance	Patient at risk, but no evidence of an event or biomarker
Monitoring	Patient has event or biomarker positive

CMV, cytomegalovirus; QNAT, quantitative nucleic acid testing.

Calibration of CMV-QNAT assays with the World Health Organization (WHO)-approved international standard[47] has improved agreement across tests.[48,49] Nevertheless, significant differences between CMV-QNAT assays remain,[48,50] and the use of a single testing platform and specimen type is recommended. These differences are seen among FDA-approved and Conformité Européenne-marked assays but tend to be larger among some laboratory-developed tests.[43,51] Several factors contribute to this inherent variability, such as extraction method, extraction platform, input sample volume, amplicon size, and primer binding site variations.[49,52-57] There is evidence that >90% of CMV DNA in plasma corresponds to non-encapsidated fragments of <100–150 bp; accordingly, the use of CMV-QNAT assays with larger amplicons may underquantify or cause false-negative results.[57-59] Antiviral drugs, especially letermovir given its mechanism of action as a terminase complex inhibitor, may affect CMV genome fragmentation.[60,61] Postcalibration, commutability must be demonstrated, ensuring patient samples and calibrators behave similarly in a given quantitative test.

Due to the logarithmic nature of the assays, changes of <0.5 $\log_{10}$ IU/mL (3-fold) may not be clinically significant. At viral loads <3 $\log_{10}$ IU/mL (1000 IU/mL), a 0.7 $\log_{10}$ IU/mL change (5-fold difference) may be the threshold for a significant change. Many current assays achieve much higher analytic precision,[62-65] indicating a need for more research on the clinical relevance of small changes.[66] Results should be reported as $\log_{10}$-transformed data to avoid overinterpreting insignificant or biologically irrelevant changes in CMV DNAemia.[67] Integer values may be reported together with $\log_{10}$ data if helpful.

The analytical sensitivity and linear range of any diagnostic QNAT are defined by the lower limit of detection and the lower and upper limits of quantification (LLOQ and ULOQ). Both LLOQ and ULOQ help determine the precision and accuracy of viral load monitoring. Most commercial and laboratory-developed CMV-QNAT assays have an LLOQ of 2–2.7 $\log_{10}$ IU/mL (100–500 IU/mL), whereas newer automated platforms have LLOQs as low as 1.5 $\log_{10}$ IU/mL (34.5 IU/mL). Accordingly, such high-sensitivity CMV-QNAT assays will result in earlier and longer detection of CMV DNAemia,[68,69] potentially leading to earlier preemptive and overall longer antiviral treatments.[70,71]

Notably, high-sensitivity CMV-QNATs may increase the rate of both detectable but not quantifiable CMV DNAemia (ie, above the limit of detection but below the LLOQ) and of the so called blips of CMV DNA detection defined as singular low results detected above the LLOQ. Some studies suggest that up to two-thirds of new-onset CMV DNA "blips" predict subsequently persistent CMV DNAemia above the LLOQ, of which approximately one-half eventually require antiviral treatment. More studies are needed to optimally evaluate risk and clinical significance of CMV DNA "blips."[72]

Consensus CMV DNAemia thresholds for preemptive treatment have been difficult to derive, given variation across different testing platforms and specimen types. Although early work has shown that higher CMV DNAemia correlates with an increased risk for CMV disease[27,73] (see the Prevention section), thresholds need to be set independently by transplant centers based on risk group, organ type, immunosuppressive regimen, specimen types, testing characteristics, and viral kinetics. Although published data are lacking, a majority of experts reported starting treatment for DNAemia at levels of 2–3.2 $\log_{10}$ IU/mL (100–1500 IU/mL) in plasma for D^+/R^- patients. This may reflect various assay LLOQs among institutions, as many believe any measurable positive CMV should be treated in high-risk recipients. Most experts reported starting treatment at higher levels ranging, for example, from 2.7 to 3.6 $\log_{10}$ IU/mL (500–4000 IU/mL) in plasma for R^+ patients. The widespread use of commercial assays offers an opportunity for collaborative studies to determine consensus thresholds in $\log_{10}$ IU/mL for different risk groups and for the 2 different blood matrices (plasma and whole blood).

CMV DNAemia testing in high-risk groups undergoing preemptive monitoring should be done weekly, whereas more frequent testing may be considered if viral kinetics are being evaluated.[29,70] There are reports that CMV replication kinetics, defined as the rate of change in CMV DNAemia levels over time, may be more accurate in predicting disease than thresholds.[27,74,75] Adapting a CMV DNA testing frequency schedule based on CMV doubling time can be challenging. Although a median of 4.3 d was reported by Lodding et al,[76] shorter doubling times have been reported[77,78] especially in D^+/R^- groups.[71] Monitoring patients on therapy can also be challenging. CMV DNAemia kinetics in patients treated with letermovir may differ compared with those treated with other antivirals such as CMV DNA polymerase inhibitors (eg, ganciclovir, cidofovir, foscarnet). Detection of CMV-RNAemia by reverse transcription-QNAT has been proposed as a more accurate alternative for quantifying replicating CMV compared with CMV DNAemia.[79]

Virus isolation in cell culture is predictive of CMV disease when using specimens from the site of end-organ involvement, such as lung biopsies or bronchoalveolar lavage (BAL) fluid in lung transplant recipients. In addition to the significant laboratory infrastructure and expertise required, however, viral culture has limited clinical utility for blood, cerebrospinal fluid (CSF), anterior chamber fluid, aqueous humor, stool, saliva, and urine due to long turnaround times and limitations in sensitivity and specificity.[80,81] Considering these factors, viral culture is no longer available as a routine test in most clinical virology laboratories, and CMV-QNAT is often performed using laboratory-developed tests on nucleic acids extracted from these specimens, for which commercial assays, approved for in vitro diagnostic use, are often unavailable.

Testing for CMV-specific antibodies has no role in the diagnosis of active CMV replication and disease posttransplantation. Serologic testing has been proposed for identifying persistent susceptibility to primary natural infection in CMV (R^-) patients who did not acquire transplant-associated CMV infection; the absence of seroconversion does not reliably indicate the absence of donor-derived CMV infection transmission, however, due to the possibility of immunosuppression delaying or inhibiting a humoral immune response.[45] The presence of CMV IgG seroconversion in CMV (D^+/R^-) patients at the end of antiviral prophylaxis may also not reliably predict protection from future CMV disease.[82,83] The measurement of antibodies neutralizing CMV infection of epithelial cells may better predict protection from future CMV disease, particularly

when combined with positive CMV-CMI results,[84] but is not typically available or performed as a clinical assay.

Diagnostics for Tissue-invasive Disease

The definitive diagnosis of CMV organ pathology relies on virus detection in tissue. Identification of cytopathic changes characteristic of CMV and the detection of CMV antigens by immunohistochemistry define proven CMV organ disease.[11,85,86] Not all antibodies and staining procedures have equal sensitivity, and performance characteristics of these methods may differ between fresh and formalin-fixed, paraffin-embedded tissue.[87]

Plasma CMV-QNAT has a high sensitivity for diagnosing gastrointestinal disease in CMV (D^+/R^-) patients, but sensitivity can decrease in (R^+) patients,[88-90] sometimes with low or undetectable CMV DNAemia. Highly sensitive CMV-QNAT (LLOQ <200 IU/mL) may improve the diagnosis of gastrointestinal disease in D^+/R^+ kidney transplant recipients. A plasma threshold of 4 $\log_{10}$ IU/mL (4063 IU/mL), quantified by the Roche Cobas AmpliPrep/Cobas TaqMan, showed a positive predictive value of 68% for gastrointestinal disease in one study.[91] Other studies have also shown diagnostic value for blood and tissue CMV-QNAT in the diagnosis of gastrointestinal CMV disease, when compared with immunohistochemistry.[92,93] As noted earlier, viral culture of tissue samples is no longer widely available and is less sensitive than molecular-based methods.[80] Nonetheless, culture may have greater sensitivity than histopathology in diagnosing gastrointestinal disease.[89] In patients with detectable CMV DNAemia, positive CMV-QNAT from tissue may originate from blood in cases where histopathology shows no evidence of viral infection.[94,95]

Low or undetectable CMV DNAemia can also be seen (rarely) in lung transplant recipients with CMV pneumonia.[96] In lung transplant recipients, the detection of CMV by QNAT in BAL fluid is thought to reflect CMV replication in the lung rather than contamination with oropharyngeal fluids (eg, shedding).[97] CMV-QNAT in BAL fluid specimens may improve the specificity for the diagnosis of possible, probable, and proven CMV pneumonia in lung and non–lung transplant recipients.[98] Higher DNA levels in BAL fluid samples may better correlate with symptomatic CMV disease and pneumonitis.[96,99-102] In a cohort of lung transplant recipients, CMV median viral load in BAL fluid in pneumonia episodes was 4.5 $\log_{10}$ IU/mL (32 940 IU/mL), compared with a median of 3.1 $\log_{10}$ IU/mL (1260 IU/mL) in cases without pneumonia (quantified by the Roche Cobas AmpliPrep/Cobas TaqMan).[103] Similar trends were reported when CMV-QNAT in BAL fluid was correlated with CMV staining in biopsy samples.[85] CMV-QNAT in BAL fluid had a higher sensitivity than plasma viral DNAemia.[103] A quantitative CMV DNA threshold normalized to cell count has also been proposed for the diagnosis of CMV pneumonia (0.32 IU/10^6 cells) in a cohort of immunocompromised individuals (including nontransplant, non–lung transplant, and lung transplant recipients).[104] Further work is needed to standardize QNAT in BAL fluid samples and optimize thresholds across diagnostic platforms.[85,96,98,102,103,105,106]

Central nervous system disease in SOT recipients is extremely rare. In the absence of further clinical studies, the presence of CMV DNA in the CSF likely represents CMV disease necessitating treatment (assuming CSF is not contaminated by blood).

The clinical diagnosis of CMV retinitis is based on ophthalmologic examination, although the degree of experience with visual diagnosis may be variable among clinicians. CMV DNAemia is rarely useful as a predictor of CMV retinitis, although it may be positive before and at the time of diagnosis. The differential diagnosis includes necrotizing retinitis caused by herpes simplex virus, varicella-zoster virus, or *Toxoplasma*. A positive CMV-QNAT in vitreous fluid, biopsy, or vitrectomy specimen may be helpful in confirming the diagnosis of CMV retinitis.

Consensus Statements and Recommendations

- We recommend performing donor and recipient CMV IgG serology pretransplantation for risk stratification (strong, high).
- We do not recommend CMV-IgM or combination CMV IgG/IgM testing (strong, low).
- We recommend repeat serologic testing at the time of transplant if pretransplantation serology is negative (strong, low).
- We recommend that in adults, an equivocal serologic assay result in the donor be assumed to be positive, whereas in the recipient, this result should be interpreted to assign the recipient to the highest appropriate CMV risk group for posttransplantation management decisions (strong, low). (For guidance on infants and children younger than 12 mo, see the Pediatric Issues in CMV Management section).
- We suggest performing CMV-CMI in CMV seropositive candidate recipients with potential false-positive antibody results due to passively transferred immunity, such as from transfusion of blood products or IVIG. A negative CMV-CMI result indicates a negative CMV infection status, whereas a positive CMV-CMI result indicates a true history of CMV infection (weak, low).
- We recommend using CMV-QNAT calibrated to the WHO standard for diagnosis, surveillance to guide preemptive antiviral treatment, and therapeutic monitoring (strong, high).
- Whenever possible, CMV-QNAT should be performed using a commercial assay that has regulatory approval as an in vitro diagnostic test (strong, high).
- We recommend that the interpretation of results should be considered on the basis of logarithmic changes in CMV DNAemia ($\log_{10}$ IU/mL units). Results should be reported as $\log_{10}$ values; both $\log_{10}$ and integer values may be reported together if helpful (strong, high).
- Although CMV-QNAT is the preferred diagnostic method, if not available, antigenemia may be considered as an alternative (strong, high).
- We recommend either plasma or whole blood specimens for CMV DNA testing, taking into account the differences in CMV DNAemia values, viral kinetics, and assay performance characteristics (strong, high).
- Specimen type should not be changed when monitoring patients (strong, high).
- We recommend that individual patients are consistently monitored with the same assay. CMV DNAemia values should not be directly compared across centers and/or laboratories unless identical testing reagents and procedures have been assured or equivalence has been documented (strong, high).

- We recommend that only changes in CMV DNAemia exceeding 0.5 $\log_{10}$ IU/mL (3-fold) or 0.7 $\log_{10}$ IU/mL (5-fold) for initial values <3 $\log_{10}$ IU/mL (1000 IU/mL) be considered to represent significant differences in CMV DNAemia (strong, low).
- Although harmonization of CMV-QNAT has improved, universal thresholds for therapy or treatment endpoints have not been established and currently published thresholds remain assay specific. Accordingly, we recommend that centers establish their own thresholds (strong, moderate).
- We recommend that CMV-QNAT be performed weekly (strong, moderate) when monitoring response to antiviral therapy.
- We do not recommend viral culture of blood, urine, stool, or oral secretions for the diagnosis of CMV infection or disease (strong, high).
- We do not recommend CMV-QNAT on urine, stool, or oral secretions for surveillance or diagnosis of CMV disease (strong, low).
- We recommend histology coupled with immunohistochemistry for the diagnosis of tissue-invasive disease (strong, moderate). CMV-QNAT and viral culture of tissue biopsies may augment the sensitivity for invasive disease.

Future Directions

- Compare and harmonize the results of the different commercially available CMV IgG serology tests.
- Further validate nonseroconversion at 12–18 mo after antiviral prophylaxis as a marker of nontransmission of donor-derived CMV infection in CMV-mismatched patients.
- Investigate whether quantitative CMV serology titers in seropositive recipients correlate with the likelihood of post-transplant CMV reactivation.
- Compare the performance characteristics of the different serologic tests and assess the utility of CMV-CMI assays and QNAT using a variety of sample types for the interpretation of passive immunity.
- Evaluate QNAT monitoring in plasma, whole blood, and BAL fluid specimens with respect to disease prediction and monitoring therapeutic response with an emphasis on using commercially available testing systems and showing comparability of results among those systems.
- Establish thresholds and kinetics for CMV DNAemia for initiating preemptive therapy in different patient populations and across different specimen types and diagnostic platforms, leveraging the increased availability of commercial assays approved for diagnostic use. Further define testing frequency in various clinical settings.
- Determine commutability and harmonization using the WHO International Standard for whole blood and BAL.
- To improve harmonization of QNAT, determine the viral form (virions, fragmented, or genomic CMV) and viral kinetics in whole blood.
- Develop, evaluate, and standardize the use of assays for quantifying porcine and other zoonotic CMV species that might occur after xenotransplantation.

PREVENTION

CMV prevention strategies are critical because they improve transplant clinical success and outcomes by decreasing the risk of CMV infection and disease, as well as the associated "indirect effects." Universal prophylaxis and preemptive therapy are the main approaches for prevention (Table 2). An additional strategy that combines both of these approaches is "surveillance after prophylaxis" (sometimes called a "hybrid" approach). Since the previous edition of the guidelines, letermovir has become an additional prophylaxis strategy for kidney transplant recipients, there are more data to lend to the debate between prophylaxis and preemptive strategy, and we have a better understanding of mammalian target of rapamycin (mTOR) inhibitor use for the reduction of CMV risk.

Universal Prophylaxis

Universal prophylaxis provides antiviral medication to all patients or a subset of "at-risk" patients, starting within 10 d after transplant. Initiation at the time of transplant versus a delayed start (up to 7 d) appears to have comparable efficacy in small case series.[107,108] Prophylaxis is given for a finite period, typically 3–12 mo. Acyclovir, valacyclovir, intravenous ganciclovir, oral ganciclovir, valganciclovir, and letermovir have all been studied for universal prophylaxis.[109] In general, CMV DNAemia monitoring while on

TABLE 2.

Comparison of prophylaxis vs preemptive therapy

	Prophylaxis VGCV	Prophylaxis LET[a]	Preemptive therapy
Early CMV DNAemia/infection	Rare	Rare	Common
Prevention of CMV disease	Good efficacy	Good efficacy	Good efficacy
Late CMV (infection/disease)	Common	Common	Rare
Resistance to the agent being used	Uncommon	Rare	Uncommon (with weekly testing)
Ease of implementation	Relatively easy	Relatively easy	More difficult
Prevention of other herpes viruses	Prevents HSV, VZV	Does not prevent	Does not prevent
Other opportunistic infections	May prevent	Unknown	Unknown
Costs	Cost of drug	Cost of drug is significant[b]	Cost of monitoring
Safety	Myelosuppression	Drug interactions	Less drug toxicity
Prevention of rejection	May prevent	Unknown	Unknown
Graft survival	May improve	Unknown	May improve

[a]Vast majority of data from kidney transplant.
[b]There is a significant cost differential between VGCV and LET as of 2024.
CMV, cytomegalovirus; HSV, herpes simplex virus; LET, letermovir; VGCV, valganciclovir; VZV, varicella-zoster virus.

universal prophylaxis is not needed. There may be circumstances such as low absorption states, compliance, variable/decreased renal function, augmented immunosuppression, and selected pediatric patients where clinicians may choose to monitor for breakthrough DNAemia.

Valganciclovir and Ganciclovir

Valganciclovir is currently the most commonly used drug for prophylaxis. Equivalent efficacy was found in a large study of D^+/R^- transplant patients comparing oral ganciclovir to valganciclovir (PV16000); however, in small subgroup analysis, tissue-invasive disease was noted at an increased incidence in liver transplant patients who received valganciclovir.[110] Although drug levels are not typically measured, high concentrations of ganciclovir are associated with higher grades of leukopenia.[111] In the PV16000 study, where 3 mo of prophylaxis was used, 18% had late-onset CMV disease by 12 mo (~30% when including investigator-treated disease).[110] This led to studies in kidney transplant evaluating 200 d of prophylaxis, which further reduced the incidence of late-onset CMV disease.[82] Oral ganciclovir is no longer available.

Valacyclovir

High-dose valacyclovir is effective for the prevention of CMV disease and CMV DNAemia in both D^+/R^- and $D^{+/-}/R^+$ renal transplant recipients compared with placebo or oral ganciclovir.[112-115] In a direct comparison of valacyclovir and valganciclovir prophylaxis in kidney transplant, both randomized trials and meta-analysis show similar efficacy in the prevention of CMV disease and CMV infection[116-118] with less leukopenia and granulocyte colony-stimulating factor use in valacyclovir prophylaxis in one study.[117] Long-term follow-up of a randomized trial showed higher incidence of acute rejection and more allograft fibrosis at 3 y after transplantation in the valacyclovir arm.[116,119] Disadvantages of valacyclovir include high pill burden and poor tolerability due to neuropsychiatric side effects, which may be decreased if initiation is postponed in patients with delayed graft function. The advantages of valacyclovir include less myelotoxicity and lower cost.[113,116,120] In summary, valacyclovir prophylaxis may serve as an alternate CMV prevention method specifically in kidney transplant recipients who cannot tolerate valganciclovir and have limited access to letermovir or a preemptive therapy strategy.

