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Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice

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Abstract

Cytomegalovirus (CMV) is one of the most common opportunistic infections that affect the outcome of solid organ transplantation. This updated guideline from the American Society of Transplantation Infectious Diseases Community of Practice provides evidence-based and expert recommendations for screening, diagnosis, prevention, and treatment of CMV in solid organ transplant recipients. CMV serology to detect immunoglobulin G remains as the standard method for pretransplant screening of donors and transplant candidates. Antiviral prophylaxis and preemptive therapy are the mainstays of CMV prevention. The lack of a widely applicable viral load threshold for diagnosis and preemptive therapy is highlighted, as a result of variability of CMV nucleic acid testing, even in the contemporary era when calibrators are standardized. Valganciclovir and intravenous ganciclovir remain as drugs of choice for CMV management. Strategies for managing drug-resistant CMV infection are presented. There is an increasing use of CMV-specific cell-mediated immune assays to stratify the risk of CMV infection after solid organ transplantation, but their role in optimizing CMV prevention and treatment efforts has yet to be demonstrated. Specific issues related to pediatric transplant recipients are discussed.

KEYWORDS

cidofovir, cytomegalovirus, foscarnet, transplantation, valganciclovir

1 | ETIOLOGY

Cytomegalovirus (CMV) is a ubiquitous β-herpesvirus that infects the majority of humans. In the Unites States, the overall CMV seroprevalence rate is 50%, although this rate varies depending on age, geography, and socioeconomic status.[1,2] Outside the Unites States, the CMV seroprevalence rate has been reported between 30% and 97%.[1,2] Primary CMV infection may be asymptomatic or manifests as a self-limited febrile illness in immunocompetent individuals. After primary infection, CMV persists as a latent virus, which then serves as reservoir for reactivation and transmission to susceptible individuals, such as solid organ transplant (SOT) recipients.[3]

Cytomegalovirus is an important cause of morbidity and mortality after SOT.[3] Accordingly, major efforts are exerted for CMV prevention, diagnosis, and treatment. This updated guideline from the American Society of Transplantation Infectious Diseases Community of Practice provides current evidence-based and expert recommendations for screening, diagnosis, prevention, and treatment of CMV in SOT recipients, with a section on specific issues that are unique to pediatric transplant recipients.

2 | EPIDEMIOLOGY, CLINICAL MANIFESTATIONS, AND DEFINITIONS

Without a prevention strategy, CMV infection and disease typically occurs during the first 3 months after SOT; this onset is delayed among patients receiving anti-CMV prophylaxis (see "postprophylaxis" delayed-onset CMV disease, discussed below).[3-9]

Consensus statements recommend the use of standardized definitions of CMV infection and disease in transplant recipients (Table 1).[10,11] While these consensus definitions are intended to ensure uniformity of reporting in clinical research,[10] the terminologies should also facilitate communication between providers in the clinical setting. The following definitions are recommended:

- CMV infection: presence of CMV replication in tissue, blood, or other bodily fluids regardless of symptomatology (this term is different, and should be distinguished, from "latent CMV"). CMV replication is detected by (a) nucleic acid testing (NAT), (b) antigen testing, and (c) viral culture. Depending on the method used, CMV replication in the blood can be termed as CMV DNAemia or RNAemia (NAT), CMV antigenemia (antigen testing), and CMV viremia (culture).[10]
- CMV disease: CMV infection that is accompanied by clinical signs and symptoms. CMV disease is categorized into (a) CMV syndrome, which typically manifests as fever, malaise, atypical lymphocytosis, leukopenia or neutropenia, thrombocytopenia, and elevated hepatic transaminases, and (b) end-organ CMV disease (eg, gastrointestinal disease, pneumonitis, hepatitis, nephritis, myocarditis, pancreatitis, encephalitis, retinitis, others) (Table 1). CMV has a predilection to invade the transplanted allograft[13]; hence, CMV more commonly causes hepatitis in liver recipients, nephritis in kidney recipients, or pneumonitis in lung recipients. The consensus definitions for these CMV diseases were recently published.[10]
- Asymptomatic CMV infection: CMV replication without clinical signs and symptoms of disease.[10]

CMV has several indirect effects resulting in part from its ability to modulate the immune system. CMV has been associated with increased risk of other infectious complications such as bacteremia,[14,15] invasive fungal diseases,[16] and Epstein-Barr virus-mediated post-transplant lymphoproliferative disorders.[17] CMV infection is associated with acute rejection and chronic allograft injury, including chronic allograft nephropathy (in kidney recipients),[18-21] bronchiolitis obliterans (in lung recipients),[22] and coronary vasculopathy (in heart recipients).[23,24] A significant association between CMV infection and a decrease in patient survival is well described in many (but not all) studies.[19,25,26]

3 | RISK FACTORS AND STRATIFICATION

The major risk factor that predisposes to the development of CMV disease after SOT is a qualitative (functional) or quantitative deficiency in global (nonspecific) and/or CMV-specific immunity.[27,28] In clinical practice, pretransplant CMV serology is the most commonly recommended measure of CMV-specific immunity. Based on the results of CMV serology in transplant candidates and prospective donors, the risk category of post-transplant CMV disease is defined. The risk of CMV disease is highest in CMV-seronegative SOT recipient without preexisting CMV-specific immunity who receives a latently infected organ from a CMV-seropositive donor (D+/R−).[27-30] On the other hand, CMV-seropositive (CMV R+) SOT recipients are at a moderate risk of CMV infection and disease due to presence of preexisting CMV-specific immunity.[31] Among CMV R+ SOT recipients, the risk of CMV infection is higher when the donor is also CMV-seropositive (D+/R+) when compared to CMV-seronegative donor (D−/R+), likely due to superinfection with donor-transmitted CMV. A CMV-seronegative recipient who receives organ from CMV-seronegative donor (D−/R−) has the lowest risk of CMV disease. Several assays are available to assess the presence of CMV-specific T cells, but their use during the pretransplant period to guide the risk of post-transplant CMV disease risk is very limited and remains investigational.[32]

Drug-induced immunosuppression, which depletes the quantity (ie, severe lymphopenia) and paralyzes the function of T cells (ie, lymphocyte anergy), increases the risk of CMV after SOT.[33,34] In particular, use of lymphocyte-depleting agents (anti-thymocyte globulins and alemtuzumab),[35,36] or high doses of maintenance immunosuppressive drugs, increases the risk of CMV.[31,37] The use of mTOR inhibitors (such as sirolimus and everolimus), in contrast, has been associated with a lower risk of CMV.[38-40] Collectively, the net functional defect of the combination of induction and maintenance immunosuppressive drugs influences the overall risk of CMV after SOT.

Allograft rejection is a major risk factor for CMV, especially when treated with lymphocyte-depleting antibodies.[41] The risk of CMV disease also varies by transplant type; lung,[25,42,43] vascularized composite allograft tissue,[44-46] and small intestinal[47-49] transplant recipients are at highest risk among SOT populations.

3.1 | Specific recommendations for pretransplant assessment of CMV risk after transplant

- All organ donors and transplant candidates should be tested for baseline CMV immune status using CMV-IgG serology prior to transplantation (**strong, high**).
  - The combined interpretation of CMV-IgG serology in the organ donor and transplant recipient should be used to categorize post-transplant CMV risk and guide CMV prevention strategies **(strong, high).** CMV-seronegative recipients who receive an organ from CMV-seropositive donor (D+/R−) are at highest risk of CMV disease after transplantation **(strong, high).**
  - Transplant candidates who are CMV-seronegative during the initial pretransplant evaluation should have repeat CMV serology immediately prior to transplantation (**strong, low**).