Letermovir

Letermovir inhibits the viral terminase enzyme complex by binding to UL56 protein, does not share cross-resistance with ganciclovir,[121] and has both an oral and intravenous formulation. Letermovir given for 200 d was found to be noninferior to valganciclovir in a multicenter trial of CMV prevention in kidney D^+/R^- transplant recipients (CMV disease at 12 mo 10.4% with letermovir versus 11.8% with valganciclovir).[122] In real-world studies of letermovir use in kidney, liver, and pancreas recipients, it was found that it was effective as primary or secondary prophylaxis.[123-125] In kidney, liver, and pancreas recipients with valganciclovir-related cytopenias during primary prophylaxis, there was a decrease in the use of granulocyte colony-stimulating factor and a reduction in the need to modify mycophenolate dosing after patients were switched to letermovir.[122,123] There are emerging data that letermovir primary or secondary prophylaxis in heart and lung transplant recipients may be effective, although this is limited to small case series, and risk of breakthrough infection and late-onset CMV disease is less clear.[126-131]

Breakthrough infection is uncommon during letermovir primary prophylaxis, similar to valganciclovir, and there is no need to routinely monitor viral loads in this setting. A 50% dose reduction of letermovir is required during concomitant use of cyclosporine and letermovir may lead to altered tacrolimus levels, so close monitoring is needed.[125] Additionally, because letermovir is not effective against other herpesviruses, acyclovir prophylaxis should be used where such prevention is indicated. Moreover, the high cost of letermovir may be prohibitive for its widespread use.

Optimal Duration of Prophylaxis

In general, late-onset CMV is associated with D^+/R^- serostatus, shorter courses of prophylaxis, higher levels of immunosuppression, and allograft rejection.[132-134] In the Improved Protection Against Cytomegalovirus in Transplantation study, a decreased risk of CMV disease was seen in patients given 200 d of prophylaxis (16.1%) in D^+/R^- kidney recipients compared with those given 100 d of prophylaxis (36.8%).[132] However, extending CMV prophylaxis from 6 to 12 mo in pediatric kidney transplant patients did not prevent CMV infection or disease.[135] Long courses of prophylaxis with valganciclovir are associated with higher rates of leukopenia and greater cost. Seropositive recipients generally need shorter courses of prophylaxis compared with D^+/R^-. Recommendations for duration of prophylaxis for various organ transplants appear in Table 3.

Longer prophylaxis may be warranted in D^+/R^- lung recipients. In a study of 136 lung transplant recipients (including both D^+/R^- and R^+), valganciclovir prophylaxis for 12 mo versus 3 mo was associated with a significantly lower CMV infection and disease incidence.[136] Other studies have shown late-onset CMV disease rates of almost 50% in D^+/R^- lung transplants that receive 6 mo of prophylaxis and 42% in those that receive it for 9 mo.[134,137] Therefore, the majority of programs use 12 mo of antiviral prophylaxis.[134,136,138-140] Some programs continue prophylaxis indefinitely after lung transplant, although there are insufficient data to support this approach.[98,141]

Preemptive Therapy

Preemptive therapy involves surveillance with CMV DNAemia testing in blood at regular intervals (usually weekly) to detect early CMV replication and initiation of antiviral treatment at a prespecified assay threshold (ideally before the patient is symptomatic) to prevent CMV disease. Considering significant variability in thresholds used for initiating treatment, diagnostic specimens (whole blood versus plasma), and testing platforms in various studies,[33-39,48,50] a universal threshold for starting therapy cannot be defined and should be determined by transplant programs.

There was a strong consensus that a lower threshold for preemptive therapy should be used in D^+/R^- compared with R^+ patients. The use of higher thresholds in D^+/R^- may result in insufficient time to begin treatment for CMV and higher rates of disease.[142] For example, one study demonstrated a median viral load doubling time of 1.54 d (range, 0.55–5.5)

TABLE 3.

Recommended approaches for CMV prevention in different organs for adult solid organ transplant recipients

Organ	Serostatus	Risk level	Recommended[a]	Alternate
All	D^-/R^-	Low	Monitoring for clinical symptoms; consider antiviral prophylaxis against other herpes infections	Preemptive therapy (if higher risk, ie, significant transfusions)
Kidney	D^+/R^-	High	6 mo of (V)GCV or 6 mo of LET or preemptive therapy	High-dose VALACY
	R^+	Intermediate	3 mo of VGCV or preemptive therapy	High-dose VALACY. If on mTOR-based immunosuppression, preemptive therapy or close clinical monitoring recommended
Liver	D^+/R^-	High	3–6 mo of VGCV or preemptive therapy	
	R^+	Intermediate	3 mo of VGCV or preemptive therapy	
Pancreas	D^+/R^-	High	3–6 mo of VGCV	Preemptive therapy
	R^+	Intermediate	3 mo of VGCV or preemptive therapy	
Islet	D^+/R^-	Intermediate	3 mo of VGCV	Preemptive therapy
	R^+	Intermediate	3 mo of VGCV or preemptive therapy	
Heart	D^+/R^-	High	3–6 mo of (V)GCV	-Preemptive therapy -Some experts add CMVIG to prophylaxis
	R^+	Intermediate	3 mo of (V)GCV or preemptive therapy	
Lung	D^+/R^-	High	12 mo of (V)GCV	-Preemptive therapy
	R^+	Intermediate	6–12 mo of (V)GCV	-Some experts add CMVIG to prophylaxis
Intestinal, composite tissue	D^+/R^-	High	Minimum 6 mo (V)GCV	-Preemptive therapy
	R^+	High	3–6 mo (V)GCV	-Some experts add CMVIG to prophylaxis

[a]When a range is given, the duration of prophylaxis may depend on the degree of immunosuppression, including the use of lymphocyte-depleting antibodies for induction. Surveillance after prophylaxis can be used in at-risk patients. LET can be considered in cases of VGCV intolerance where prophylaxis is used. VGCV is approved by the EMA but not the FDA in liver transplants.

CMV, cytomegalovirus; D, donor; EMA, European Medicines Agency; FDA, Food and Drug Administration; GCV, intravenous ganciclovir; LET, letermovir; mTOR, mammalian target of rapamycin; R, recipient; VALACY, valacyclovir; VGCV, valganciclovir; (V)GCV, ganciclovir or valganciclovir.

in D^+/R^- compared with 2.67 d (range, 0.27–26.7) in the D^+/R^+ recipients ($P < 0.0001$).[71] Although prior guidelines mentioned that some experts, given the unpredictable viral kinetics (especially in D^+/R^-), recommended starting treatment with any detectable DNAemia,[71,143] with increasingly sensitive assays, many experts felt that very low results should not always result in initiation of treatment, even in D^+/R^- recipients (see the Diagnostics section). Thresholds used for preemptive therapy in various research publications since the last guidelines are summarized in Table 4.

Advantages of preemptive therapy include a reduced rate of late CMV, selective drug use, and potentially decreased drug cost and toxicities. Preemptive therapy can be difficult to coordinate, given the logistics of weekly testing, reviewing results, initiating therapy rapidly after positive assays, and performing subsequent monitoring and management. Preferably, 1 assay and specimen type (whole blood or plasma) should be used for an individual patient to ensure comparability of results. Preemptive therapy may not prevent the indirect effects of CMV infection, including effects on graft and patient survival; studies have demonstrated conflicting data.[158-161] Second episodes of replication are observed in about 30%–75% of those treated for CMV DNAemia,[151,162] so the specter of late CMV remains. Patients managed with the preemptive approach should receive oral acyclovir (or similar) for the prevention of herpes simplex infections.[163]

Universal Prophylaxis Versus Preemptive Therapy

Randomized trials have compared universal prophylaxis with preemptive therapy in mixed populations of high- and intermediate-risk kidney transplant recipients.[151,158-161] In kidney transplant studies using weekly monitoring for 4 mo posttransplant with reported high compliance rates, no difference in the incidence of CMV disease was found compared with universal prophylaxis.[158,159,164] Whether prophylaxis prevents acute rejection is unclear. A meta-analysis showed that universal prophylaxis significantly decreased the incidence of acute rejection versus placebo or no prophylaxis; however, the randomized trial by Reischig et al[151] did not show a statistically significant difference in acute rejection rates at 12 mo post–kidney transplant. Several studies have looked at long-term kidney graft survival depending on whether patients received prophylaxis or preemptive therapy. Two studies,[156,165] one of which was a large retrospective study of >2000 transplant recipients,[156] showed comparable rates of long-term graft survival with either strategy. One study showed that the development of CMV DNAemia >3.1 $\log_{10}$ (2000 IU/mL) in whole blood, rather than the method of prevention (prophylaxis or preemptive therapy), predicted graft loss.[166] However, a large prospective national cohort study, which included mostly kidney and liver transplant recipients, found an increased risk of graft loss in patients managed by preemptive strategy, with notably shorter follow-ups (approximately 1 y).[167] In contrast, preemptive therapy was better than valacyclovir prophylaxis for long-term graft survival.[168] It should be noted that less frequent screening (ie, less than weekly) results in higher rates of CMV disease and inferior long-term graft survival compared with prophylaxis.[160,161] Comparison of approaches among D^+/R^- patients is limited by a low proportion of the D^+/R^- group in randomized trials.[158-160] Nevertheless, the results seemed to be comparable even in higher-risk patients.

One recent randomized study directly compared preemptive approach and prophylaxis in liver transplantation.[144]

TABLE 4.

Thresholds used for preemptive therapy in research publications since the last guidelines

Study design	Participants	CMV monitoring	Threshold for treatment	Reference
D^+/R^-				
RCT	Adult LTX (n = 205), D^+/R^-	Plasma RT-PCR	Any level of DNAemia (detection level >20 IU/mL)	144
Retrospective real-world effectiveness	LTX (N = 50), D^+/R^-	Plasma RT-PCR	Any level of DNAemia (detection level >20 IU/mL)	145
R^+				
Long-term outcomes of RCT	Adult KTX (n = 299), any R^+	Plasma RT-PCR	>400 copies/mL	146
Retrospective	Adult and pediatric KTX (n = 132), any R^+	Whole blood RT-PCR	>4000 copies/mL	147
Retrospective	Adult LTX (n = 124), R^+	Whole blood RT-PCR	≥4000 IU/mL	148
Retrospective	Adult KTX (n = 540), any R^+	Initially pp65, then plasma RT-PCR	≥10 pp65 positive cells or symptoms attributable to CMV with any positivity. RT-PCR ≥5000 IU/mL or symptoms attributable to CMV with any DNAemia	46
Retrospective	Adult KTX (n = 251), any R^+	Plasma RT-PCR	Significant CMV DNAemia defined as ≥10^4 IU/mL. Threshold treatment not specified	149
Retrospective	Adult HTX (n = 563), any R^+	Plasma or whole blood RT-PCR	Treatment thresholds individual to each site	150
Mixed: R^+ with or without D^+/R^- and D^-/R^-				
RCT	Adult KTX (N = 140), any R^+, D^+/R^-	Whole blood RT-PCR	≥1000 IU/mL	151
Retrospective	Adult LTX, KTX, LKTX, D^+/R^- and any R^+	Whole blood RT-PCR	Any R^+: >3000 genomes/mL. D^+/R^-: >3000 genomes/mL (old protocol); >200 genomes/mL (168 IU/mL; new protocol)	152
Retrospective	Adult KTX (n = 556), any D^+, R^+ as well as D^-/R^-	pp65 or RT-PCR (biosample not specified for PCR)	Any positive value for high-risk patients. Treatment individualized for low risk patients	153
Retrospective	Adult and pediatric KTX (n = 87), any R^+ or D^+ or D unknown	pp65 CMV antigenemia	>10 pp65 positive cells in 200 000 neutrophils in peripheral blood (for D^+/R^-, any pp65 positive cell)	154
Retrospective	Adult and pediatric lung TX (n = 129)	Whole blood RT-PCR or pp65 and BAL RT-PCR	≥100 pp65 positive cells/2 × 10^5 leukocytes, Blood CMV PCR >300 000 DNA copies/mL, BAL CMV >100 000 DNA copies/mL	155
Retrospective	Adult KTX (n = 2198), D^+/R^- or R^+	Plasma CMV PCR	>600 IU/mL plasma (1000 IU/mL plasma from March 2021).	156
Retrospective	Pediatric KTX (N = 126), R^+ or D^+/R^-	Plasma CMV PCR	Low viral load threshold (>400 but <2000 IU/mL) compared with high viral load threshold (≥2000 IU/mL)	157

BAL, bronchoalveolar lavage; CMV, cytomegalovirus; D, donor; HTX, heart transplant; KTX, kidney transplant; LKTX, liver and kidney transplant; LTX, liver transplant; R, recipient; RCT, randomized controlled trial; RT-PCR, real-time polymerase chain reaction.

In this study of D^+/R^- recipients, antiviral therapy was initiated with any positive DNA level. This showed that preemptive therapy was superior to prophylaxis in the prevention of CMV disease (9% versus 19%) and was less costly than prophylaxis.[144,169] A post hoc analysis of this study performed to assess long-term mortality in those that survived to 1 y showed that, although long-term mortality was lower in the preemptive therapy arm, the majority of deaths were not related to CMV.[170] In contrast, a retrospective study in D^+/R^- liver transplant recipients showed a greater rate of ganciclovir resistance in the preemptive therapy group.[171] Several meta-analyses with significant numbers of liver transplant recipients have confirmed similar efficacy of prophylaxis versus preemptive therapy in prevention of CMV disease and no difference in mortality, graft loss, and acute rejection. As expected, CMV DNAemia is more common with preemptive therapy, whereas late-onset CMV DNAemia or disease and neutropenia is more common with prophylaxis.[172-176] Other herpes viral infections are more common with the preemptive strategy.[174]

In summary, preemptive therapy and universal prophylaxis are both comparable methods of CMV disease prevention for D^+/R^- and/or R^+ kidney and liver transplant recipients (Tables 2 and 3). Preemptive therapy assumes that patients will adhere to weekly monitoring for 12–16 wk and that results can be obtained and reviewed by the clinical team promptly. Notably, repeated courses of antivirals are sometimes required in high-risk patients when using a preemptive therapy strategy.[71]

The preemptive approach is not well studied in non–renal and non–liver transplant recipients. A retrospective multicenter study of R^+ heart transplant recipients comparing preemptive therapy and prophylaxis showed that the preemptive therapy group had an increased risk of CMV infection, CMV-related hospitalization, and increased acute rejection.[177] Thus, we suggest universal prophylaxis in D^+/R^- heart and lung transplant recipients, given the high rates of CMV disease and CMV indirect effects.[138,178] There are no studies available to prove the efficacy of the preemptive approach in R^+ lung transplant; thus, universal prophylaxis is preferred in the majority of lung transplant centers.[179]

Surveillance After Prophylaxis

A hybrid approach comprising "surveillance after prophylaxis" is often adopted for early detection of late CMV infection by many of the consensus experts, despite limited trial evidence to support this practice.[179-188] Most studies of surveillance after prophylaxis vary in the duration and frequency of monitoring. Although the incidence of late postprophylaxis CMV DNAemia is high with surveillance after prophylaxis strategy,[180,182-187] there does not appear to be an impact on long-term graft and patient survival.[185,186] There is also variability in whether patients with late DNAemia progress to CMV disease.[180,184-186] Therefore, the use of surveillance after prophylaxis may be considered in patients at increased risk for postprophylaxis CMV disease (D^+/R^-, R^+ with induction therapy, recent augmentation of immunosuppression, lung transplantation, and others deemed at high risk). Based on what is known from clinical trials of preemptive therapy (see earlier), surveillance after prophylaxis is likely most beneficial if monitoring is done weekly for 8–12 wk after the end of prophylaxis; less frequent may not capture early infection. CMV DNAemia thresholds for initiating treatment in asymptomatic patients when using this approach have not been defined but are usually similar to those adopted for preemptive therapy. Implementation of surveillance after prophylaxis can be challenging due to patient adherence to regular weekly surveillance.

Thresholds for Triggering Preemptive Therapy (or Surveillance After Prophylaxis)

Specific viral load thresholds for triggering therapy in asymptomatic patients have not been well defined. This is due to significant interassay and interinstitutional variations seen with CMV DNA testing, as well as the variable impact of underlying immunity (primary versus reactivation infection, intensity of immunosuppression, impact of various immunosuppressive agents used for induction and maintenance). Although low viral loads are likely to be more clinically significant in those at higher risk for infection, using a viral load threshold that is too low (especially with ultrasensitive assays) can result in unnecessary treatment. Programs may wish to define their own local thresholds based on their assay, specimen type, and patient risk factors. Table 4 highlights recent thresholds used in various research studies using diverse assays.

Some groups have suggested that the kinetics of the CMV DNA doubling time may be a valuable diagnostic parameter for preemptive therapy, given that quantitative real-time PCR assays show linearity above their limit of quantification and may allow for direct comparison of results obtained across centers using similar or different quantitative real-time PCR assay.[189-191] Viral replication kinetics have shown that viral load in the first surveillance sample and the rate of increase define the risk of subsequent CMV disease; this risk is different in CMV-naive patients undergoing primary CMV infection versus those with prior immunity.[27,192]

Prevention Strategies for CMV D^-/R^-

When both donor and recipient are seronegative for CMV, there is minimal risk of CMV infection, and routine prevention of CMV is not recommended, provided that leukodepleted or CMV-seronegative blood products are used. Antiviral prophylaxis against other herpes infections (especially disseminated varicella and herpes simplex) with acyclovir, famciclovir, or valacyclovir should be considered. Optimal length of such prophylaxis has not been determined; some programs use the same duration as for valganciclovir, whereas others use shorter intervals.

Secondary Antiviral Prophylaxis and Recurrent Infection

Recurrent DNAemia upon completion of treatment and/or preemptive therapy occurs, particularly in high-risk transplant patients,[143,193] although viral load replication may be slower and subsequent peak viral load significantly lower than the initial episode,[71] possibly due to an emerging immune response. Data are limited on routine monitoring after an episode of CMV infection, although some experts monitor for recurrent CMV infection weekly in specific patients at risk for recurrence, similar to surveillance after prophylaxis. The duration is dependent on the ongoing risk, including the presence or absence of CMI, often for 8–12 wk. Although many transplant centers treat all recurrent episodes of CMV DNAemia irrespective of a relevant threshold,[143] some episodes of recurrent CMV DNAemia (especially when <3 $\log_{10}$ IU/mL [1000 IU/mL]) may resolve spontaneously.[193]

Secondary prophylaxis appears to prevent CMV infection while patients are receiving antivirals but does not appear to reduce the overall rate of recurrences after discontinuation.[194-197] There have been no prospective randomized trials of secondary antiviral prophylaxis for the prevention of recurrences of CMV infection and/or disease. Although secondary prophylaxis is not routinely recommended, the vast majority of consensus conference experts reported using secondary prophylaxis in specific situations where the patient is at risk of CMV recurrence (Figure 1). Risk factors for recurrent CMV among study populations have not been adequately defined and may differ from those associated with primary infection or disease.[196,198] Consensus experts considered secondary prophylaxis in patients with CMV D^+/R^- serostatus, lung transplant, a high CMV viral load at presentation, recent use of antilymphocyte agents or augmentation of immunosuppression, low absolute lymphocyte count (ALC), negative CMI assays, and in patients who struggle with recurrent CMV.[162,194-196,198-200]

Although valganciclovir has been the antiviral used most commonly for secondary prophylaxis, letermovir as secondary prophylaxis has also been studied in a few case reports and case series.[124,129,201]

Prevention During Augmented Immunosuppression

Prophylaxis may be preferred over preemptive therapy in certain high-risk patients, including those who have received lymphocyte-depleting antibodies, second signal inhibitors (eg, belatacept), and other potent immunosuppression including desensitization or ABO-incompatible protocols (including those on rituximab, bortezomib, eculizumab, and plasmapheresis and other desensitization agents).[202] This is based on several observational studies that show an increase in rates of CMV infection or CMV tissue-invasive disease in patients receiving therapy for acute rejection treated with the above modalities.[203-209] Although the duration of prophylaxis is not well defined, a preventive strategy (either prophylaxis or preemptive

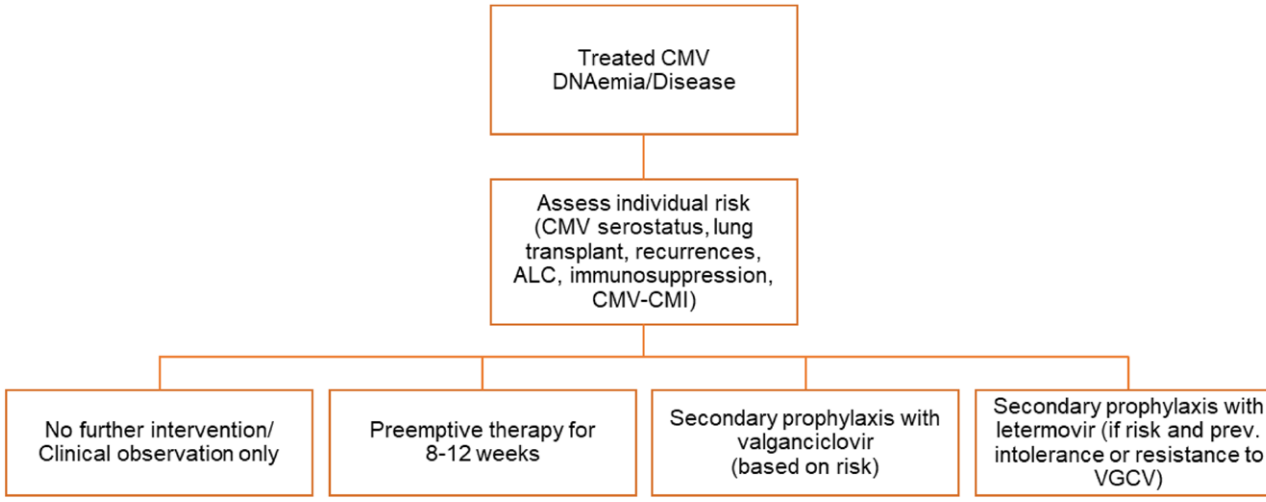

FIGURE 1. Suggested options for secondary prevention after an episode of treated CMV DNAemia/disease. In R^+ kidney recipients, consider switching from mycophenolate to mTOR and reduce CNI. ALC, absolute lymphocyte count; CMI, cell-mediated immunity; CMV, cytomegalovirus; CNI, calcineurin inhibitor; mTOR, mammalian target of rapamycin; VGCV, valganciclovir.

therapy) for the duration of augmented immunosuppression is reasonable.