TABLE 1 Consensus definitions of cytomegalovirus infection and disease

	Proven or definite	Probable
CMV syndrome	Not defined	Detection of CMV in the blood by viral isolation, rapid culture, antigenemia, or QNAT Plus, at least two of the following: 1. Fever ≥38°C for at least 2 d 2. New or increased malaise or fatigue 3. Leukopenia or neutropenia on 2 separate measurements 4. 5% atypical lymphocytes 5. Thrombocytopenia 6. Hepatic aminotransferases increase to two times ULN (except non-liver transplant recipients)
Gastrointestinal CMV disease	Presence of upper and/or lower GI symptoms plus macroscopic mucosal lesions plus CMV documented in tissue by histopathology, virus isolation, rapid culture, immunohistochemistry, or DNA hybridization techniques	Presence of upper and/or lower GI symptoms and CMV documented in tissue but without macroscopic mucosal lesions CMV documented in blood by NAT or antigenemia alone is not sufficient for diagnosis of CMV GI disease
CMV pneumonia	Clinical symptoms and/or signs of pneumonia such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea combined with CMV documented in lung tissue by virus isolation, rapid culture, histopathology, immunohistochemistry, or DNA hybridization techniques	Clinical symptoms and/or signs of pneumonia such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea combined with detection of CMV by viral isolation and rapid culture of BALF, or quantitation of CMV DNA in BALF
CMV hepatitis	Abnormal liver tests plus CMV documented in liver tissue by histopathology, immunohistochemistry, virus isolation, rapid culture, or DNA hybridization techniques plus the absence of other documented cause of hepatitis	Not defined
CMV retinitis	Typical ophthalmological signs as assessed by an ophthalmologist experienced with the diagnosis of CMV retinitis If the presentation is atypical or an experienced ophthalmologist is not available, the diagnosis should be supported by CMV documented in vitreous fluid by NAT	Not defined
CMV encephalitis	CNS symptoms plus detection of CMV in CNS tissue by virus isolation, rapid culture, immunohistochemical analysis, in situ hybridization, or quantitative NAT	CNS symptoms plus detection of CMV in CSF without visible contamination of blood ("bloody tap") plus abnormal imaging results
Refractory CMV infection	CMV DNAemia or antigenemia increases (ie, >1 log10 increase in CMV DNA levels in blood between peak viral load within the first week and the peak viral load at 2 wk or more) after at least 2 wk of appropriately dosed antiviral therapy	Viral load persistence (at the same level or higher than the peak viral load within 1 wk but <1 log10 increase in CMV DNA titers) after at least 2 wk of appropriately dosed antiviral therapy
Refractory CMV disease	Worsening in signs and symptoms or progression into end-organ disease after at least 2 wk of appropriately dosed antiviral therapy	Lack of improvement in clinical signs and symptoms after at least 2 wk of appropriately dosed antiviral therapy
Resistant CMV	Presence of viral genetic alteration that confer reduced susceptibility to one or more antiviral drugs	

BALF, bronchoalveolar lavage fluid; CMV, cytomegalovirus; CNS, central nervous system; NAT, nucleic acid amplification test; QNAT, quantitative NAT; ULN, upper limit of normal.
References (Ljungman et al and Chemaly et al).[10,12]

- A serologic assay that measures CMV-IgG is recommended **(strong, high).**
  - Unless clinically indicated (ie, if primary CMV infection is suspected), CMV-IgM is not routinely recommended due to potential for false-positivity **(strong, low).** CMV-IgM false-positivity may lead to erroneous assignment of risk profile (eg, recipient is miscategorized as CMV D+/R+ instead of D+/R−), and resulting in severe clinical consequences.
- Recent blood transfusion or receipt of immunoglobulins and other blood products should be considered in the interpretation of CMV serology, as they may cause false-positive results due to passive transfer of CMV antibodies (**strong, low**). The clinical

consequences for miscategorizing D+/R− as a D+/R+ due to false-positive results can be severe.

- For organ donors and transplant candidates with borderline or indeterminate CMV-IgG serology results, the assignment of baseline serologic status should consider the "highest-risk" scenario for CMV prevention purposes **(strong, low).**
  - If a donor CMV-IgG serology is borderline or indeterminate, it should be considered as positive **(strong, low).**
  - If the recipient CMV-IgG is borderline or indeterminate, the result should be considered in the context of donor serology, as described below **(strong, low).**
    - If donor CMV serology is positive, the recipient with borderline or indeterminate CMV-IgG will be considered CMV-seronegative (ie, CMV D+/R−) **(strong, low).**
    - If donor CMV serology is negative, the recipient with borderline or indeterminate CMV-IgG will be considered CMV-seropositive **(strong, low).**
- CMV-specific T-cell immune responses may be assessed in transplant candidates prior to transplantation to determine baseline CMV immune status **(weak, low)**, but the role of CMV-specific T-cell assay as a predictor of the risk of CMV after transplantation remains under clinical investigation.

4 | LABORATORY DIAGNOSIS

The laboratory methods for the detection of CMV after SOT are (a) molecular assays, (b) antigenemia, (c) histopathology, and (d) culture. Measures to detect immune response to CMV after SOT are serology and CMV-specific T-cell assays (various platforms are available).

4.1 | Molecular assays

Molecular tests that detect CMV DNA or RNA (collectively termed NAT) are the preferred methods for detection of CMV replication in clinical specimens, thereby aiding in rapid diagnosis of CMV infection and disease, guiding the initiation and duration of antiviral therapy, and monitoring treatment responses.[50] Detection of CMV RNA is a highly specific indicator of CMV replication (although there is currently no commercial assay available), while CMV DNA may or may not always reflect CMV replication since a highly sensitive NAT may simply amplify latent viral DNA (particularly in cell-containing samples). For assays that detect and amplify DNA, a quantitative NAT (QNAT) assay is preferred over qualitative assay. CMV QNAT may differentiate CMV replication (associated with high viral load) from latent virus (low-level CMV DNAemia).[50,51] The kinetics of viral replication, as measured by the rate of increase in viral load, is an equally important marker of CMV disease risk[52-54]; the faster the rise in CMV viral load, the higher the risk of CMV disease.[53,54]

Plasma and whole blood are used as clinical samples for detection of CMV DNA by QNAT; higher viral load values are detected in whole blood compared to plasma.[55-57] Higher viral loads are also generally observed during primary CMV disease in CMV D+/R− compared to reactivation in CMV R+ SOT recipients.[57,58] Higher viral load values in blood are also generally associated with end-organ disease, while lower values are seen with asymptomatic CMV infection, and intermediate-range viral loads are seen with CMV syndrome, although there is overlap in viral load values among categories.[52,57-59] A significant correlation between end-organ CMV disease and CMV QNAT in blood has been observed during primary gastrointestinal CMV disease in CMV D+/R− SOT recipients. However, the sensitivity of CMV QNAT in blood is lower among CMV R+ patients with gastrointestinal CMV disease [60,61]; this suggests that CMV QNAT in blood may not be able to detect compartmentalized CMV cases (such as CMV retinitis and some cases of gastrointestinal CMV disease without systemic dissemination).[60,61] CMV QNAT has also been used to quantify viral load in other body fluids such as bronchoalveolar fluid (BALF) and cerebrospinal fluid (CSF).[43] Detection of CMV DNA in CSF suggests probable CNS disease.[10] CMV QNAT in BALF may serve as a less invasive method for diagnosis of probable CMV pneumonia, particularly when risk of performing transbronchial biopsy is prohibitive.[10,43] Higher viral load in BALF was correlated with biopsy-proven CMV pneumonia when compared to asymptomatic shedding, although BALF viral load values reported among different studies are highly variable.[10,43] Hence, further research is needed to standardize bronchoscopy procedures and CMV QNAT values in BALF.

The major drawback to CMV QNAT is the lack of widely applicable thresholds for various clinical indications. While the implementation of WHO International Standard for calibration has markedly improved the degree of agreement in viral load values among various assays,[51] there remains clinically significant variability in viral load values reported for the same sample when it is tested by different CMV QNAT assays.[63] Accordingly, viral load results of one assay cannot be directly extrapolated as equal to that of another assay.[63] Factors that account for viral load variability among WHO-calibrated assays are differences in assay platform,[63] clinical samples (plasma or whole blood),[57] gene target and amplicon size,[63] and extraction techniques, among others.[64,65] Hence, for CMV surveillance and monitoring after SOT, one should rely on the use of only a single CMV QNAT using a similar sample (eg, plasma only or whole blood only). Moreover, because viral load results vary among different assays, it is strongly recommended that each transplant center work with their clinical laboratories to define and validate relevant center-specific and assay-specific viral load thresholds for various clinical applications.[59]

4.2 | Antigenemia

The use of pp65 antigenemia assay, a semiquantitative assay that detects pp65 antigen in CMV-infected peripheral blood leukocytes, has significantly declined as it has been replaced in most centers by molecular assays.[50] Studies have shown that pp65 antigenemia is comparable to CMV NAT in guiding preemptive therapy, in rapid and sensitive diagnosis of CMV disease, and in guiding treatment responses.[66,67] The main disadvantages of antigenemia are the need to process the clinical

sample within few hours (due to short lifespan of neutrophils) and the lack of assay standardization across centers. Since the test relies on leukocytes, it has limited utility in SOT patients with leukopenia.[50]

4.3 | Histopathology

Histopathology remains as the gold standard for the definitive diagnosis of end-organ CMV diseases (with the exception of CMV retinitis, where ophthalmologic examination by expert ophthalmologist is sufficient; Table 1).[10] An invasive procedure is required to obtain tissue samples for CMV diagnosis. Hence, its use has declined in recent years due to the availability of less invasive tests to demonstrate CMV replication in the blood[60,61] or other bodily fluids such as CSF and BALF.[43] Histopathology is strongly recommended when another concomitant pathology (eg, acute allograft rejection) or copathogens are suspected, especially when patients do not adequately respond to anti-CMV treatment. Histopathology may be needed when CMV disease is suspected but CMV QNAT in blood is negative, such as in some cases of compartmentalized gastrointestinal CMV disease.[60,61] Repeat histopathology to document clearance of CMV infection from the affected organ, such as gastrointestinal tract, is not necessary in most cases, unless there is severe tissue involvement at the time of initial diagnosis.[61]