Lower-dose Valganciclovir Prophylaxis

Some centers, in hopes of improving tolerability and reducing costs, use half the recommended dose of valganciclovir for prophylaxis (ie, 450 mg daily in patients with normal renal function), sometimes called "mini-dosing."[210] This is based on pharmacokinetic (PK) data showing comparable ganciclovir exposure between valganciclovir 450 mg/d and oral ganciclovir 3 g/d.[211,212] Since the previous edition of the guidelines, there have been numerous published studies of low-dose valganciclovir prophylaxis. The vast majority are retrospective observational studies in CMV seropositive kidney transplant recipients.[213-221] These studies show similar CMV outcomes but are likely not powered to show differences in CMV outcomes. In addition, many studies lack information on precise renal function and immunosuppression, which makes it difficult to determine whether the "mini-dose" was in fact lower than the appropriate renal dosed valganciclovir. A study of 585 SOT recipients showed that breakthrough infections on prophylaxis are more likely to occur in recipients of estimated glomerular filtration rate (eGFR)-adjusted prophylaxis doses below the manufacturer's recommendations.[216] Moreover, a study that used high-throughput sequencing showed the presence of ganciclovir resistance mutations in those with breakthrough CMV due to subtherapeutic plasma ganciclovir concentrations.[222] Low-dose valganciclovir prophylaxis is less studied in D^+/R^- patients, but a few studies have shown a higher risk of breakthrough infection with low-dose prophylaxis compared with standard doses, a greater severity of CMV disease in those that develop breakthrough on low-doses and numerically more ganciclovir resistance.[213,223] Data on low-dose valganciclovir prophylaxis are limited in thoracic transplant recipients.[224,225] The use of low-dose valganciclovir prophylaxis is not recommended; dosing should be according to renal function (Table 5).

TABLE 5.

Dosage recommendations for ganciclovir and valganciclovir and valacyclovir for adult patients with impaired kidney function (using the Cockcroft-Gault formula)

CrCL, mL/min	Treatment dose	Maintenance/prevention dose
Intravenous ganciclovir (adapted from[226])		
≥70	5.0 mg/kg q12h	5.0 mg/kg q24h
50–69	2.5 mg/kg q12h	2.5 mg/kg q24h
25–49	2.5 mg/kg q24h	1.25 mg/kg q24h
10–24	1.25 mg/kg q24h	0.625 mg/kg q24h
<10	1.25 mg/kg 3×/wk after hemodialysis	0.625 mg/kg 3×/wk after hemodialysis
Oral valganciclovir (adapted from[227,228])		
≥60	900 mg q12h	900 mg q24h
40–59	450 mg q12h	450 mg q24h
25–39	450 mg q24h	450 mg q48h
10–24	450 mg q48h	450 mg twice weekly
<10	200 mg 3×/wk after hemodialysis[a]	100 mg 3×/wk after hemodialysis[a]
Oral valacyclovir (high dose)[112]		
>75	–	2000 mg 4×/d
51–75	–	1500 mg 4×/d
26–50	–	1500 mg 3×/d
10–25	–	1500 mg 2×/d
<10 or dialysis	–	1500 mg 1×/d

[a]Oral solution must be used in this instance (as valganciclovir tablets cannot be split).
CrCL, creatinine clearance.

CMV Immunoglobulin for Prophylaxis

CMV immunoglobulin (CMVIG) was first licensed for use in the prevention of primary CMV disease in renal transplant recipients.[229,230] Its role in prophylaxis is limited in the era of potent antivirals, primarily due to limited effectiveness as a single agent compared with antivirals, as well as expense- and infusion-related toxicity. Adequately powered, randomized trials measuring the additive benefit

have not yet been performed. There are in vitro differences between immunoglobulin products with respect to titers of CMV antibody (higher in CMVIG), but clinical differences have neither been evaluated nor demonstrated. In vitro studies show consistently enhanced functional antibodies against CMV in CMVIG compared with regular IVIG.[231,232] CMVIG may be useful for prevention in combination with antivirals in higher-risk (CMV D^+/R^-) lung or small bowel transplant recipients, based on older studies, before the use of more prolonged antiviral prophylaxis.[139,233-235] The combination demonstrated reduced incidence of CMV disease, and bronchiolitis obliterans syndrome (chronic rejection), with improved survival in a cohort of lung transplant recipients.[236] Use of the combination has been based, in part, on the demonstration of synergy between antibody (serum) and ganciclovir in animal models of lethal CMV infection.[237] CMVIG should not be used as the sole agent for CMV prevention in lung transplant recipients. CMVIG has been used in patients for prophylaxis with prolonged neutropenia who are intolerant of ganciclovir, but alternative options such as letermovir may also be considered. It has also been used in patients with refractory CMV disease and hypogammaglobulinemia.[238] In summary, CMVIG is not generally recommended for use, although there may be specific circumstances, especially in thoracic organs, when used in combination with antivirals, in which some benefit has been demonstrated (see the Immunologic Monitoring, Vaccines and Cellular Therapy section).

Role of mTOR Inhibitors

There are now 10 systematic reviews and meta-analyses showing that the incidence of CMV infection/disease is lower among patients receiving immunosuppressive regimens containing mTOR inhibitors in kidney and heart transplant recipients.[239-248] Most of the supportive evidence is from de novo use of mTOR inhibitor with reduced calcineurin inhibitor (CNI) regimens in kidney transplant recipients.[249-255] In the TRANSFORM study, the incidence of CMV infections was lower in the everolimus group compared with the mycophenolate group (3.6% versus 13.3%; $P < 0.001$).[252] In some studies, mTOR inhibitors lowered the risk of CMV infection as low as 0%–10%, which may reduce or eliminate the need for universal antiviral prophylaxis.[239,255,256] Conversion from mycophenolate to mTOR inhibitor with reduced CNI either later posttransplant or after a first episode of CMV infection/disease also reduced recurrence of CMV infection in kidney transplant recipients.[256,257] These benefits are largely limited to CMV seropositive recipients, plus those who are of low immunological risk for rejection and are able to receive reduced doses of CNI. Efficacy of mTOR inhibitors to reduce CMV infection was highly dependent on whether patients could tolerate mTOR inhibitors without discontinuing them.[252,253] Fewer studies also show the benefit of de novo use of mTOR inhibitors in reducing CMV infection/disease in liver,[258] heart,[259,260] lung,[261-264] and pediatric kidney transplant recipients.[265] Posttransplant conversion to everolimus together with valganciclovir prophylaxis has also been shown to reduce CMV infection/disease in heart transplant recipients.[266] The antiviral effects of mTOR inhibitors have been linked to improvement in T-cell functionality/memory and inhibition of select pathways involved in CMV replication.[267]

Consensus Statements and Recommendations

General CMV Prevention Recommendations

- We recommend a CMV prevention strategy with prophylaxis OR surveillance with preemptive therapy for all at-risk transplant recipients (Table 3; strong, high).
- The CMV prevention strategy may be tailored by the individual center, according to the local CMV infection/disease incidence, individual patient risk as well as logistic and economic feasibility of surveillance and/or antiviral medication (expert opinion).
- We do not recommend routine CMV DNAemia monitoring while on appropriate dosing of prophylaxis (strong, moderate).

D^+/R^- Recommendations

- For D^+/R^- kidney transplant recipients, we recommend the use of either prophylaxis (strong, high) or preemptive therapy (strong, moderate).
- We recommend that either valganciclovir, ganciclovir, or letermovir be used for primary prophylaxis in D^+/R^- kidney transplant recipients (strong, high).
- For D^+/R^- liver transplant recipients, we recommend the use of either prophylaxis (strong, moderate) or preemptive therapy (strong, high).
- We suggest prophylaxis may be preferred in D^+/R^- liver and kidney transplant patients at greater risk of CMV, such as those receiving higher immunosuppression exposure with lymphocyte-depleting antibodies, second signal inhibitors, desensitization protocols, treatment of steroid-resistant acute cellular rejection, treatment of antibody-mediated rejection, and those with HIV (weak, moderate).
- For D^+/R^- heart and lung transplant recipients, we suggest the use of prophylaxis over preemptive therapy based on literature suggesting the former strategy is associated with lower incidence of CMV infection/disease and less indirect effects on graft function and mortality (weak, low).
- For D^+/R^- lung, heart, liver, or kidney transplants where prophylaxis is used, if there is intolerance to valganciclovir or ganciclovir, we suggest switching to preemptive therapy or to letermovir prophylaxis (weak, low).
- For other D^+/R^- SOTs (pancreas, islet, intestinal, and vascularized composite allotransplantation, such as hand, face, etc), we suggest prophylaxis because data regarding the role of preemptive therapy are limited (weak, very low).

D^+/R^- Durations

- For D^+/R^- kidney recipients, we recommend prophylaxis for 6 mo (strong, high).
- In D^+/R^- liver, heart, and pancreas recipients, we recommend prophylaxis for 3 mo (strong, moderate) to 6 mo (strong, low).
- For D^+/R^- islet recipients, prophylaxis for 3 mo is suggested (weak, low).
- For D^+/R^- lung transplant recipients, we recommend 12 mo prophylaxis (strong, moderate). Some experts may extend prophylaxis beyond 12 mo based on high rates of CMV infection (expert opinion).
- For D^+/R^- vascularized composite (eg, hand, face) and intestinal transplant recipients, we suggest a minimum of 6 mo of prophylaxis (weak, low).

- When a range is given, consider the degree of immunosuppression to determine the duration of prophylaxis, including the use of lymphocyte-depleting antibodies for induction.

R+ Recommendations

- We recommend either prophylaxis (strong, high) or preemptive therapy (strong, moderate) for seropositive recipients (R+) after kidney transplant. Where CMV-CMI testing is available, this can be used to determine and tailor the strategy in kidney transplant (see CMV-CMI recommendations).
- We recommend either prophylaxis (strong, moderate) or preemptive therapy (strong, high) for seropositive recipients (R+) after liver transplant.
- We suggest prophylaxis may be preferred in R+ liver and kidney transplant patients at greater risk of CMV, such as those receiving higher immunosuppression exposure with lymphocyte-depleting antibodies, second signal inhibitors, desensitization protocols, treatment of T cell–mediated rejection, steroid-resistant acute rejection, treatment of antibody-mediated rejection, and those with HIV (weak, moderate).
- For R+ heart and lung transplant recipients, we suggest the use of prophylaxis over preemptive therapy based on literature suggesting a lower incidence of CMV infection/disease with the former strategy and less indirect effects on graft function and mortality (weak, low).
- For R+ lung, heart, liver, or kidney transplants where prophylaxis is used, if there is intolerance to valganciclovir or ganciclovir, we suggest switching to preemptive therapy or to letermovir prophylaxis (weak, low).
- For other R+ SOTs (pancreas, islet, intestinal, and vascularized composite allotransplantation, such as hand, face, etc), we suggest using prophylaxis because data regarding the role of preemptive therapy are limited (weak, very low).

R+ Durations

- When a prophylaxis strategy is used for prevention in R+ patients (with either D+ or D–), 3 mo of antiviral medication is recommended for routine kidney (strong, high), pancreas, liver, and heart (strong, moderate) and islet (weak, low) transplant recipients. Where CMV-CMI testing is available, it can be used to determine and tailor the strategy in kidney transplant.
- For those receiving more potent immunosuppression (lymphocyte-depleting antibodies, desensitization protocols) or vascularized composite and intestinal transplant recipients, between 3 and 6 mo of prophylaxis is suggested (weak, low).
- For R+ lung transplant recipients, 6–12 mo of prophylaxis is recommended (strong, moderate).

Preemptive Therapy

- With preemptive therapy, we recommend CMV monitoring at least once weekly for 12–16 wk after transplant; longer monitoring would be indicated if there is perceived ongoing increased risk for CMV disease (strong, moderate). Less frequent monitoring increases the risk of CMV disease (strong, moderate).
- We recommend using lower CMV DNAemia thresholds for initiating preemptive therapy in D+/R– than R+ subgroups (strong, moderate). Individual centers need to decide the CMV DNAemia threshold according to the assay, type of blood sample used, and local CMV infection/disease profile.
- In asymptomatic patients with CMV DNAemia above prespecified threshold, we recommend starting treatment with valganciclovir (strong, high) and treating until resolution of CMV DNAemia (see the CMV Treatment section), with a minimum of 2 wk of treatment. Intravenous ganciclovir is a less preferred option unless concerns about absorption exist. Resume weekly CMV DNAemia monitoring to complete the duration of preemptive therapy and continue beyond according to immune assessment.

Surveillance After Primary Prophylaxis

- We suggest surveillance after prophylaxis in patients at increased risk for postprophylaxis CMV disease (weak, low). The value is probably greatest if done weekly for 8–12 wk. Monitoring every 2 or 4 wk may be insufficient for optimal preemptive interventions.

Other Strategies to Prevent CMV

- In CMV D–/R– or when using letermovir as prophylaxis, or when using a preemptive strategy, antiviral prophylaxis against other herpes infections (varicella and herpes simplex) with acyclovir, famciclovir, or valacyclovir should be considered (strong, high).
- To avoid transfusion-transmitted CMV, we recommend the use of leukoreduced or CMV-seronegative blood products, especially in D–/R– (strong, moderate).
- We do not recommend the routine use of secondary prophylaxis after treatment of CMV disease or infection (weak, low).
- We suggest secondary prophylaxis to delay and/or prevent recurrent CMV infection in high-risk situations such as increased immunosuppression, low ALC, low CMV-CMI, repeated recurrences, or inability to monitor patients for CMV replication (weak, low).
- The choice of agents for secondary prophylaxis and duration of secondary prophylaxis can be individualized (expert opinion). Typical duration for secondary prophylaxis is 8–12 wk. Further personalization can be based on the evaluation of immune status.
- We do not recommend the routine use of low-dose valganciclovir for CMV prophylaxis (weak, low).
- Local practices should guide relevant thresholds to initiate treatment given that there is insufficient evidence for an optimal cutoff or threshold (weak, low).
- In R+ kidney transplant patients given de novo mTOR-based immunosuppression, we recommend either a preemptive strategy or close clinical monitoring (strong, high).
- After a first episode of CMV infection/disease, we suggest considering switching to mTOR inhibitor from an antiproliferative agent in low immunological risk R+ kidney transplant recipients to reduce the rate of recurrent CMV infection (weak, moderate).
- We recommend that treatment of rejection with lymphocyte-depleting antibodies in at-risk recipients should result in reinitiation of prophylaxis or preemptive therapy for 4–12 wk (weak, moderate); a similar strategy may be considered during treatment of rejection with high-dose steroids or apheresis (weak, very low).
- CMVIG and IVIG are not generally recommended for use in prevention, although there may be specific circumstances

for CMVIG use, especially in thoracic organs, when used in combination with antivirals, or for IVIG those with severe hypogammaglobulinemia, some benefit has been demonstrated (weak, low).

Future Directions

- Defining cutoffs for preemptive therapy in various risk groups would help to standardize this strategy.
- More data are needed for letermovir prophylaxis, especially in non–kidney organ groups and R+ kidney recipients, especially related to breakthrough infections and tolerability. A pharmacoeconomic analysis of letermovir use in various organ groups is also needed.
- More PK studies of valganciclovir dosing based on renal function are needed.
- Further studies incorporating CMV-CMI in prophylaxis and preemptive strategies would help further define the role of CMV-CMI.

IMMUNOLOGIC MONITORING, VACCINES, AND CELLULAR THERAPY

The immune system is a key factor in CMV management after SOT, and both innate and adaptive immune mediators are necessary for control of CMV after transplantation.[268,269]

Innate Factors

Single nucleotide polymorphisms of innate immune genes (eg, Toll-like receptors, mannose-binding lectin) have been associated with an increased risk of CMV disease.[270,271] Lower C3 levels early after transplant have been associated with a higher incidence of CMV disease.[272] Lower levels of natural killer cells[273] and inhibitory killer cell immunoglobulin-like receptor genotypes have been described as a predisposing factor for CMV reactivation.[274-276] γδ T cells have both innate and adaptive characteristics and play a role in the immune response to CMV.[277,278] Longitudinal surveillance of Vδ2-γδ T cells in kidney transplant recipients has predicted CMV infection resolution.[279] Although these associations are important for understanding the pathogenesis of CMV, they have not been sufficiently studied to be implemented into practice.