4.4 | Viral culture

While it is highly specific for the diagnosis of CMV infection, the use of viral culture has markedly declined due to poor sensitivity and slow turnaround time, compared to the more sensitive and rapid molecular tests.[50] Viral culture of urine is of low clinical utility in adult CMV R+ SOT patients since urinary viral shedding is common (see its use in pediatrics below).[32,50,68] The clinical utility of viral culture for phenotypic antiviral drug resistance testing has been supplanted by genotypic assays that provide a more rapid method of detecting mutations that confer resistance to antiviral drugs (see the Refractory and Resistant CMV section below).[69,70]

4.5 | CMV serology

Due to immunosuppression, SOT recipients have impaired ability to mount a robust antibody response.[73] Accordingly, CMV seroconversion has a limited utility (and is not recommended) for the diagnosis of CMV disease after SOT. CMV serology may be used after SOT to determine ongoing susceptibility among CMV-seronegative SOT recipients, although its predictive ability is only modest.[73] In interpreting CMV serology results after SOT, one should consider potential false-positive results from passively transferred antibodies among patients who received blood products (including IVIg) during or after transplantation.

4.6 | Cellular immunity assays

Immune monitoring to measure nonspecific and CMV-specific T-cell quantity and/or function is emerging as a clinical tool to assist in CMV risk stratification and management after SOT.[74,75] Nonspecific measures such as absolute lymphocyte count, CD4+ T-cell count, and nonspecific (mitogen) T-cell immune responses have been correlated with the risk of CMV disease after SOT.[27,34,76] In addition, several platforms are available to assess CMV-specific T-cell responses, including interferon-gamma release assays (IGRA),[27,75] enzyme-linked immunosorbent spot (ELISPOT) assays,[77,78] intracellular cytokine staining (ICS) for interferon-gamma (or other cytokines) using flow cytometry,[80,81] and major histocompatibility complex (MHC)-multimer-based assays that directly stain peptide-specific T cells.[34] Numerous studies, often single-center and observational, have highlighted the potential role of immune assays in CMV risk assessment.[27,34,75,83] In general, regardless of the assay that is used, the absence of adequate CMV-specific CD4+ and/or CD8+ T-cell immunity correlates with a higher risk of CMV disease, treatment failure, and CMV relapse.

4.6.1 | Specific recommendations for laboratory diagnosis of CMV in SOT recipients

- CMV QNAT is the laboratory method of choice for rapid diagnosis of CMV infection in blood after SOT **(strong, high).** CMV QNAT is the preferred laboratory method for CMV surveillance to guide preemptive therapy (**strong, high**). See the Preemptive Therapy section for specific details.
  - pp65 antigenemia is an alternative laboratory method for surveillance and diagnosis of CMV infection after SOT **(strong, high).**
- CMV QNAT assays should be calibrated using the WHO International Reference Standard **(strong, high).**
  - Studies should report CMV viral load in IU/ml using QNAT assays that have been calibrated to the WHO International Reference Standard **(strong, high).**
  - Even if viral loads are reported in IU/ml, the viral load values are not similar among CMV QNAT assays, and should not be interpreted interchangeably during clinical care (**strong, high**).
- Transplant centers are encouraged to derive specific viral load thresholds depending on the CMV QNAT assay they use and the population at risk **(strong, high).**
  - CMV QNAT for surveillance and diagnosis should be performed using the same assay (**strong, high**). In reporting viral load values, the name of the CMV QNAT assay should be specified (**strong, high**).
- Whole blood and plasma are the recommended clinical samples for the detection of CMV replication by QNAT in the peripheral blood (**strong, high**).
  - CMV viral load is higher in whole blood than in plasma. CMV monitoring should only use one sample type (plasma only or whole blood only) (**strong, high**).
  - CMV QNAT in BAL fluid may be used for the diagnosis of probable CMV pneumonia, but the viral load threshold to suggest end-organ lung disease vs asymptomatic shedding needs to be defined **(weak, low).**

- CMV QNAT of CSF may be used for the diagnosis of probable central nervous system CMV disease **(strong, high)**.
- CMV QNAT of urine sample should not be used for diagnosis and surveillance in adult CMV R+ SOT recipients **(strong, low).**

- The diagnosis of CMV syndrome should be supported by the demonstration of CMV by QNAT in whole blood or plasma **(strong, high).**
  - CMV QNAT of whole blood or plasma may also be used as a surrogate method for the diagnosis of probable end-organ CMV disease, when the risk of performing invasive procedure such as biopsy is prohibitive **(strong, moderate).**
  - A negative CMV QNAT in the blood does not completely rule out the presence of end-organ CMV disease, particularly among CMV R+ SOT recipients with gastrointestinal disease **(strong, moderate).**
- The diagnosis of most end-organ CMV diseases should be confirmed by histopathology **(strong, high).** Histopathology with or without immunohistochemical staining remains as the standard method for definitive diagnosis of most end-organ CMV diseases **(strong, high).**
  - Patients suspected to have end-organ CMV disease but with negative QNAT in blood or negative pp65 antigenemia should have tissue biopsy and histopathology to confirm the clinical suspicion of CMV disease **(strong, moderate).**
  - Histopathology is not necessary for the diagnosis of CMV retinitis. A detailed ophthalmologic examination by expert ophthalmologist is sufficient **(strong, high).** Only in atypical cases, the demonstration of CMV by NAT in vitreous fluid is suggested **(strong, high).**
- Viral culture of blood and urine has limited clinical utility for prediction, diagnosis, and management of CMV disease in adult SOT patients and is not recommended in routine practice **(strong, high).**
- CMV-IgM and -IgG serology should not be used for the diagnosis of CMV disease after SOT **(strong, high).**
- Immunologic monitoring after SOT may be used to stratify the risk of CMV disease.
  - Absolute lymphocyte count and CD4+/CD8+ T-cell subsets may be used to stratify the risk of CMV disease after SOT, but specific lymphocyte thresholds will need to be clinically validated (**weak, low**).
  - Hypogammaglobulinemia is associated with CMV disease, and measurement of total immunoglobulin G levels may be used to assess the risk **(weak, low).**
  - Measures of global (nonspecific) and CMV-specific CD8+ and/or CD4+ T cells may be used to stratify the risk of CMV disease after SOT **(strong, moderate).**

5 | PREVENTION OF CMV DISEASE

The approaches to CMV prevention in SOT recipients vary among different transplant populations and risk profiles. The two major strategies for CMV disease prevention after SOT are (a) antiviral prophylaxis and (b) preemptive therapy (Table 2). Antiviral prophylaxis entails the administration of an antiviral drug to all "at-risk" patients for a defined period of time after SOT. In contrast, preemptive therapy is the administration of antiviral drug only to asymptomatic patients with evidence of early subclinical CMV replication, as measured by CMV QNAT, with the aim of halting its progression to CMV disease. While most transplant centers employ either one of these two major strategies for CMV prevention, others have used a hybrid approach wherein antiviral prophylaxis (of varying duration) is followed by CMV surveillance and preemptive therapy during the period of CMV risk.[84,85] Table 3 lists the antiviral drugs for prevention and treatment.

Antiviral prophylaxis and preemptive therapy have their specific advantages and disadvantages (Table 2). There are only a limited number of clinical trials that have directly compared preemptive therapy and antiviral prophylaxis.[20,21,86,87] These few small-scale studies, which were performed mainly in kidney recipients, demonstrate that both strategies are similarly effective for CMV disease prevention, even in CMV D+/R− patients. A recently concluded randomized controlled clinical trial in 205 CMV D+/R− liver recipients demonstrated that the incidence of CMV disease at one year was significantly lower among patients who were managed with CMV DNA surveillance and preemptive therapy compared to antiviral prophylaxis for 3 months (9% vs 19%).[88] Indirect outcomes, including the incidence of opportunistic infection, rejection, and all-cause mortality, were not significantly different between antiviral prophylaxis and preemptive therapy.[88] The specific recommendations for CMV prevention among SOT populations are summarized in Table 4.

5.1 | Antiviral prophylaxis

The antiviral drugs for CMV prophylaxis are valganciclovir and intravenous ganciclovir.[5] Oral ganciclovir is no longer commercially available.[6] For kidney recipients, high-dose valacyclovir is an alternative.[7] Letermovir, a novel viral terminase inhibitor, was recently approved for CMV prophylaxis after allogeneic hematopoietic stem cell transplantation,[89] but this is not approved for use in SOT recipients. A randomized controlled clinical trial comparing letermovir and valganciclovir is ongoing for the prevention of CMV in CMV D+/R− kidney recipients (ClinicalTrials.gov NCT03443869). In selected patient populations (eg, heart and lung and intestinal transplant recipients), immunoglobulin preparations are occasionally used as an adjunct in combination with antiviral drugs. Acyclovir should not be used for anti-CMV prophylaxis.