Adaptive Humoral Immunity

The protective role of antibody response against CMV envelope proteins has been described in the SOT setting.[280] Antibodies targeting the glycoprotein B (gB) and gH[281] and the gH/gL/pUL128-pUL130-pUL131A complex block CMV entry into target cells.[282-284] Antibodies against nonneutralizing epitopes of envelope proteins can recruit complement and promote antibody-dependent cell-mediated cytotoxicity and phagocytosis.[280]

The protective role of antibodies against CMV infection was first suggested in passive immunization studies using intravenous immunoglobulin preparations. There are 2 formulations available: CMVIG and IVIG. CMVIG is an immunoglobulin preparation derived from pooled human plasma selected for higher anti-CMV antibody titers, with a significant correlation observed between anti-CMV IgG ELISA and CMV neutralizing titers.[231,232] CMVIG has 3–10 times higher CMV-specific antibody concentrations and 4-fold higher neutralizing activity compared with IVIG, suggesting higher CMV neutralization capacity by CMVIG compared with standard IVIG.[231,285] CMV-specific IgG titers in IVIG can vary between lots.[231,285]

Although immunoglobulin preparations are approved for prophylaxis by the FDA in SOT and IVIG by the European Medicines Agency for the treatment of difficult-to-control infections in secondary antibody deficiencies (including SOT), optimal use in the era of widespread antiviral prophylaxis is not clear (**Table S3, SDC,** http://links.lww.com/TP/D243).[233,238,286–298,299] Although IVIG/CMVIG are sometimes combined with antivirals, there are no recent randomized controlled trials (RCTs) indicating superiority for prophylaxis or treatment. Case series suggest the potential role of adjunctive CMVIG in difficult-to-control or resistant CMV disease in thoracic organ transplant recipients, and many experts at the meeting use CMVIG in those contexts.[294] For adjunctive therapy, IVIG and CMVIG protocols are heterogeneous, with recommended doses of IVIG ranging from 200 to 400 mg/kg every 3–4 wk and CMVIG doses ranging from 50 to 150 mg/kg every 1–4 wk for prophylaxis, with increased doses and frequency for treatment.[300]

Risk factors for IgG hypogammaglobulinemia include patients with left ventricular assist device, use of extracorporeal membrane oxygenation, ABO-incompatible transplantation, and use of desensitization protocols and/or lymphocyte-depleting antibodies.[301,302] A meta-analysis demonstrated that severe hypogammaglobulinemia (IgG <400 mg/dL) during the first year posttransplant significantly increased the risk of CMV disease.[303] Multicenter studies showed that heart, lung, and kidney recipients with moderate hypogammaglobulinemia early posttransplant were at higher risk of CMV disease.[272,304–306] Interventional studies in heart transplant recipients with hypogammaglobulinemia have shown that CMVIG or IVIG replacement may prevent CMV disease.[238,295,296]

Anti-CMV monoclonal antibodies are in development although none have been approved for clinical use[297,307–309] (**Table S3, SDC,** http://links.lww.com/TP/D243). Administration of monoclonal antibodies seems to be safe, although no combination used in RCTs met primary efficacy endpoints, such as reduction in viremia and need for preemptive therapy.

Lymphopenia and Global Immune Biomarkers

Low ALC has been independently associated with increased risk for CMV infection in a growing number of studies (**Table S4, SDC,** http://links.lww.com/TP/D243).[194,200,310–323] Pretransplant lymphopenia is a strong predictor of CMV disease among liver recipients.[317] Early posttransplant, low ALC was predictive of a first episode of CMV infection.[318–321] After an initial episode, ALCs were lower in patients who developed recurrent CMV infection.[194,200] Low lymphocyte subsets such as CD4+/CD8+ T-cell counts are associated with CMV infection, but there is insufficient evidence to recommend routine monitoring.[322]

Several new pathogen-agnostic (global) biomarkers aiming to measure the net state of immunosuppression as well as predict CMV and other infections are now available.[324,325] The ImmuKnow Cell Function Assay (Eurofins Viracor, USA) measures overall immune function by measuring ATP

produced by CD4+ T cells in response to whole blood stimulation by phytohemagglutinin.[326] The QuantiFERON-Monitor (Qiagen, USA) measures global immune function after stimulation of whole blood with a lyosphere containing R848 and anti-CD3.[327–329] Torque Teno virus is a nonpathogenic anellovirus with a seroprevalence of ~90%. Commercial PCR assays are available, and higher levels of Torque Teno virus DNAemia correspond with higher degrees of immunosuppression.[330,331] Several immunological scores incorporating biomarkers and clinical factors have been developed and validated to identify patients at higher risk of CMV infection, but none have widespread uptake thus far.[332–341]

Adaptive Cellular Immunity

In the past 2 decades, multiple studies have assessed the value of CMV-CMI assay for predicting CMV events in SOT recipients[300,342,343] with the goal of individualizing preventive approaches.[342] There are several CMV-specific T-cell assays available, many of which have moved from the experimental to the clinical setting (Table 6). Commercially available assays rely on the detection of interferon-gamma (IFN-γ) after stimulation of whole blood or peripheral blood mononuclear cells with CMV-specific antigens or overlapping peptides.

Apart from CMV-specific stimuli, all tests include a polyclonal stimulus as a positive control, allowing for the assessment of general immune responsiveness. Nonresponse after polyclonal stimulation (ie, a lack of response of the positive control) has been associated with a higher incidence of CMV disease.[344] Test sensitivity decreases in lymphopenic patients because an adequate number of cells are required for IFN-γ production, particularly with the ELISA-based test.

Currently, several commercial CMV-CMI assays are available: T-SPOT.CMV (Oxford Immunotec, Abingdon, UK), T-TRACK CMV (Mikrogen, Neuried, Germany), and QuantiFERON-CMV (QF-CMV, Qiagen, Hilden; Germany; Table 6). The QF-CMV assay is a commercially available ELISA-based IFN-γ release assay that detects CD8 T cells after peptide stimulation, whereas the ELISPOT-based assays measure both IFN-γ-producing CD4+ and CD8+ T cells. A fourth test using intracellular cytokine staining, CMV inSIGHT T-Cell Immunity Panel (Eurofins Viracor, KN), is commercially available in the United States, but further data are needed to help define optimal use.[345] Advances in flow cytometry, such as the ability to test several markers simultaneously (eg, with CyTOF technology) or major histocompatibility complex multimer-based assays that directly stain peptide-specific T cells, can increase our understanding of immune control although these are available in the research setting only. There are scarce data comparing the different Elispot assays and the QF-CMV head-to-head,[346] so it is difficult to recommend the use of one test over another.[347,348]

Clinical Scenarios Evaluating CMV-CMI Assays

General Scenarios

CMV-CMI assays have been used in multiple observational studies in different clinical settings, including R+ candidates before transplantation,[349–351] R+ recipients early after transplant before starting a preventive strategy,[346,349,352,353] high-risk D+/R− patients and R+ receiving lymphocyte-depleting antibodies during antiviral prophylaxis,[344,346,349,352,323,354–357] patients with asymptomatic CMV DNAemia, and at the end of antiviral therapy (Table 7).[197,358,359] Although most studies showed that patients with detectable CMV-CMI were at lower

TABLE 6.

Advantages and limitations of various assays for immune monitoring of CMV

Assay	Advantages	Limitations	Comments
ELISA	Whole blood assay with low blood volume (3 mL) is simple to perform, and results are available after 30–40 h. Knowledge of HLA is not necessarily required, can be done in any center, and stimulated plasma can be sent to a reference laboratory	CD8+ responses only. Sensitive to lymphopenia. Rare patients whose HLA types are not covered in assay	Commercial availability (approved in Europe QuantiFERON-CMV (Qiagen, Germany)
ELISpot	Identifies both CD4+/CD8+ T cells. Knowledge of HLA is not necessarily required. Results available after 30–40 h	Need for purified PBMC from 10 mL blood (approximately 1×10^6 PBMC). Cannot differentiate CD4+ and CD8+ T cells	Potential to freeze PBMCs and ship to reference laboratory for testing. Commercial availability (T-SPOT.CMV and T-TRACK CMV CE marketed in Europe; T-SPOT.CMV is LDT in the United States)
ICS	Whole blood assay with low blood volume (1 mL) or PBMC, short incubation time, and results available after 8 h. Identifies CD4+ and CD8+ T cells. Knowledge of HLA is not necessarily required. Provides quantitative and qualitative characterization	Needs access to a flow cytometer. Not standardized	Most data are available with this technique. Potential to freeze PBMCs and ship to reference laboratory for testing. Commercial availability (VIRACOR Insight in the United States)
MHC-multimer staining	Fast assay (1–2 h). Whole blood assay with low blood volume (0.5–1.0 mL) or PBMC	CD8+ responses only. Needs access to a flow cytometer. HLA and epitope specific. No information about the function is available unless combined with ICS. Not standardized	Unlikely to be used on a widespread basis in clinical diagnostics

CMV, cytomegalovirus; ELISpot, enzyme-linked immunosorbent spot; ICS, intracellular cytokine staining; LDT, laboratory-developed test; MHC, major histocompatibility complex; PBMC, peripheral blood mononuclear cell.

TABLE 7.

Potential clinical uses and management based on CMV-specific immune monitoring

Clinical setting	Viral load	CMI result	Action	Interpretation
Pretransplant				
Pretransplant R+	NA	Negative	Prophylaxis or surveillance	Indicates low-level protection
		Positive	Low accuracy for predicting immune protection. New posttransplant CMV-CMI test recommended.	Induction immunosuppression may hamper a positive pretransplant CMV-CMI and induce a negative CMV-CMI result
R+ 14 d posttransplantation	NA	Negative	Prophylaxis or surveillance	Indicates low-level protection
		Positive	Stop prophylaxis/reduce intensity of monitoring	Indicates protection
Pretransplant seropositive patients with potential passive antibodies	NA	Negative	Assign CMV infection status	Passive immunity (T cells are not transferred)
		Positive		True Infection
Posttransplant prophylaxis				
End of prophylaxis	NA	Positive	Stop prophylaxis	Indicates protection
		Negative	Continue prophylaxis or stop prophylaxis and do surveillance	Indicates lack of protection
R+ on lymphocyte-depleting antibodies during prophylaxis	NA	Positive	Stop prophylaxis	Indicates protection
		Negative	Continue prophylaxis or stop prophylaxis and do surveillance	Indicates lack of protection
Posttransplant preemptive therapy				
Asymptomatic R+ patients (>1 mo posttransplant)	Negative	Positive	Continue surveillance	Low risk; indicates protection
	Negative	Negative	Close surveillance	Increased risk; indicates lack of protection
	Positive	Positive	No treatment; close monitoring	Low risk; indicates sufficient immunity
	Positive	Negative	Treatment	Indicates lack of protection
End of treatment	Negative	Positive	Stop treatment	Low risk of relapse, sufficient immunity
	Negative	Negative	Secondary prophylaxis	High risk of relapse, lack of protection

CMI, cell-mediated immunity; CMV, cytomegalovirus; R+, CMV seropositive.

risk for CMV events, large differences in positive and negative predictive values have been observed, depending on CMV serostatus, assay used, and endpoints assessed (DNAemia versus disease). These assays have demonstrated the best predictive value in intermediate-risk patients, namely R+ kidney transplant recipients not receiving lymphocyte-depleting antibodies. They perform less well in D+/R− patients, as only a minority of these patients will develop a detectable CMV-CMI by the end of prophylaxis.[344,354,357,360]

Since the publication of the last guidelines, 4 RCTs have been performed.[361–364] Evidence is therefore stronger in the scenarios investigated by these trials (below). Recommendations are tailored according to the transplant type included, with caution advised to extrapolate findings to other SOT populations.

Pretransplant and Early Posttransplant Periods

Assessment of CMV-CMI pretransplant in R+ recipients can identify patients without detectable CMV-CMI who are at higher risk of posttransplant CMV events.[349,350,365] Given that some patients may experience a significant reduction in CMV-CMI after transplantation, an early assessment on posttransplant day 15 offers better predictive value.[365] This was confirmed in an RCT of antiviral prophylaxis versus a preemptive approach in R+ kidney transplant recipients, where CMV-CMI pretransplant and early posttransplant assessments were used to stratify the risk of CMV events.[361] Patients with a positive CMV-CMI test early posttransplant had significantly lower rates of CMV DNAemia and disease, regardless of the preventive strategy used, especially in those not receiving lymphocyte-depleting antibodies.

Posttransplant Period During Antiviral Prophylaxis

Two RCTs used CMV-CMI testing to guide early discontinuation of prophylaxis after transplantation versus fixed duration of prophylaxis.[362,364] Both showed a reduction in the duration of prophylaxis in the intervention arm by a mean of 30 d[362] and 26 d.[364] Rates of CMV replication were similar between groups. Notably, in these 2 trials, the incidence of CMV disease was low in R+ patients, although a surveillance after prophylaxis approach was implemented.[362,364] An additional multicenter study of CMV-CMI guided prophylaxis showed utility for tailoring the duration of prophylaxis in R+ transplant patients receiving lymphocyte-depleting antibody induction.[366]

In an RCT involving 118 lung transplant recipients, patients were randomly assigned to receive either a fixed duration of antiviral prophylaxis (5 mo) or a duration based on the results of the QF-CMV assay.[363] CMV replication was significantly lower in the intervention group, likely due to receiving longer prophylaxis.[363] A follow-up study including 263 lung transplant recipients demonstrated a high correlation between CMV serostatus and CMV-CMI, with a reduction in CMV infection with extended prophylaxis regardless of CMV-CMI results.[354]

Preemptive Therapy and Relapse After Antiviral Therapy

A small cohort study showed that QF-CMV could identify patients with asymptomatic CMV DNAemia in whom spontaneous resolution occurred.[359] Another study showed that adding clinical variables, such as age and type of donor, increased the negative predictive value of CMV-CMI for identifying CMV infection needing antiviral treatment.[367] In a nonrandomized trial, the QF-CMV assay was used to identify patients at higher risk for relapse after completion of antiviral therapy. Relapse of CMV DNAemia was seen in a minority of patients with a positive QF-CMV, although patients with a negative result received secondary prophylaxis.[197]

T-cell Therapy and Vaccines

Adoptive T-cell Therapy

Multiple case reports[368–372] and phase 1/2 trials[373–378] have demonstrated the use of CMV-specific T cells for resistant/refractory CMV infection in SOT recipients (Table 8). In general, CMV-specific T cells from the recipient (autologous), the donor in hematopoietic cell transplantation (HCT), or third-party donors are infused into the recipient after enrichment or expansion with CMV peptides or viral lysates. These approaches have led to the reconstitution of CMV immunity, reduction in CMV viral loads, and/or resolution or improvement of CMV events. Cells can be obtained from the transplant recipient; however, an important limitation is that the process of generating adequate numbers of effector cells can take several weeks and thus may not be feasible for patients requiring urgent therapy and is more difficult to obtain from CMV-naive individuals. In vitro-expanded autologous CMV-specific T cells have been successfully obtained in 20 of 21 SOTs with refractory CMV in a phase 1 clinical trial, and 84% of the 13 infused patients showed improved symptoms without significant adverse events.[373,374] There is increasing interest in "off-the-shelf" T cells using HLA-matched third-party banked cells.[379] This method could also allow the generation of cells active against multiple viruses, including CMV, Epstein-Barr virus, and adenovirus, and have been tested with good safety in SOT.[375] Commercialization of third-party CMV-specific T cells may increase use for resistant/refractory CMV in SOT recipients.[380,381] With additional data supporting efficacy and safety from RCTs, the use of cellular therapies earlier during CMV events as a complement to antiviral therapy in patients at high risk for clinical and/or virologic failure could be considered.[382] Additional studies are needed to identify the best protocols for CMV-specific T-cell enrichment and expansion, the optimal timing of use, and the influence of different immunosuppressive therapies on treatment efficacy. Safety and efficacy need to be confirmed in RCTs before routine use.[382] Other cellular types are under current evaluation, such as natural killer cells and γδ T cells.[378]

CMV Vaccines

CMV vaccines represent an attractive approach by targeting the underlying immune deficits that predispose to CMV infection and disease. Multiple CMV vaccine platforms have shown preliminary evidence of safety and variable degrees of immunogenicity and/or efficacy, but none thus far appear to be adequately protective. Several CMV vaccines have been or are currently under study in RCTs, but none are available for routine clinical use or approved by regulatory authorities. Types of vaccines include live-attenuated, recombinant/chimeric viral vectors, recombinant subunit, or gene-based vaccines (DNA, mRNA)[383] (Table 9). Pretransplant vaccination of adult CMV-seronegative and seropositive candidates with a live-attenuated vaccine based on the Towne strain of CMV was found to be safe and decreased the severity of CMV disease but failed to prevent infection; this vaccine is no longer being developed.[385] Pretransplant vaccination with a recombinant gB subunit vaccine with MF59-adjuvant was shown to induce neutralizing antibodies[395] and to reduce CMV DNAemia and days of antiviral drug during preemptive therapy, particularly in D^+/R^- patients.[390] Trials of gB/pp65-based DNA plasmid vaccine in CMV seropositive HCT recipients and D^+/R^- SOT recipients did not demonstrate a reduction in CMV DNAemia.[387,389] A peptide-based vaccine, CMVPepVax (peptide derived from pp65 and adjuvanted with imiquimod), in 10 seronegative kidney transplant candidates showed an immune response in 50% of patients, and none of these responders experienced reactivation within 18 mo posttransplantation.[396] Posttransplant vaccination with Triplex vector vaccine (poxvirus, modified vaccinia Ankara), encoding CMV pp65, IE-1, and IE-2 antigens, was safe and reduced CMV incidence by ~50% in a phase 2 trial in adult CMV seropositive allogeneic HCT recipients.[397] A trial of the Triplex modified vaccinia Ankara vaccine in CMV-seronegative liver transplant candidates is underway with expected completion in 2028.[398] A CMV mRNA (mRNA-1647) vaccine that is undergoing phase 3 study in women of child-bearing age for prevention of congenital CMV infection is also being evaluated in CMV seropositive HCT recipients.[399] Multiple other CMV vaccines are in earlier stages of development.

Consensus Statements and Recommendations

Innate and Humoral Immunity

- IgG hypogammaglobulinemia is associated with an increased risk of CMV disease after transplantation. Measurement of serum IgG is suggested in SOT recipients at high risk for IgG hypogammaglobulinemia within the first month after transplantation and retesting in situations where CMV is difficult to control (ie, severe disease, resistant/refractory CMV, antiviral intolerance; weak, moderate).
- Although CMVIG or IVIG is not recommended routinely for the prevention of CMV infection, it can be considered in combination with antiviral agents in specific circumstances, including thoracic organ transplantation, D^+/R^- serostatus, and severe IgG hypogammaglobulinemia (IgG <400 mg/dL; weak, low).
- Adding IVIG or CMVIG to antiviral treatment is not routinely recommended but may be considered for patients with severe disease, resistant/refractory CMV, antiviral intolerance, and/or if total IgG levels are <400 mg/dL, especially in thoracic organ transplant recipients (weak, low).
- There is no clinical evidence to recommend one preparation of immunoglobulins over the other (weak, low). Some experts prefer the use of CMVIG given enhanced CMV titers.

Global Immune Biomarkers

- We suggest that while no clear threshold has been widely validated, patients with lower ALC should be considered at higher risk for CMV infection (weak, low).