The efficacy of ganciclovir, valganciclovir, and valacyclovir prophylaxis was demonstrated in clinical trials.[5,6] In a randomized clinical trial of 372 CMV D+/R− kidney, liver, pancreas, and heart recipients, CMV disease rate was comparable between patients who received 3 months of oral ganciclovir vs valganciclovir prophylaxis (17.2% valganciclovir vs 18.4% ganciclovir at 12 months).[5] In subgroup analysis, there was a higher incidence of end-organ CMV disease among liver recipients who received valganciclovir

TABLE 2 Characteristics of antiviral prophylaxis and preemptive therapy

	Antiviral prophylaxis	Preemptive therapy
Clinical efficacy	Yes (based on large randomized controlled clinical trials)	Yes (based on fewer and smaller trials), including D+/R− kidney and liver recipients
Ease of application	Easier to coordinate	More difficult to coordinate Viral load thresholds not defined; each program should develop viral load thresholds for various clinical indications
Delayed-onset CMV disease	Common in CMV D+/R− transplant recipients (post-prophylaxis delayed-onset CMV disease)	Less common
Cost	Higher drug costs	Higher laboratory costs
Toxicity	Greater drug toxicity (myelosuppression)	Lesser drug toxicity with shorter courses of antiviral therapy
Indirect effects (graft loss, mortality, and opportunistic infections)	Positive impact (meta-analyses and limited comparative trials)	Very limited data
Drug resistance	Yes	Yes

Risks and benefits may help guide the choice for CMV prevention after solid organ transplantation.

prophylaxis.[5] Hence, valganciclovir was not approved by US FDA for CMV prophylaxis after liver transplantation. The improved bioavailability of valganciclovir and its lower pill burden make it the preferred drug for CMV prophylaxis, even in liver recipients.[90] The recommend dose of valganciclovir prophylaxis is 900 mg once daily (for patients with normal renal function).[8] Because of the risk of leukopenia, some transplant centers use "mini-dose" valganciclovir prophylaxis (450 mg orally),[91] but this has been shown to be associated with the emergence of drug-resistant CMV, especially for CMV D+/R− patients.[92]

Because of postprophylaxis delayed-onset CMV disease, which occurs most commonly during the first 3-6 months after completion of antiviral prophylaxis in CMV D+/R− patients,[5] a randomized clinical trial was performed to assess the efficacy of extended (200 days) valganciclovir prophylaxis.[8] In this study of 318 CMV D+/R− kidney recipients, the incidence of CMV disease was reduced to 16.1% with 200 days compared to 36.8% with 100 days of valganciclovir prophylaxis.[8] Similar studies to assess the duration of prophylaxis in liver, heart, and pancreas recipients have not been performed, although some transplant centers have extrapolated these kidney-specific trial results in the prevention of CMV disease in liver, heart, and pancreas recipients.

Among SOT populations, lung,[25,42,43] intestinal,[47,48] and vascularized composite tissue allograft [44,45] recipients are at highest risk of CMV infection and disease. There are no randomized clinical trials to assess the optimal duration of antiviral prophylaxis in these patients. Among lung recipients, the rates of CMV infection and disease are high with <6 months of antiviral prophylaxis.[93] The rates of CMV infection and disease were significantly reduced when antiviral prophylaxis is given for at least 6 months.[94] In a multicenter randomized clinical trial, CMV D+/R− and CMV D+/R+ lung recipients who received 12 months of valganciclovir prophylaxis had significantly lower rates of CMV disease and infection (4% and 10%) compared to those who received 3 months of valganciclovir prophylaxis (34% and 64%).[42,95]

The efficacy of prophylaxis with either CMV immunoglobulin or intravenous immune globulin in SOT recipients was suggested in a few trials.[96,97] A pooled analysis of previous studies suggests that the addition of immunoglobulin preparations to antiviral prophylaxis may reduce severe CMV disease and mortality,[98] but this finding has been debated.[99]

5.1.1 | Postprophylaxis delayed-onset CMV disease

Despite extending antiviral prophylaxis to 6 months after kidney transplantation or 12 months after lung transplantation, CMV disease commonly occurs in CMV D+/R− SOT recipients during 3-6 months after completion of antiviral prophylaxis. The term "postprophylaxis delayed-onset CMV disease" has been suggested to distinguish this entity from the truly late-onset CMV diseases that occur many years after transplantation.[4] In contrast to the truly late-onset CMV disease, the risk factors for postprophylaxis delayed-onset CMV disease are predictably similar to the "traditional-onset" CMV, such as D+/R− status, allograft rejection, severe lymphopenia, and intense immunosuppression.[4,34] Because postprophylaxis delayed-onset CMV disease remains associated with poor long-term outcome, there have been numerous efforts to develop strategies for its prevention and treatment, as follows:

- *Close clinical follow-up with early treatment of CMV disease when symptoms occur.* SOT recipients (especially CMV D+/R−) should be advised of the heightened risk of CMV disease within 3-6 months after discontinuation of antiviral prophylaxis and that they should immediately seek medical assistance when signs and symptoms of CMV disease occur. Clinicians should have a low threshold for considering CMV disease as a diagnosis in SOT patients presenting with compatible signs and symptoms after cessation of antiviral prophylaxis.