TABLE 8.
Cellular therapies

Cell therapy	Heterologous autologous	Transplant population(s)	Expansion from R+ and R− patients	Manufacturing	Indication	Level of evaluation and main results	Adverse events	Reference
Clinical trial								
Anti-CMV CD8+ T-cell therapy	Autologous	Kidney, lung, heart	R+ and R−	PBMC stimulated by CMV peptide pool of pp65, pp50, IE-1, gH, and gB, with IL-21 and IL-2. Total expansion duration of 14 d	Refractory CMV infection or disease, CMV recurrence, CMV with contraindication of antiviral drugs	Phase 1 single-arm open-label trial. 11/13 improved symptoms and viral load	Only grade 1 or 2: malaise; fatigue	373,374
Multiple specificity including anti-CMV adoptive CD8+ T-cell therapy	Third-party, heterologous, ≤2 HLA I matching	Kidney, liver, lung, heart, small intestine	R+ donor	PBMC from healthy donors, CMV Pepmix (pp65, IE-1), IL-4, and IL-7. Total expansion duration 11–12 d. Quadrivalent VST	Refractory or PCR CMV >500 IU/mL with coinfection with EBV, adenovirus, or BKV	Open-label phase 2 in SOT. Complete resolution: 40% KTR, 66% LiTR; 50% HTR; 50% LuTR	3% of acute rejection within the 4 wk after infusion	375
Anti-CMV adoptive CD8+ T-cell therapy	Third cryopreserved party, on matching for ≥2 HLA alleles	HCT	R+ donor	CD3+-enriched T-cell fractions, isolated from PBMCs by depletion of adherent monocytes and immunoadsorption of NK cells, irradiated autologous CAMS or EBV-BLCLs loaded with a pool of overlapping pentadecapeptides from CMV pp65, with weekly restimulations, and supplementation with IL-2 beginning at day 10–16. 28 d of culture	Refractory CMV infection	Phase 1/2 trials. Of 59 patients with refractory CMV, 64% had complete durable response	13% had possibly related AE (9% recurrent possibly related hypoxia)	376
Anti-CMV CD8+ T-cell therapy	DD VSTs and TP VSTs with ≥2 HLA alleles	HCT	R+ donors	DD or TP PBMC were stimulated with Pepmix (pp65, IE-1), IL-4, and IL-7. Total expansion duration 11–12 d. Quadrivalent VST	CMV replication >500 IU/mL and/or invasive infection	Phase 1/2 trial, retrospective comparison of DD (n = 37) and TP (n = 22). 56% response, but no difference between 2 protocols	Equal AEs but small cohort and not precisely described	377
NK cell therapy	Ex vivo expansion from haploidentical HCT donor	HCT	R+	PBMCs from 20 donors were cocultured with irradiated K562-mbIL21-41BBL APCs at a 1:1-cell ratio with 1000 IU/mL human IL-2 and autologous serum for 7 d. The medium was refreshed daily. NK cells were expanded for 14 d and 21 d	CMV prevention in R+	Ex vivo mbIL21/4-1BBL-expanded NK cells transfused at 20 ± 3 d and 27 ± 3 d posttransplantation, with subcutaneous injection of IL-2 (4×10^5 IU/m^2) 3 times a week for 3 wk after first adoptive NK cell infusion. In vitro, higher function of expanded NK; in vivo, higher number of NK cells in tissues, higher antiviral function. In 20 patients after NK infusion, refractory CMV disease was less common vs the historical group (30 vs 65%)	No major AEs but not precisely described	378

Continued next page

TABLE 8. (Continued)

Cell therapy	Heterologous autologous	Transplant population(s)	Expansion from R+ and R- patients	Manufacturing	Indication	Level of evaluation and main results	Adverse events	Reference
Experimental work								
γδ-T-cell therapy	Heterologous or autologous	Envisaged in kidney and HCT	R+ and R- equally	Under the Takeda license (DOT cells), a cocktail of cytokines and OKT3 for 21 d		In vitro and mouse models. In vitro: successful expansion from patients with refractory CMV and CMV- and CMV+ healthy donors all show similar cytotoxicity and IFN-γ production to CMV-infected cells. In vivo: control CMV after adoptive transfer in immunodeficient mice	NA	378

AE, adverse event; 4-1BBL APC, antigen-presenting cell expressing 4-1BB ligand; BKV, BK polyomavirus; CAMS, cytokine-activated monocyte; CMV, cytomegalovirus; DD, donor derived; DOT, delta one therapy; EBV-BLCL, Epstein-Barr virus transformed B lymphoblastoid cell line, HCT, hematopoietic cell transplantation; HTR, heart transplant recipient; IL, interleukin; KTR, kidney transplant recipient; LiTR, liver transplant recipient; LuTR, lung transplant recipient; NK, natural killer; OKT3, muromonab-CD3; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction; SOT, solid organ transplant; TP, third party; VST, virus-specific T cell.

Immune Monitoring

General

- Immune monitoring is a tool that has shown utility for delineating CMV preventive strategies in SOT recipients. Its implementation depends on the availability of the assays at a center and national level. If the assays are not available, the recommendations shown in the Prevention section and the CMV Treatment section should apply.
- Each assay type is unique and trial data should not be assumed to be comparable across different assays.

Pretransplant and Early Posttransplant (<1 mo) Periods

- A positive result of a CMV-CMI test at day 15 posttransplantation among R+ kidney transplants who did not receive lymphocyte-depleting antibodies can identify patients at low risk for CMV infection. More data are needed to confirm whether no preventive strategy is necessary for these patients (weak, moderate).

Posttransplant Prophylaxis (≥1 mo After Transplant)

- If available, we recommend performing a CMV-CMI test in R+ kidney transplant recipients with (strong, moderate) or without (weak, very low) lymphocyte-depleting antibodies and discontinuing antiviral prophylaxis in case of a positive test. Although a precise time point for performing the CMV-CMI test cannot be recommended, we suggest a single time point at 1 mo posttransplant or once per month during prophylaxis. A surveillance after prophylaxis approach is suggested (weak, moderate).
- We suggest not routinely using CMV-CMI tests in D+/R- recipients for any organ type. Immune monitoring appears to be less predictive given the large number of patients in whom CMV-CMI remains undetectable or who have indeterminate responses (weak, low).

Other Clinical Scenarios

- A CMV-CMI assay may be used for guiding the need for secondary antiviral prophylaxis in patients after treatment of CMV infection/disease, including cases with CMV refractory/resistant CMV infection, although data are limited in this clinical setting (weak, low).

Cellular Therapy

- We suggest that cellular therapies can be considered in patients with resistant-refractory CMV infection (weak, low). Clinical trials are needed to establish their safety, efficacy, optimal regimens, and further indications before routine integration into clinical practice. Secondary outcomes could include markers of CMV-specific immune reconstitution.

Vaccine

- CMV vaccines are currently under clinical investigation in pre- and posttransplant settings. The primary goal of a CMV vaccine should be to prevent or mitigate CMV infection/disease. Target groups could include CMV R- and R+ patients.
- We suggest that quantitative CMV DNAemia be considered a primary endpoint for future studies (weak, moderate). Measures of markers of CMV-specific immunity could

TABLE 9.

Summary of clinical trials of CMV vaccines

Vaccine type	Description of vaccine	Transplanted organ	Study design	Participants	Side e	Key outcome/status	Reference
Towne	Live, passaged attenuated clinical strain	Kidney (R^-)	RCT (placebo)	91	Well tolerated	Slight decrease in CMV disease	384
		Kidney (R^-)	RCT (placebo)	237	Well tolerated	Slight decrease in CMV disease	385
		Kidney (R^-)	RCT (placebo)	89 vs 88	Well tolerated	Decrease of CMV disease	386
ASP1003	DNA (2 plasmids: gB, pp65) + adjuvant (poloxamer + benzalkonium chloride)	Kidney	RCT (placebo)	75 vs 74	Well tolerated (similar to placebo)	No decrease in CMV infection	387
		Allo HCT	Single arm	10	Well tolerated	7/9 developed antigenemia	388
		Allo HCT	RCT	246 vs 255	Well tolerated	Did not reduce CMV infection	389
Glycoprotein B	Protein with adjuvant (MF59)	Kidney, liver	RCT (placebo)	140 (67 vaccines vs 73 placebo)	Well tolerated (similar to placebo)	Reduction of days for ganciclovir and duration of DNAemia in mismatch	390
HB-101	Viral vector (2 nonreplicating LCMV vectors [gB, pp65])	Kidney	Randomized, parallel assignment	83	4/59 grade ≥3 side effects	No reduction of CMV infection (50%)	391
Triplex	Viral vector: Modified vaccinia Ankara encoding 3 key CMV antigens (pp65, IE-1, IE-2)	Pre liver, R^-	RCT (placebo)	Enrolling now	NA	NA	391
		Allo HCT, R^+	Single arm	17	Well tolerated	Showed favorable T-cell immunity	392
With PF03512676 adjuvant (tetanus-CMV peptide)	Chimeric peptide composed of a cytotoxic CD8 epitope from pp65 and tetanus T-helper epitope	Allo HCT	Phase 2	61	Well tolerated	Better CD8 response but failed to demonstrate clinical efficacy	393
		Allo HCT	Phase 1, RCT	18 vs 18			394

CMV, cytomegalovirus; HCT, hematopoietic cell transplantation; LCMV, lymphocytic choriomeningitis virus; R^-, CMV seronegative; R^+, CMV seropositive; RCT, randomized controlled trial.

be used for the assessment of vaccine immunogenicity as a secondary endpoint (weak, low).

Future Research

- Global immune biomarkers may be promising but require further study.
- More studies are needed regarding the use of immune monitoring in recipients other than kidney transplants (liver, heart), and especially in lung transplant recipients. The value of CMV-CMI in lung transplant recipients beyond serostatus alone has not been well established.
- More studies are needed regarding the use of a CMV-CMI assay to guide the need for antiviral therapy with asymptomatic DNAemia and to stop prophylaxis in patients intolerant to antivirals.
- Cost-effectiveness studies are needed to evaluate the economic benefits of incorporating CMV-CMI assays into routine clinical practice, particularly for reducing healthcare costs associated with CMV management and improving patient outcomes.

CMV TREATMENT

Initial Treatment

Oral valganciclovir and intravenous ganciclovir treatment are associated with similar long-term outcomes in SOT recipients with CMV syndrome and tissue-invasive CMV disease based on the VICTOR study conducted in adult renal, liver, heart, and lung transplant recipients.[162] Although both may be used for non-life-threatening CMV disease, valganciclovir is preferred when feasible due to its oral formulation, which may reduce or prevent hospital stays and minimize the infectious and vascular access complications associated with intravenous therapy. Intravenous ganciclovir is preferred as the initial treatment of life-threatening or sight-threatening CMV disease when optimal drug exposure is essential. Furthermore, there are limited PK data to confirm adequate valganciclovir bioavailability in patients with severe gastrointestinal CMV disease.

Second-line Treatment

In patients intolerant of valganciclovir or ganciclovir during the treatment phase, maribavir[400] or foscarnet[401] are recommended second-line treatments. Considerations for maribavir treatment include cost and regulatory availability to the prescribing practitioners. Foscarnet may be preferred in clinically unwell patients with high-level CMV DNAemia, although drug-induced nephrotoxicity risk and tolerance must be considered when introducing foscarnet. Letermovir is not recommended for treatment due to its low barrier to developing resistance.[402]

Intravenous immunoglobulin has been used as adjunctive therapy in CMV disease treatment.[403,404] Immunoglobulin

treatment may be performed with either CMVIG or IVIG. Systematic reviews of the use of CMVIG in SOT did not show better effect than ordinary pooled IVIG.[298]

Most use of immunotherapy with CMV-specific T cells has been in HCT, as summarized in the study by Garcia-Rios et al.[405] Recent studies of T-cell therapy in SOT are limited[373,406] (see the Immunologic Monitoring, Vaccines and Cellulary Therapy section).

Management

Appropriate antiviral drug dosing is essential in the management of CMV disease (Table 5). Suboptimal dosing may increase the risk for clinical treatment failure and the development of resistance,[407] whereas supratherapeutic doses may increase toxicity.[408] Kidney function should be assessed with regular monitoring of serum creatinine (see the Therapeutic Drug Monitoring section). In addition, complete blood counts should also be monitored at regular intervals to assess for hematologic toxicity (eg, leukopenia). Instead of reducing antiviral doses, discontinuation of other myelosuppressive therapies should be tried. The use of colony-stimulating factors has been shown to be safe and could be considered.[409]

The intensity of immunosuppressive therapy can impact the treatment outcomes associated with CMV disease.[410,411] Multiple studies include a reduction in immunosuppression as a component of therapy. In the VICTOR trial, double (versus triple) immunosuppressive therapy and lower blood concentrations of CNIs were significantly associated with "eradication" of CMV DNAemia at 21 d.[410]

Treatment Duration

CMV viral load should be monitored at weekly intervals to guide the duration of therapy. Although whole blood is more sensitive than plasma in detecting residual DNAemia, it is not a better predictor of recurrent CMV disease.[35] Failure to "eradicate" plasma DNAemia at the end of treatment is the major predictor of virologic recurrence.[162] Suppression of plasma CMV DNAemia measured with an assay calibrated to the WHO standard predicts clinical response to valganciclovir or ganciclovir.[412] Reduction in antiviral dosing in the setting of persistent CMV DNAemia at day 21 is associated with a significant risk of ganciclovir resistance by day 49.[413] Therefore, treatment doses of valganciclovir or ganciclovir are recommended until CMV DNAemia has decreased below an institutional, laboratory-specific, threshold. With the use of modern highly sensitive assays, a completely undetectable viral load may not always be achievable, which is why below LLOQ on a single highly sensitive (LLOQ <200 IU/mL) assay or 2 consecutive weekly samples on a less sensitive assay may be an appropriate target (see also the Diagnostics section). Very prolonged treatment courses are associated with increased resistance rates and this risk should be balanced against the goal of viral clearance. Continued weekly monitoring of CMV DNAemia for 1–3 mo may be considered for patients with higher risk of recurrence. CMV DNAemia may not accurately reflect the clinical disease status in all situations, and clinical signs should also be considered when determining treatment length. Longer courses of treatment may be needed in some tissue-invasive gastrointestinal diseases, pneumonitis in lung transplant recipients, and central nervous system or retinal disease.

Secondary Prophylaxis and Prevention

Secondary prophylaxis, defined as continuing prophylactic dosing after discontinuing treatment dosing, is not generally associated with fewer relapses after suppression of CMV DNAemia in retrospective studies.[90,194-196,414,415] The majority of consensus experts use secondary prophylaxis at least sometimes in patients with CMV D^+/R^- serostatus, lung transplant, a high CMV viral load at presentation, recent use of lymphocyte-depleting antibodies or augmentation of immunosuppression, low ALC, negative CMI assays, and in patients who struggle with recurrent CMV.[162,194-196,198-200] Switching to an mTOR inhibitor in selected CMV IgG seropositive kidney transplant recipients has been shown to reduce the recurrence rate of CMV.[256] The choice of agents for secondary prophylaxis and duration of secondary prophylaxis can be individualized, and the typical duration for secondary prophylaxis is 1–3 mo (see the Prevention section for full details).

Therapeutic Drug Monitoring

It has been proposed that the 24-h area under the concentration-time curve (AUC_{24h}), rather than C_0-targeted, therapeutic drug monitoring (TDM), results in better target achievement of systemic ganciclovir exposure.[416] An AUC_{24h} target of 80–120 mg·h/L (ie, AUC_{12h} 40–60 mg·h/L) has been suggested, but not validated.[417] PK/pharmacodynamic models and clinical experiences indicate that standard weight- and kidney function-based dosing of valganciclovir or ganciclovir results in a large proportion of drug exposures outside the suggested target range and leads to a slower than desired decline of CMV viral load.[417,418] This concern particularly applies to the pediatric population,[419,420] as well as in cases of unstable or low kidney function and dialysis because kidney clearance is the main route of ganciclovir elimination.[416] The specific group of lung transplant recipients with cystic fibrosis is also at higher risk of exposure outside target ranges.[421] Subtherapeutic ganciclovir exposure may increase the selection of resistant mutants and the subsequent risk of treatment failure.[422,423] Various studies have investigated whether TDM and population PK Bayesian dosing models may be useful to individualize valganciclovir or ganciclovir doses to optimize antiviral activity and the safety profile.[424,425] Nevertheless, most of them failed to show an association between ganciclovir exposure and clinical efficacy or toxicity.[426–429] Only a few single-center studies, often including nontransplant patients, have suggested that exposure below the suggested therapeutic window may be related to poorer clinical outcomes.[430] Therefore, robust data are still lacking to define the validity of TDM and a useful therapeutic window for ganciclovir.

Kidney Function Monitoring

It should be noted regarding kidney function monitoring during valganciclovir or ganciclovir dosing that in the package insert and in the PV16000[110] and VICTOR[162] trials, creatinine clearance (using the Cockcroft-Gault formula[431]) was used, not eGFR formulas (eg, Chronic Kidney Disease Epidemiology Collaboration[432]) which are more commonly reported in hospitals for easy assessment of kidney function. Although newer eGFR formulas (eg, Chronic Kidney Disease Epidemiology Collaboration) have proven superior

in estimating GFR, there is no evidence that these formulas (either creatinine or cystatin C based) give better prediction of ganciclovir elimination. Clinicians should be cognizant of these differences. Another important issue is that Cockcroft-Gault estimated creatinine clearance is not adjusted for body surface area (BSA, mL/min), whereas most eGFR equations are (mL/min/1.73 m^2). It is the individual absolute GFR (mL/min) that is relevant in drug dosing.[433] In addition, the thresholds and ranges for kidney function, as well as the changes in the dosing, are quite large for ganciclovir and valganciclovir. Consequently, even small variations in creatinine levels, for example, due to dehydration or other confounding causes, may result in large changes in dosing unrelated to the true drug elimination.

Consensus Statements and Recommendations

- For initial and recurrent episodes of CMV disease, oral valganciclovir (900 mg every 12 h) or intravenous ganciclovir (5 mg/kg every 12 h) are recommended as first-line treatment in adults with normal kidney function (strong, moderate).
- Oral valganciclovir is recommended in patients with mild to moderate CMV disease who can tolerate and adhere to oral medication (strong, moderate).
- Intravenous ganciclovir is recommended in life-threatening and severe diseases (strong, low).
- After clinical improvement, intravenous ganciclovir may be transitioned to valganciclovir in patients who are able to tolerate oral therapy (strong, moderate).
- Oral ganciclovir, acyclovir, or valacyclovir are not recommended for the treatment of CMV disease (strong, moderate).
- There is insufficient evidence to support the use of letermovir monotherapy for the treatment of CMV infection. There is a low barrier to the development of resistance in the setting of CMV infection.
- Changing antiviral agents is not recommended for clinically improving patients with unchanged or rising CMV DNAemia in the first 2 wk of therapy (strong, moderate). CMV DNAemia commonly rises during the first week of therapy.
- Drug resistance should be suspected in patients with a prior cumulative antiviral drug exposure that exceeds 4 wk and clinical treatment failure despite at least 2 wk of appropriately dosed antiviral treatment (see the Antiviral Drug Resistance and Treatment-Refractory Disease section; strong, moderate).
- Adjunctive IVIG or CMVIG for antiviral treatment of CMV disease is not routinely recommended but may be considered for patients with severe disease, resistant/refractory CMV disease, antiviral drug intolerance, and/or if IgG levels are <400 mg/dL, especially in thoracic organ recipients (weak, low).
- In patients without concomitant rejection, reduction of immunosuppression is suggested in the following settings: severe CMV disease, inadequate clinical response, high viral loads, and cytopenia (weak, very low).
- During the treatment phase, weekly CMV DNAemia testing is recommended, using an assay calibrated to the WHO standard, to monitor response (strong, high).
- During the treatment phase, frequent monitoring of kidney function (nonnormalized GFR, such as Cockcroft-Gault formula ie, mL/min) is recommended to guide valganciclovir or ganciclovir dosage adjustments (strong, moderate).
- Antiviral dosage reductions are only recommended during the treatment phase to adjust for worsening kidney function, as suboptimal dosing may be associated with increased risk of clinical failure and/or antiviral resistance (strong, low).
- Systematic TDM for ganciclovir is not generally recommended (weak, low). If available, however, it may be considered in patients receiving dialysis, with unstable or low kidney function, with cystic fibrosis, or with suspected poor gastrointestinal absorption of oral therapy (weak, low).
- In the setting of leukopenia, attempts should be made to continue the use of valganciclovir or ganciclovir. Options include consideration of interventions such as the use of granulocyte colony-stimulating factor and/or adjusting other myelosuppressive therapies. We do not recommend reducing the dose of valganciclovir or ganciclovir based on leukopenia alone (strong, moderate).
- In patients who are intolerant to valganciclovir or ganciclovir during the treatment phase, maribavir or foscarnet are recommended second-line treatments (strong, low). The choice of drug should be considered on the basis of viral load, risk of nephrotoxicity, and severity of CMV disease.
- Antiviral treatment should be continued for a minimum of 2 wk, until clinical resolution of disease and decrease in CMV DNAemia below the institutional, laboratory-specific, threshold (strong, moderate). This may be below the LLOQ on a single sample with a highly sensitive assay (LLOQ <200 IU/mL) or on 2 consecutive weekly samples with less sensitive assays (see the Diagnostics section).
- We do not recommend the routine use of secondary prophylaxis after treatment of CMV disease or infection (weak, low).
- We suggest secondary prophylaxis to delay and/or prevent recurrent CMV infection in high-risk situations such as high immunosuppression, low ALC, low CMV-CMI, repeated recurrences, inability to monitor patients for CMV replication (weak, low). The choice of agents for secondary prophylaxis and duration of secondary prophylaxis can be individualized (expert opinion). The typical duration for secondary prophylaxis is 8–12 wk. Further personalization can be based on the evaluation of immune status (see the Prevention section).

Future Directions

Prospective studies in the following areas are needed to evaluate novel strategies to optimize the treatment of CMV disease:

- Optimal use of maribavir as second-line treatment.
- Role of secondary prophylaxis.
- The role of immunoglobulin therapy, either IVIG or CMVIG.
- The role of switching to an mTOR inhibitor.
- The role of TDM of ganciclovir and its clinical correlation, particularly in subpopulations with variable PK.
- Combination antiviral therapy.

ANTIVIRAL DRUG RESISTANCE AND TREATMENT-REFRACTORY DISEASE

Drug resistance is defined as a viral genetic alteration that decreases susceptibility to ≥1 antiviral drugs,[40] as measured

by the drug concentration required to reduce viral growth by 50% in cell culture (EC_{50}). Treatment-refractory CMV infection was recently defined for clinical trials as plasma viral load that persists or increases by ≥1 $\log_{10}$ or a progression or lack of improvement in signs and symptoms after ≥2 wk of antiviral therapy with appropriately dosed treatment.[11] The definition used in the pivotal maribavir trials also included a failure to achieve >1-$\log_{10}$ decrease in CMV DNA after ≥14 d of antiviral treatment.[400,434] Not all treatment-refractory infection is attributable to drug resistance, and treatment-refractory infection by itself does not imply treatment failure when assessed at 7–8 wk.[75,435]

Risk Factors, Frequency, and Clinical Consequences

The risk of drug resistance rises with prolonged antiviral drug exposure and ongoing active viral replication facilitated by lack of prior host CMV immunity (D^+/R^- serostatus), type and degree of immunosuppression,[205,436] and inadequate antiviral drug dosing, delivery, or potency.[437,438] Viral mutations will emerge more readily if they confer high levels of drug resistance while preserving growth fitness, denoting a lower genetic barrier to resistance that varies among drugs.[439]

During prophylaxis, the incidence of resistance is low if viral replication is effectively suppressed, typically in the 0%–3% range as reported for 100–200 d of valganciclovir or ganciclovir prophylaxis in D^+/R^- kidney recipients[440] or letermovir prophylaxis in stem cell or kidney recipients.[122,441]

Among solid organ recipients, the usual reported incidence of resistance in observational studies of valganciclovir or ganciclovir therapy is 2%–12%.[442–446] In large-scale treatment trials with specified durations of therapy, the reported incidence of valganciclovir or ganciclovir resistance after 7 wk was 2.3%–3.6%, respectively,[413] and of maribavir resistance after 8 wk was 9%–26%.[447,448] or 4-fold higher than for valganciclovir in a controlled trial.[435,448] There are no letermovir treatment trial data to provide an incidence of resistance, only case reports and uncontrolled series.[449–451] Development of drug resistance correlates with increased morbidity and mortality.[438,452,453]

Diagnosis of Drug Resistance

When to Test

Antiviral drug resistance should be suspected when there is treatment-refractory CMV infection[40,400] after receiving appropriately dosed antiviral therapy for at least 2 continuous weeks, with a cumulative antiviral exposure of 4 wk or more.[438,447] A viral load rebound while on therapy was highly suggestive of emerging maribavir resistance in clinical trials.[447,448,454] Without adverse host factors and/or high viral loads, ganciclovir resistance usually takes >6 wk of cumulative exposure to develop; the median was 5 mo in one series.[438] Maribavir resistance was detected at a median of 8 wk of therapy.[435,447] Persistent viral loads in the first 2 wk of treatment, or an increase in DNAemia at week 1, are not predictive of drug resistance.[75,143,413]

How to Test

CMV drug resistance is detected by genotypic assays for indicative mutations in viral DNA sequences directly amplified from clinical specimens. Usually, the same blood specimens as for CMV viral load quantitation are used. Most genotypic testing to date has involved traditional Sanger dideoxy DNA sequencing. Results are more reliable if the CMV DNA load in the specimen is at least 3 $\log_{10}$ IU/mL (1000 IU/mL).[455] Genotyping artifacts may occur, especially as mixed mutant populations from low-load specimens.[441,456] Clinically questionable readouts may require retesting to resolve. Sanger sequencing is insensitive in detecting mutant subpopulations of <20%.[455] Evolving deep sequencing technologies may offer earlier detection of smaller resistant subpopulations but require careful validation of each test platform.[457–460] Resistance mutations may localize at sites of CMV end-organ disease (eg, eye, CSF, graft) and require a tissue-specific specimen for detection.[461–464]

Gene Regions to Test

In patients initially treated with valganciclovir or ganciclovir, viral *UL97* kinase gene mutations appear first in about 90% of cases, affecting drug phosphorylation that is necessary for antiviral action.[437,438,465] *UL54* DNA polymerase gene mutations usually emerge later, conferring increased ganciclovir resistance and likely cross-resistance to cidofovir and/or foscarnet, but may uncommonly be the first mutation detected. Genotypic testing should routinely include both *UL97* (codons 335–665) and *UL54* (codons 290–1000). For letermovir, the important region for genotyping is *UL56* (codons 229–369),[465] although some low-grade resistance mutations have been identified elsewhere in genes *UL56* (C25F),[466] *UL51*,[467,468] and *UL89*.[469] In selected maribavir refractory cases, *UL27* analysis could also be included.

Interpretation of Genotypic Data

An online resource is available for querying the published phenotypes of mutations associated with drug resistance (https://www.unilim.fr/cnr-herpesvirus/outils/codexmv/database/all_references).[470]

UL97 mutations conferring ganciclovir resistance (Figure 2; Table 10) are clustered at codons 460, 520, or 590–607[437,457,471] and do not affect foscarnet or cidofovir susceptibility, whereas *UL54* drug resistance mutations may confer resistance to multiple drugs (Figure 3).[437] The most common maribavir resistance mutations in clinical trials[435,447,448,454] were *UL97* T409M and H411Y, along with C480F in those with prior exposure to ganciclovir. *UL97* C480F and F342Y confer maribavir-ganciclovir cross-resistance, as do a number of other unusual mutations (Figure 2).[472] *UL27* mutations conferring low-grade maribavir resistance have been observed mostly in vitro.[473] Letermovir resistance often involves *UL56* codon 325 mutations (Figure 4).[474,473]

Resistance mutations are associated with specific levels of drug resistance as determined by recombinant phenotyping, whereby a mutation is transferred into a reference CMV strain, and the resulting virus is tested for susceptibility to antiviral drugs in a standardized cell culture assay.[437] The level of resistance is reported as the fold change in EC_{50} from the wild-type level. The reported fold changes may vary according to the assay technique and calibration to control strains.

In gene *UL97* (Table 10), the usual ganciclovir resistance mutations confer a moderate 5- to 15-fold increased EC_{50}, whereas some others confer a low-grade 2- to 5-fold increased EC_{50}. The most common maribavir resistance mutation *UL97* T409M confers a higher 80-fold increased EC_{50}. The combined effect of *UL97* and *UL54* mutations

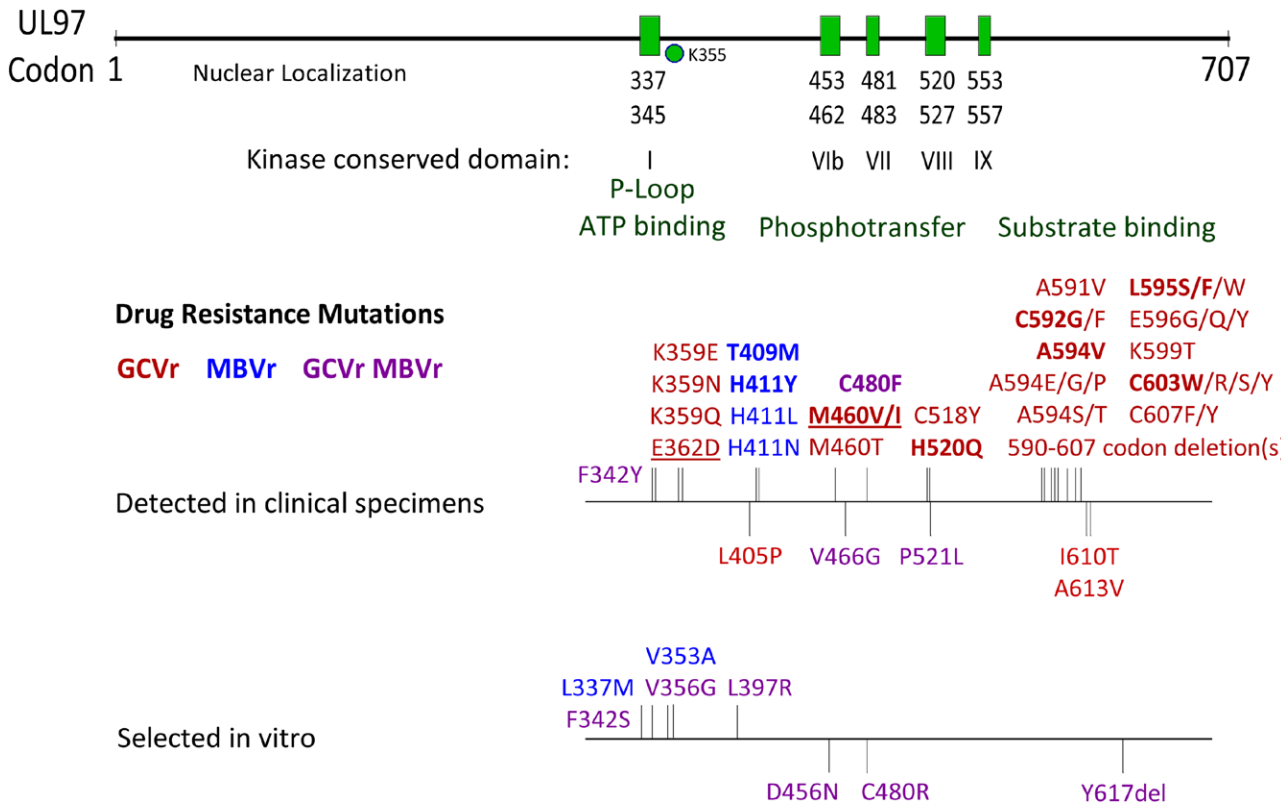

FIGURE 2. CMV *UL97* kinase gene mutation map. Mutations in bold are most commonly encountered in clinical specimens. Corresponding phenotypes are color coded as shown by the drug abbreviations. Underlined mutations confer increased MBV susceptibility. Updated from previous publication.[457] CMV, cytomegalovirus; GCVr, ganciclovir resistant; MBVr, maribavir resistant.

TABLE 10.

Relative levels of drug susceptibility of CMV *UL97* mutants

	Fold-increase in EC_{50}[a]			
Drug	**<2.0**	**2.0–4.9**	**5–15**	**>15**
Ganciclovir	T409M, H411Y, K599E/R, L600I, T601M, D605E	K359E/Q, E362D, L405P, C480F, A591V, **C592G**, A594E/S, E596G, E596del, L600del, L600del2, I610T, A613V	F342Y, **M460V/I**, V466G, C518Y, **H520Q**, P521L, A594V/G/T, **L595S/F**/W/del, E596Y, K599T, **C603W/R**, C607Y, A591del4, L595del, N597del3, T601del3	
Maribavir	E362D, M460V/I, H520Q, A594V, L595S, C603W	F342Y	V353A, H411N	**H411Y**, **T409M**, H411L, **C480F**

[a]Interpretation of EC_{50} ratios (fold increases):
<2.0: mutation does not change susceptibility enough to prevent the use of the drug in question.
2.0–4.9: may be possible to continue effective therapy with the drug with careful monitoring for evolving mutations further degrading drug efficacy. Ganciclovir dosage can be increased if tolerated. Maribavir treatment success for F342Y is not documented.
5.0–15: therapeutic efficacy is decreased by more than half and strong consideration should be given to alternative therapy.
>15: expect no therapeutic efficacy. Notably, in maribavir clinical trials, no patient who developed T409M (EC_{50} ratio 80×) was considered a treatment responder. C480F is highly maribavir-resistant (EC_{50} > 200×) with low-grade ganciclovir cross-resistance (EC_{50} 2.3×).
Del refers to in-frame codon deletion, with a suffix indicating the number of codons deleted if >1.
The most commonly encountered mutations are in bold. Maribavir increased sensitivity is underlined.
CMV, cytomegalovirus; EC_{50}, half maximal effective concentration.

may result in high-level ganciclovir resistance at 20- to 30-fold increased EC_{50}, which can be estimated by multiplying the fold changes in resistance conferred by each mutation alone.[475] Foscarnet resistance mutations typically confer 2- to 5-fold increases in EC_{50} and frequently attenuate viral growth.[437] *UL54* exonuclease domain mutations may confer 10- to 20-fold increases in cidofovir EC_{50}.[437] Letermovir resistance mutations at *UL56* codon 325 confer absolute resistance (>3000-fold increased EC_{50}; Figure 4).[439,441]

The predicted level of resistance may influence the selection of antiviral therapy. CMV infections involving low-level resistance, such as *UL97* C592G and C480F for ganciclovir, have been successfully treated with ganciclovir.[447,476] Continued use of ganciclovir in the presence of *UL97* mutations conferring 5- to 12-fold increased EC_{50} was associated with a decreased treatment response rate of 16% to 27%.[447] No cases are documented of successful treatment with maribavir in the presence of *UL97* T409M

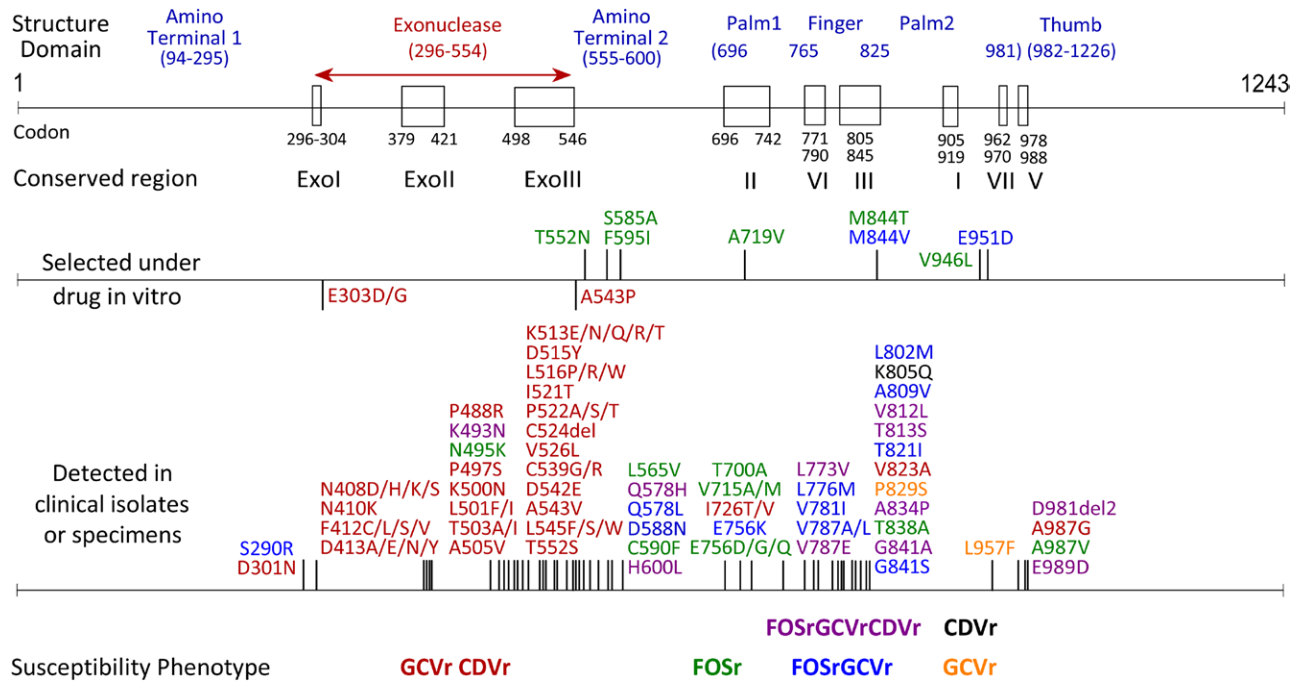

FIGURE 3. CMV *UL54* DNA polymerase gene mutation map. Most resistance mutations map to conserved structure domains. Their corresponding phenotypes are color coded as shown at the bottom of the figure. Updated from previous publications.[3,457] CDVr, cidofovir resistant; CMV, cytomegalovirus; FOSr, foscarnet resistant; GCVr, ganciclovir resistant.

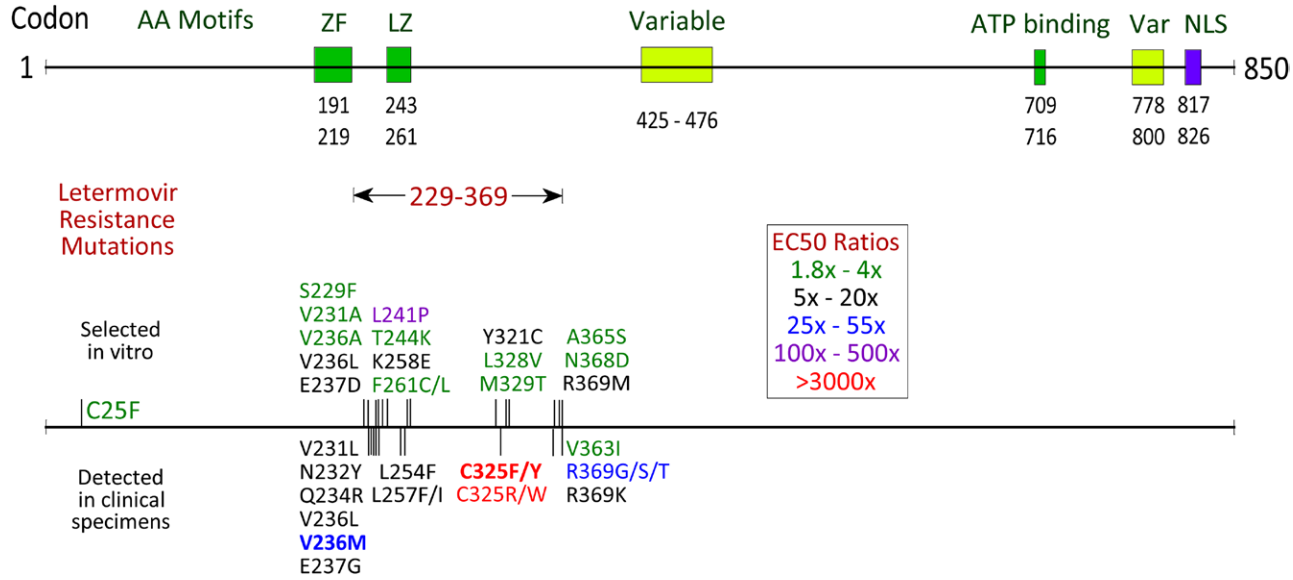

FIGURE 4. CMV *UL56* terminase gene mutation map. Letermovir resistance mutations are color coded according to the level of resistance listed under EC_{50} ratios. Mutations at codon 325 are the most frequent and confer absolute resistance.[474] Updated from previous publication.[457] CMV, cytomegalovirus; EC_{50}, drug concentration required to reduce viral growth by 50% (stated as fold change from baseline).

or letermovir in the presence of *UL56* C325 mutations, which confer high levels of resistance.

Treatment Alternatives for Refractory and Drug-resistant CMV Infection

Treatment-refractory infection (as defined in the maribavir clinical trials[400,434]) does not imply treatment failure. A major randomized trial (VICTOR) in solid organ recipients reported that viral eradication, defined as <600 copies/mL,[75] was achieved in 45% of valganciclovir recipients at 21 d, rising to 67% at 49 d. A more recent randomized trial found an 83% response rate at 8 wk, even for those "refractory" to valganciclovir at 2 wk.[435,448] These data discourage the premature withdrawal of first-line therapy in those tolerating valganciclovir or ganciclovir.

There is limited controlled trial evidence for the optimal management of drug-resistant CMV infection. Results from the phase 3 SOLSTICE trial in SOT or HCT recipients with treatment-refractory CMV infection (with or without drug resistance)[400] led to the FDA approval of maribavir for

this indication. Patients were randomized to investigator-assigned standard therapy (ganciclovir, valganciclovir, foscarnet, or cidofovir), or to maribavir. The overall treatment response rate was 56% for maribavir and 24% for standard therapy as judged by clearance of viral DNA at 8 wk ($P < 0.001$). The advantage of maribavir was clear-cut in cases with known baseline resistance to standard therapy (response rate of 63% versus 20%, $P < 0.001$).[477] For those with baseline genotyping showing no drug resistance mutation, the respective response rates were 44% and 32% for maribavir and standard therapy ($P = 0.17$), respectively.[477] For those without baseline resistance and treated with valganciclovir or ganciclovir, the response rate was 44% (7/16), equivalent to maribavir.[447] Factors contributing to the lower response rate for standard therapy included premature discontinuation for adverse effects, participant withdrawals, and use of valganciclovir or ganciclovir in patients with known ganciclovir resistance mutations. For maribavir, treatment-emergent drug resistance reduced the response rate.

The starting viral load affected the maribavir response rate.[477] More than half of maribavir-treated patients (56%) had a starting viral load of <3.7 $\log_{10}$ IU/mL (5000 IU/mL) and they had a response rate of 67%, whereas those with starting loads of >4.7 $\log_{10}$ IU/mL (50 000 IU/mL) had a response rate of 30%. For standard therapies, the same 25% response rate was observed across baseline loads of <3.7–>4.7 $\log_{10}$ IU/mL.[477] Responsiveness to foscarnet could be close to 70% (10/14) if the treatment was tolerated for >52 d,[447] but most patients had their foscarnet therapy prematurely stopped. None of 6 patients treated with cidofovir responded.[447]

Baseline maribavir resistance was uncommon in clinical trials.[435,447] Prior ganciclovir exposure can occasionally select for UL97 mutations, such as F342Y that confer maribavir cross-resistance and treatment failure.[447,472] Treatment-emergent maribavir resistance increases with higher baseline viral loads or a treatment-refractory condition at 2 wk[435,447,454] and is a leading cause of maribavir treatment failure.

Based on the above evidence, a flowchart is proposed for the management of suspected CMV drug resistance (Figure 5). Recommended practices for refractory infection include optimization of host factors by reducing immunosuppression as feasible and ensuring adequate antiviral drug dosing and bioavailability. Genotypic testing is important for confirming drug resistance and assists in the selection of alternative treatments.

The flowchart algorithm is usually first applied in cases of suspected ganciclovir resistance, with antiviral treatment chosen according to baseline viral load, clinical condition, and viral genotyping information. Continued use of valganciclovir or ganciclovir may be a good option in the absence of resistance mutations, assuming no dose-limiting side effects and a plan for viral load and genotypic monitoring. Because of oral bioavailability and a good safety profile, maribavir is preferred in cases with lower starting viral loads and ganciclovir resistance mutations, especially with UL97 M460I/V, which confer increased sensitivity to maribavir.[472] For high starting viral loads (≥4.7 $\log_{10}$ IU/mL on plasma), the benefit of maribavir is less compelling and limited by the risk of emergent drug resistance;[435,477] foscarnet is suggested for clinically unwell cases if tolerated. Maribavir is an important alternative treatment when foscarnet resistance or intolerance exists. Unlike standard polymerase inhibitors, maribavir has no activity against herpes simplex and varicella-zoster viruses, for which separate prophylaxis may be needed. Clinical trials excluded patients with CMV retinitis or central nervous system disease, for which the efficacy of the highly protein-bound maribavir is unknown.

If the chosen salvage treatment does not work after several weeks, options are to switch drugs among available approved therapies or try empiric combinations, except that the combination of maribavir and ganciclovir is strongly antagonistic in vitro.[478] There is no solid evidence base to determine the best treatment options, which involve a tradeoff of viral and disease burden, antiviral toxicities and potency, logistical complexity, cost, and risk of drug resistance. Foscarnet may be used in combination with ganciclovir or maribavir as tolerated or switched to maribavir after the viral load reaches a low level (optimally <3.7 $\log_{10}$ IU/mL).

Maribavir resistance is an important clinical concern especially with higher starting viral loads, development of a treatment-refractory condition, or rebound of viral load while on therapy. In clinical trials, emergent maribavir resistance was usually manageable by switching back to standard therapy.[435,447] Repeated genotyping at the time of retreatment is recommended because resistance mutations selected after antiviral drug exposure may fade away weeks to months after the selected drug is discontinued.[479] Undetected residual minor subpopulations of the mutant virus may facilitate the reemergence of resistance after renewed treatment with the same drug.

Unapproved and experimental therapies can be considered, but the evidence is weak and limited to anecdotal reports. Letermovir does not have controlled trial data supporting its use as a treatment for active infection, including refractory or resistant CMV infection. Observational studies suggest possible utility in cases with lower starting viral loads[450,451,480] or as secondary prophylaxis,[481] and draw attention to emergent high-grade drug resistance as a concern.[449–451,482] CMVIG[483] and adoptive infusions of CMV-specific T cells[373,484] may improve antiviral host defenses. Several drugs used for other purposes, including mTOR inhibitors (sirolimus and everolimus), leflunomide, and artesunate, are reported to have anti-CMV effects but lack sufficient evidence to recommend as treatment for resistant CMV infection.[485]

Consensus Statements and Recommendations

- We recommend that a CMV genotypic assay be used to diagnose drug resistance after extended antiviral drug exposure (minimum 4 wk) and suboptimal (treatment-refractory) viral load response after a minimum of 2 wk of optimally dosed antiviral treatment (strong, high).
- We recommend that resistance genotyping should be done on specimens with viral loads of >3 $\log_{10}$ IU/mL (1000 IU/mL) for increased reliability of mutation readouts (strong, high).
- We recommend that inferred phenotypes of CMV drug resistance mutations be used to estimate the level of drug resistance conferred and residual utility of the affected drug (strong, high).

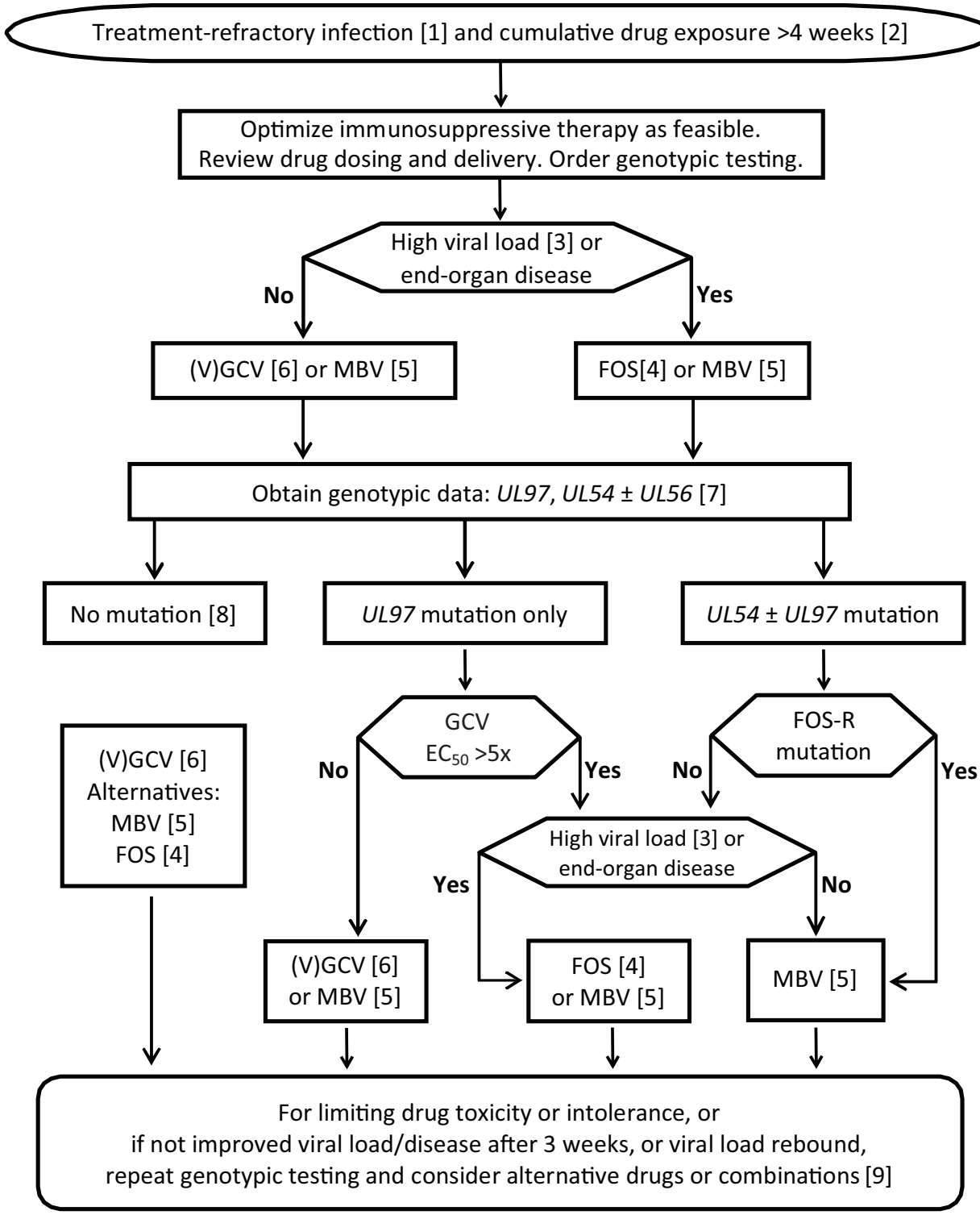

FIGURE 5. Flowchart for management of suspected drug-resistant CMV infection. **[1]** Treatment-refractory: ≤1 $\log_{10}$ decrease in plasma or blood viral load after ≥2 wk of therapy, new or worsening CMV disease. **[2]** GCV resistance is rare with drug exposure of <6 wk. **[3]** High viral load: ≥50 000 (4.7 $\log_{10}$) IU/mL (plasma). **[4]** Avoid FOS if there is renal dysfunction or metabolic intolerance. FOS is suggested for high viral loads in clinically unwell patients. **[5]** Avoid MBV for CNS disease or retinitis. Treatment-emergent resistance to MBV may limit efficacy. Do not use if any MBV resistance mutations are detected. MBV works better with lower viral loads, see the text. M460I/V, as the sole *UL97* mutation, favors the use of MBV. **[6]** GCV dose 5 mg/kg bid IV, optionally 10 mg/kg bid (high dose), or VGCV dose 900 mg bid, optionally 1800 mg bid (high adult dose; adjusted for renal function). **[7]** *UL56* genotyping If previous exposure to letermovir. **[8]** Includes sequence variants conferring <2-fold EC_{50} change. Repeat genotyping with tissue-specific samples for end-organ disease, if available. **[9]** Consider combination therapy as tolerated. The MBV-GCV combination is antagonistic; do not use it. MBV may be suitable as a step-down treatment after the initial response to FOS when a viral load of <5000 (3.7 $\log_{10}$) IU/mL. Cidofovir performed poorly in a clinical trial, see the text. Letermovir has no clinical trial evidence for efficacy in treating refractory/resistant infection, see the text. Emergent MBV and letermovir resistance is often high grade and requires genotypic monitoring. Other unapproved therapies (weak evidence) include mTOR inhibitors, augmentation of host immunity using adoptive T-cell transfers, and CMV immunoglobulins. CMV, cytomegalovirus; CNS, central nervous system; FOS, foscarnet; GCV, ganciclovir; MBV, maribavir; mTOR, mammalian target of rapamycin; (V)GCV, ganciclovir or valganciclovir.

- We recommend optimization of immunosuppression and drug dosing as feasible in the setting of resistant and refractory CMV infection (strong, low).
- We recommend that refractory CMV infection without detected drug resistance be managed by monitoring current treatment or switching to another approved therapy based on viral load trajectory, disease condition, adverse effects, availability, and cost (strong, moderate).
- We recommend maribavir as the principal alternative therapy in cases of resistance to either ganciclovir or foscarnet (strong, high).
- We suggest foscarnet as initial therapy in clinically unwell cases with high viral loads and suspected or proven ganciclovir resistance. A higher genetic barrier to drug resistance offsets a higher incidence of limiting toxicity (weak, low).
- Although no specific high viral load threshold can be defined, many experts suggested that viral loads of ≥4.7 log10 IU/mL (50 000 IU/mL) on plasma may be useful for clinical decision-making (eg, choosing foscarnet), especially in patients who are clinically unwell (expert opinion).

Future Directions

- Prospective studies are needed to define the clinical and virologic outcomes of drug-resistant CMV under various management options, especially for those with higher initial viral loads and end-organ disease.
- New therapeutic options are needed, with improved safety, potency, and avoidance of cross-resistance, including drug combinations directed at different viral targets.
- Genotypic resistance testing needs improved quality control and standardized reporting. Next-generation genotyping technology requires validation for each individual technical platform.

PEDIATRIC ISSUES IN CMV MANAGEMENT

Prevention and treatment of CMV infection and disease in pediatric and adolescent SOT recipients present several unique issues described here, incorporating and expanding on previous guidelines.[1-3,486]

Burden of CMV in Pediatric SOT

There are limited data on the exact CMV burden in pediatric SOT. Nonuniform approaches to diagnosis and variable prevention and monitoring strategies hamper data interpretation. Epidemiological pediatric studies conducted before the advent of prophylaxis or preemptive therapy indicated up to 40% of liver and 15% of kidney transplant recipients developed CMV disease.[487,488] With the introduction of prevention strategies in pediatric SOT, CMV disease initially decreased to 10%–25%[489] with further declines to 0%–10% in more recent reports across all organs.[157,184,490–503]

CMV DNAemia after pediatric SOT is common, with variable rates reported globally, most likely reflecting different seroprevalence, prevention, and monitoring strategies. Incidence rates of CMV DNAemia in the first year after pediatric SOT occurring during (ie, breakthrough) and after prophylaxis range from 10% to 35% in liver, 5.2% to 43% in kidney, 16% to 34% in heart, 13% to 33% in lung, and 29% to 67% in multivisceral abdominal transplants.[184,497–500,504–511] For cohorts using preemptive therapy, CMV DNAemia occurs more frequently in liver (20%–71%) and kidney (31%–86%) but results in initiation of antiviral therapy in only 37%–63% of events.[135,157,491,496,512–517]

TABLE 11.

Assignment of donor/recipient serostatus in infants younger than 12 mo

Donor	Recipient	Suggested risk categorization
+	+ or −	D^+/R^{-a}
−	+	D^-/R^+
−	−	D^-/R^-

[a]If recipient confirmed positive by CMV NAT, assign D^+/R^+.
CMV, cytomegalovirus; D/R, donor/recipient (serostatus); NAT, nucleic acid testing.

Primary Risk Factors for the Development of CMV Disease in Children

As with adults, CMV disease risk in pediatric transplant recipients varies with donor and recipient serostatus. Interpretation of serostatus for donors and recipients younger than 12 mo is confounded by the potential presence of transplacentally acquired maternal CMV IgG. Testing for CMV DNA in urine or saliva can confirm that an infant is infected, but because CMV shedding is intermittent, a negative DNA test does not exclude prior infection. Thus, it is safe to presume that seropositive donors to recipients younger than 12 mo could transmit infection, and seropositive recipients are at risk for either reactivation or acquisition (Table 11).

Children are more often CMV-naive at the time of transplant compared with adults. In addition to CMV acquisition from a seropositive donor, children are more likely to acquire primary CMV infection through household and community exposures, including daycare and school attendance. Community acquisition likely accounts for the fact that up to 7% of pediatric CMV D^-/R^- recipients develop primary CMV infection in the first year after transplantation.[511]

As with adults, the choice of immunosuppression impacts the risk for CMV in pediatric SOT. Tacrolimus increased the risk for CMV DNAemia 4-fold compared with cyclosporine in one study of pediatric kidney transplant recipients.[518] mTOR-based immunosuppression has been associated with decreased CMV risk in both pediatric kidney and heart transplant recipients.[265,519]

Indirect Effects of CMV in Pediatrics

An important rationale for CMV prevention is the potential indirect effects of CMV, including graft rejection, impaired graft function, and/or risk for other infections. However, fewer data exist in children compared with adults, and study design limits interpretation. The publications, summarized in **Table S5** (**SDC,** http://links.lww.com/TP/D243),[157,184,293,491,494,496,499,501,511,514,515,517,520–527] provide mixed and often contradictory results, with potential differences noted by organ type. For example, early studies in pediatric kidney transplant recipients suggested an association between CMV and biopsy-proven graft rejection and/or impaired graft function, which was mitigated by antiviral prophylaxis.[514,515] However, more recent studies did not find these associations.[497,498,503,525-527] Similar contradictory

TABLE 12.

Recommended regimens for CMV prevention in children

Organ	Serostatus[a]	Risk level	Recommended prevention strategies		
			Prophylaxis	Surveillance after short-term prophylaxis	Preemptive therapy
All except small bowel	D^-/R^-	Low	Not routinely recommended	Not routinely recommended	Some experts recommend monitoring due to the risk for CMV acquisition[b]
Kidney	R^+	Intermediate	3–6 mo of (V)GCV	2–4 wk of (V)GCV with surveillance after prophylaxis	Yes
	D^+/R^-	High	3–6 mo of (V)GCV		Yes
Liver	R^+	Intermediate	3–4 mo of (V)GCV	2–4 wk of (V)GCV with surveillance after prophylaxis	Yes
	D^+/R^-	High	3–4 mo of (V)GCV	2–4 wk of (V)GCV with surveillance after prophylaxis	Yes
Heart	R^+	Intermediate	3–6 mo of (V)GCV	2–4 wk of (V)GCV with surveillance after prophylaxis	
	D^+/R^-	High	3–6 mo of (V)GCV	4 wk (V)GCV with surveillance after prophylaxis	
Lung	R^+	High	6–12 mo of (V)GCV		
	D^+/R^-	High	12 mo of (V)GCV		
Small bowel[c]	D^-/R^-	Low	Not routinely recommended	2 wk GCV with surveillance after prophylaxis	Yes
	R^+	High	3–12 mo of (V)GCV	2 wk GCV with surveillance after prophylaxis	
	D^+/R^-	High	3–12 mo of (V)GCV		

Blank cells indicate lack of data.
[a]Refer to serostatus recommendation for infants younger than 12 mo.
[b]Risk of CMV infection in D^-/R^- is ~5%–7% within 12 mo of transplantation.
[c]VGCV should be used with extreme caution due to concerns for malabsorption in small bowel transplant recipients.
CMV, cytomegalovirus; D, donor; GCV, ganciclovir; R, recipient; (V)GCV, ganciclovir or valganciclovir.

results have been reported for heart, lung, and liver pediatric transplant recipients (**Table S5, SDC,** http://links.lww.com/TP/D243). Two recent retrospective studies conducted among pediatric SOT recipients receiving antiviral prophylaxis found that CMV DNAemia was associated with rejection but only in liver transplant recipients.[496,501] However, the absence of precise data on the timing of rejection and viral reactivation precludes concluding causality.

Prevention of Pediatric CMV

Summary

As a first step in CMV disease prevention, leukodepleted or CMV-negative blood products are suggested for pediatric SOT recipients, especially if CMV D^-/R^-. Additional prevention strategies in pediatric SOT recipients include antiviral prophylaxis, preemptive therapy, or a sequential approach of brief prophylaxis followed by CMV DNAemia surveillance. Although no pediatric trial has directly compared the relative efficacies of these 3 strategies, favorable outcomes for each have been reported. There is broad collective evidence to support the use of valganciclovir prophylaxis ranging from 3 to 12 mo in pediatric SOT recipients, but its use may be impacted by bone marrow suppression. Conversely, preemptive therapy may avoid the toxicities of antiviral exposure but requires somewhat intensive weekly CMV DNAemia surveillance. Recent single-center studies have addressed potential CMV DNAemia thresholds for preemptive therapy, but the generalizability of these values across centers has not been evaluated.[157,496] The rate of CMV disease has been reported to be as low as 4% in relatively small studies of children managed preemptively.[157,496,528,529] The surveillance after prophylaxis approach limits the duration of prophylaxis to the period of most intense immunosuppression. This approach has been used successfully in pediatric liver and heart recipients, with reported CMV disease rates of 8%–10%.[492,516] The reported duration of prophylaxis in this setting typically ranges from 2 to 4 wk; however, the optimum prophylaxis duration in this approach has not been defined.[492,516,530] Recommended regimens for CMV prevention in children appear in Table 12.

Antiviral Pharmacologic Considerations in Pediatrics

Several recent studies have evaluated the PK of intravenous ganciclovir and oral valganciclovir in pediatric SOT recipients.[531-538] Regardless of the dosing regimen used, there is substantial interindividual variability in ganciclovir/valganciclovir PK in children such that attainment of area under the curve targets (AUC_{24} 40–60 mg·h/L for prophylaxis and 80–120 mg·h/L for treatment) is both infrequent and unpredictable. It should be noted that the extent to which these AUC targets translate into efficacy in pediatrics has not been comprehensively studied. The most used dosing regimens for ganciclovir (5 mg/kg QD [prophylaxis] or 5 mg/kg BID [treatment]) result in AUC values below target in roughly half of children, particularly in those with normal or high GFRs.[533-535,538]

There are generally 2 dosing approaches for valganciclovir in children: BSA-based dosing[539,540] and body weight (BW)-based dosing,[541] each with pros and cons (Table 13). When

TABLE 13.
Valganciclovir dosing in pediatric SOT

Valganciclovir dosing in pediatric SOT recipients	BSA-based dosing	BW-based dosing
Formula for determination of dose[a]	7 × BSA[b] × CrCL[c]	15–18 mg/kg
Dosage	Higher, especially in children younger than 6 y	Lower
GCV AUC exposure	Higher	Lower
Attainment of designated AUC-based targets[d]	More frequent	Less frequent
Rate of hematologic toxicities	Higher (26%–69%)	Lower (8%–53.6%)
Incidence of breakthrough CMV DNAemia	4.8%–16%	10%–16%
CMV DNAemia in the first year posttransplant	15.9%–33%	14%–34%

[a]Prophylactic dosing is typically given once daily; treatment dosing is typically twice daily; the maximal dose is 900 mg/dose for both approaches.
[b]BSA is calculated using the Mosteller equation: BSA (m^2) = √(height [cm] × weight [kg]/3600).
[c]CrCL is calculated using the updated bedside Schwartz equation: CrCL (mL/min/1.73 m^2) = 0.413 × height (cm)/serum creatinine (mg/dL). Per the package insert, a maximal value of 150 mL/min/1.73 m^2 should be used for CrCL calculations exceeding 150 mL/min/1.73 m^2.
[d]AUC-based targets used in major studies are 40–60 mgh/L for prophylaxis and 80–120 mgh/L for treatment.
AUC, area under the curve; BSA, body surface area; BW, body weight, CMV, cytomegalovirus; CrCL, creatinine clearance; GCV, ganciclovir; SOT, solid organ transplant.

estimating GFR for dosing using the BSA-based method, the bedside Schwartz formula based on the enzymatic creatinine method with the k constant of 0.413 for all ages is currently recommended.[542-544] BSA-based dosing generally results in larger dosages compared with BW-based dosing, especially in infants and children younger than 6 y, typically resulting in higher ganciclovir exposures (ie, AUCs) and more frequent attainment of the putative target levels,[420,531,534-536] but also more frequent development of toxicities, primarily cytopenias. The reported rates of breakthrough CMV DNAemia during prophylaxis may be similar between the dosing regimens,[545] although no prospective comparative effectiveness studies have been performed. However, neutropenia and lymphopenia occurred more often with BSA dosing, and this was associated with premature discontinuation or dose reduction of valganciclovir.[545] Alternative dosing strategies based on kidney function and age may better achieve therapeutic targets, according to pharmacologic simulations[532-535] but have not been adequately prospectively evaluated. Regardless of the dosing strategy used, dosages should not be empirically decreased in the setting of hematologic toxicities as this may increase the likelihood of breakthrough DNAemia.[497]

As a result of the large variability in ganciclovir PK and low AUC target attainment in children, some experts advocate for TDM of ganciclovir/valganciclovir in pediatric SOT recipients, using the same AUC-based targets as adults. Unfortunately, TDM requires the collection of multiple blood samples to estimate AUC because the correlation between ganciclovir troughs and AUC is poor.[532,533,546,547] Although TDM could help inform ganciclovir/valganciclovir dosing and improve the likelihood of AUC target attainment, in theory, there are no pediatric studies linking the use of TDM to improved clinical outcomes (decreased breakthrough infection and/or toxicity) for these drugs.

Letermovir has shown promising efficacy and a favorable safety profile in adult hematopoietic stem cell and kidney transplant recipients. Letermovir has been approved for high-risk (CMV D^+/R^-) kidney transplant patients aged 12 y and older and weighing at least 40 kg based on adult experience, although data in pediatric SOT are limited to anecdotal reports. Pediatric dosing has been established but only in pediatric hematopoietic stem cell transplant recipients older than 6 mo.[548,549]

As with adults, appropriate replacement for hypogammaglobulinemia is suggested. The practice of administering CMVIG and IVIG in combination with antivirals or preemptive therapy to prevent CMV lacks definitive data for or against this practice as the pediatric studies report variable results.[528,529,550,551] In pediatric heart transplant recipients, SRTR data showed an improvement in recipient and graft survival for those who received CMVIG with or without antivirals; however, this improvement was not different from that demonstrated with antivirals alone.[552,553] Furthermore, there was no difference in outcomes after the discontinuation of routine use of CMVIG for prevention in a pediatric heart transplant cohort, although the data set was limited.[505] Additional studies in pediatric lung and liver transplant recipients failed to show an association between CMVIG use and protection against CMV disease, although CMV infection was decreased in the lung recipients who received CMVIG.[489,550]

Immunologic Monitoring in Pediatrics

There remain limited data to support monitoring for general or CMV-specific immune reconstitution in pediatric SOT. In small, mostly single-center studies, CMV-specific T-cell responses have been quantified using commercial or in-house assays that primarily measure intracellular IFN-γ responses to ex vivo stimulation with CMV-infected cell lysates, antigens, or peptide panels. Most pediatric transplant recipients had detectable $CD4^+$ and $CD8^+$ T-cell responses within the first year posttransplant, with an increase in responses as immunosuppressive therapy was tapered.[546] Lower responses were associated with viral reactivation and higher CMV viral loads.[554] However, the benefits of including these assays as immune surveillance to predict outcomes or alter management remains uncertain.[555]

Treatment of Pediatric CMV Disease

Many of the principles that guide therapy in children are similar to those in adults. Valganciclovir has been shown to be an effective treatment of asymptomatic CMV DNAemia in the setting of preemptive therapy, providing a rationale for its use in mild to moderate CMV disease.[157,496,515,556]

Maribavir is approved in patients aged 12 y or older, weighing at least 35 kg, with posttransplant CMV that is refractory to treatment with other antivirals. Despite the lack of pediatric SOT data, clinical data inferred from adult studies and population PK modeling showed that the

adult dosing could be extended to adolescents.[556] However, data are lacking on the PK, safety, and efficacy in younger children.

In addition to the lack of pediatric letermovir dosing data, the low threshold for letermovir resistance in adults precludes CMV treatment with letermovir monotherapy.[402]

Cellular therapy for the treatment of CMV in pediatric SOT recipients represents a potential option for children with resistant/refractory CMV who cannot tolerate or who do not have access to alternative antivirals. A single-center experience used partially HLA-matched, ex vivo generated, multivalent, virus-specific T cells for several viral pathogens, including CMV, in 19 adult and 7 pediatric SOT recipients.[375] Five of the 7 children had a complete response, whereas 2 remaining children were deemed not evaluable due to additional use of antiviral therapy. There were no significant adverse events or rejections associated with the therapy.

Ganciclovir Resistance in Pediatric Organ Transplantation

With increased rates of risk factors for CMV antiviral resistance like CMV D^+/R^- status and breakthrough CMV DNAemia under prophylaxis in pediatric SOT,[557,558] antiviral resistance becomes a significant potential concern,[559] although published reports from prior pediatric cohorts report a low incidence of ganciclovir resistance of only 1%–4%.[497,544,560,561] It is unclear if the reported incidence is due to low resistance burden, lack of generated data, or underreporting. The currently available agents for the treatment of ganciclovir-resistant CMV in children are similar to those available in adults, except maribavir, which has limited dosing data for children younger than 12 y or weighing <35 kg.

Consensus Statements and Recommendations

- In general, the principles that guide prevention and treatment strategies in children are similar to those in adults as directed by the organ transplanted and CMV donor and recipient serostatus (strong, moderate).

CMV Serostatus

- We recommend performing CMV IgG serology in all children, including those younger than 12 mo (strong, high).
- In CMV seropositive infants aged 12 mo or younger, due to the possible presence of maternal antibodies, we recommend that risk assessment in this age group should assume the highest risk level for purposes of CMV prevention (strong, moderate; Table 10).
- It should be noted that the negative predictive value of a NAT from urine or saliva is limited by intermittent CMV shedding.

Prevention Strategies

- Retrospective data provide support for each of the 3 prevention strategies and as such all 3 are recommended (strong, moderate). No pediatric trials have adequately evaluated the comparative efficacy of prophylaxis, preemptive therapy, or surveillance after short-term prophylaxis. The decision to pursue specific strategies is dependent on organ type and CMV D/R serostatus (Table 12).

Prophylaxis

- We suggest monitoring for CMV DNAemia during prophylaxis due to the higher incidence of breakthrough CMV infection in pediatrics (weak, low; Table 12). Data are too limited to suggest a specific frequency of monitoring. Individual centers need to decide on CMV DNAemia threshold to switch from prophylaxis to treatment dosing according to risk stratification of the individual, assay, and type of blood sample.
- There is insufficient evidence to recommend the routine use of letermovir as primary prophylaxis in pediatric SOT recipients.

Preemptive Therapy Strategy

- We suggest following adult recommendations of weekly testing for at least 12–16 wk posttransplant when performing surveillance for CMV DNAemia among patients being managed preemptively (strong, low).
- We suggest using lower CMV DNAemia thresholds for initiating preemptive therapy in D^+/R^- than R^+ subgroups (strong, low).
- Individual centers need to decide on the CMV DNAemia threshold to initiate treatment according to the risk stratification of the individual, assay, and type of blood sample.
- Duration of surveillance may be modified on the basis of net state of immunosuppression (strong, low).

Secondary Prophylaxis

- We suggest consideration of secondary prophylaxis after a first episode of CMV disease in children (weak, very low).
- We suggest using secondary prophylaxis in children with discrete, repeated episodes of CMV DNAemia requiring treatment and/or CMV disease (weak, low).
- The duration of secondary prophylaxis depends on immunosuppression regimen, age, presence of other opportunistic infections, and other risk factors. There are no data to suggest a specific duration of prophylaxis in these circumstances.
- Conversion to mTOR inhibitor–based immunosuppression in pediatric kidney transplant recipients may provide some protection against recurrent CMV (strong, moderate).
- We recommend reinitiation of either prophylaxis or preemptive therapy in children at risk for CMV infection/disease who receive significantly intensified immunosuppression for rejection (eg, lymphocyte-depleting antibodies, intravenous steroids), primary disease recurrence, or other complicating conditions (strong, low). There are no data to suggest a specific duration of prophylaxis or monitoring in these circumstances.

Surveillance After Monitoring Strategy

- We recommend monitoring for CMV DNAemia for non–kidney organs during the 8–12 wk after discontinuation of antiviral agents used for prevention or treatment (strong, moderate).
- We suggest considering monitoring for CMV DNAemia for kidney transplant recipients during the 8–12 wk after discontinuation of antiviral agents used for prevention or treatment (weak, low).
- There is insufficient evidence to recommend the use of CMV-CMI to guide prevention or treatment decisions in children. No studies have shown that routine monitoring of

T-cell responses impacts decision-making in pediatric transplant recipients.

Valganciclovir Dosing

- We suggest using either BSA-based dosing or BW-based dosing of valganciclovir in pediatric SOT recipients (weak, moderate). BSA-based dosing leads to the use of larger doses than BW-based dosing, especially in infants and younger children (younger than 6 y), which results in higher exposures (ie, ganciclovir AUC), more frequent attainment of AUC-based therapeutic targets, and also increased frequency of toxicities (Table 12).
- Empiric dose reduction for presumed antiviral hematologic toxicity is not recommended (strong, moderate).
- We do not suggest the routine performance of TDM of ganciclovir in pediatric SOT recipients (weak, low).

Treatment

- We recommend using oral valganciclovir therapy in children with asymptomatic CMV DNAemia requiring treatment or with mild/moderate CMV disease (strong, moderate).
- We suggest considering intravenous ganciclovir therapy for patients with concerns about adherence, issues with absorption, or high risk for progression to severe disease (weak, low).
- We recommend intravenous ganciclovir for severe or life-threatening disease (strong, moderate).
- We recommend maribavir as an option in pediatric SOT recipients aged 12 y or older and weighing ≥35 kg with CMV infection/disease that is resistant/refractory to treatment (strong, low).
- There is insufficient evidence to recommend maribavir as an option in pediatric SOT recipients younger than 12 y or weighing <35 kg.
- We do not recommend the use of letermovir monotherapy for the treatment of CMV DNAemia or disease in pediatric SOT recipients (strong, low).
- We recommend immunosuppression reduction where feasible in the management of CMV DNAemia or disease (strong, low).
- Adjunctive IVIG or CMVIG for antiviral treatment of CMV disease is not routinely recommended but may be considered for patients with severe disease, resistant/refractory CMV, and/or hypogammaglobulinemia (weak, low).
- We suggest considering the use of cellular therapies (whether as CMV-specific or multivirus-specific T-cell therapy) for pediatric patients with refractory/resistant CMV in whom alternative antiviral therapy is not available or for those who cannot tolerate the side effects of these alternative agents (weak, low). Where possible, cellular therapy should be used as part of a research protocol.

Future Directions

- Reporting of the epidemiology and outcomes, including CMV infection and disease rates, with current preventive strategies and delineation of the short- and long-term indirect effects of CMV in pediatric transplant recipients is encouraged. Such reporting should be done using uniform criteria to enable comparisons across studies.
- Current therapeutic targets for ganciclovir and valganciclovir have been extrapolated from adult studies but are unproven in children. Prospective comparative effectiveness studies are needed to define optimal ganciclovir/valganciclovir dosing strategies (BSA- and BW-based) in children balancing both short-term (eg, toxicity, breakthrough DNAemia) and long-term (eg, rejection, CMV infections) outcomes and cost.
- Given the significant interindividual variability in ganciclovir PK in children, studies evaluating the utility of TDM could help determine the effectiveness of this practice and potentially inform the most appropriate therapeutic target(s) for use in pediatric SOT recipients.
- Additional investigation into the use of novel technologies to enhance remote monitoring strategies, such as self-acquired dried blood, could improve practice.
- Additional work is required on the utility of immunogenetic biomarkers and adjunctive immunologic monitoring to guide treatment strategies. Such work should consider age-related immune maturity issues that might influence the optimal performance of assays (eg, IFN-γ release assays).
- Pediatric data should be obtained for emerging antiviral agents and CMV-specific cellular therapies to expand the opportunities to prevent and treat CMV.

CONCLUSIONS

We hope that these new international CMV guidelines serve as a useful and valuable resource for the transplant community to improve the management of CMV in our patients. As with all guidelines, the recommendations should be considered in the context of any new and emerging information. Fortunately, we are in an era where numerous new, well-designed clinical trials related to CMV are either underway or planned. Although it is difficult to provide an in-depth summary of the numerous new recommendations in this version of the guidelines, some key highlights are provided: In the Diagnostics section, a greater emphasis exists on CMV-QNAT testing calibrated to the WHO standard while moving away from the older CMV antigenemia assay. Guidance related to caution in the clinical interpretation of small viral load changes is provided. In the Prevention section, letermovir is a new additional potential option for primary CMV prophylaxis in D^+/R^- kidney transplant recipients, as well as in other patient groups who are intolerant of valganciclovir. Also, more data supporting the use of preemptive therapy in D^+/R^- liver transplant recipients as an option for prevention are highlighted. Although no precise viral load thresholds for preemptive therapy are possible based on current data, lower thresholds are recommended for higher-risk patients. In patients receiving prophylaxis, a surveillance after prophylaxis approach is commonly used by experts, although more rigorous data are needed. In the Immunologic Monitoring, Vaccines and Cellular Therapy section, CMV-CMI testing is now recommended posttransplant in R^+ kidney transplant recipients (if available) to help personalize the duration of prophylaxis. Further data are needed in other groups, and currently, we do not suggest a utility for these assays in D^+/R^- patients. In the CMV Treatment section, valganciclovir and ganciclovir remain the mainstays of CMV treatment, with the former preferred in most cases of mild to moderate CMV disease. Precise CMV DNAemia thresholds to guide discontinuation of therapy were challenging to derive from existing literature. In the Antiviral Drug Resistance and Treatment Refractory Disease section, maribavir is recommended as the principal alternative therapy in cases of drug resistance unless

patients are clinically unwell with high viral loads when foscarnet would be preferred. New data on combination therapy and other strategies for difficult-to-treat patients are needed. Finally, in the Pediatric Issues in CMV Management section, 1 of 3 strategies is recommended for prevention: prophylaxis, preemptive therapy, or surveillance after short-term prophylaxis. Additional rigorous clinical trials in CMV management are needed in the pediatric population, including data on the use of letermovir and maribavir. In summary, this new edition of the guidelines provides a comprehensive look at best practices related to CMV management after organ transplantation. The future of CMV management looks very promising and we are well on our way to defeating the "troll of transplantation."[562]

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