TABLE 3 Antiviral drugs for cytomegalovirus prevention and treatment in solid organ transplant recipients

Drug	Treatment[a]	Prophylaxis	Comments on use and toxicity
Valganciclovir	900 mg[b] po twice daily	900 mg[b] po once daily	Ease of administration Leukopenia is major toxicity
IV ganciclovir	5 mg/kg IV every 12 h	5 mg/kg IV once daily	Intravenous access and its associated complications Leukopenia is major toxicity
Valacyclovir	NOT recommended	2 g po four times daily	For kidney transplant recipients only NOT recommended for heart, liver, pancreas, lung, intestinal, and composite tissue transplant recipients High pill burden Neurotoxicity NOT recommended for treatment of CMV disease or asymptomatic infection
Foscarnet	60 mg/kg IV every 8 h (or 90 mg/kg every 12 h)	NOT recommended	Second-line alternative agent for treatment Highly nephrotoxic Used for *UL97*-mutant ganciclovir-resistant CMV infection or disease NOT recommended for preemptive therapy
Cidofovir	5 mg/kg once weekly ×2, then every 2 wk thereafter	NOT recommended	Third-line agent Highly nephrotoxic May be used for *UL97*-mutant ganciclovir-resistant CMV infection or disease NOT recommended for preemptive therapy

Intravenous or CMV-specific immunoglobulin has been used by some centers as an adjunct to antiviral prophylaxis, especially in heart, lung, and intestinal transplant recipients. The efficacy of this approach is debated. The doses of the antiviral drugs are for adults and should be adjusted based on renal function.

[a]These treatment doses are also recommended for preemptive therapy of asymptomatic CMV replication. Foscarnet, valacyclovir, oral ganciclovir, and cidofovir are not recommended for preemptive therapy. Letermovir is not approved for prevention and treatment of CMV in solid organ transplant recipients.

[b]Pediatric valganciclovir Dose is mg = 7 × BSA × Creatinine clearance.

- *Viral surveillance after completion of antiviral prophylaxis*. Patients who completed antiviral prophylaxis may be monitored using CMV QNAT periodically for a period of time.[84] The optimal duration and frequency of CMV monitoring are not defined. A few small-scale studies indicate that less frequent monitoring (every 2 weeks) [100] and for short-term monitoring (up to 2 months only)[101] were not clinically helpful in capturing postprophylaxis delayed-onset CMV disease in CMV D+/R− SOT recipients. However, one study reported no end-organ CMV disease occurred when CMV surveillance was performed once weekly for 3 months after completion of antiviral prophylaxis.[102]
- *Further prolongation of antiviral prophylaxis*. Some centers have observed postprophylaxis delayed-onset CMV disease in CMV D+/R− lung recipients despite 12 months of antiviral prophylaxis and have extended the duration of prophylaxis beyond 12 months (sometimes anticipated as lifelong).[25,103] However, this was associated with significant myelotoxicity.[103]
- *Immunologic monitoring at the end of antiviral prophylaxis, and thereafter*. Patients who are completing or who have recently completed antiviral prophylaxis may be tested for nonspecific and CMV-specific immune recovery to assess their risk of post-prophylaxis delayed-onset CMV disease.[27,104] CMV serology at the end of antiviral prophylaxis was not highly predictive of subsequent risk.[73] In contrast, studies have suggested that lymphopenia (absolute lymphocyte count, CD4+ T-cell count)[33,34] and lack of CMV-specific (and nonspecific) T-cell response[27,34] are associated with an increased risk of postprophylaxis delayed-onset CMV disease. However, the immune cell thresholds for protection among various measures are not yet fully defined.

5.1.2 | CMV after use of lymphocyte-depleting drug for treatment of acute rejection

The use of lymphocyte-depleting therapy, such as anti-thymocyte globulin or alemtuzumab, for the treatment of acute cellular rejection significantly increases the risk for CMV disease.[36,105,106]

TABLE 4 Recommendations for cytomegalovirus prevention in solid organ transplant recipients

Organ	Risk category	Recommendation/Options (see Table 3 for dose and text for special pediatric issues)	Level of evidence
Kidney	D+/R−	Antiviral prophylaxis Drugs: valganciclovir (preferred), intravenous ganciclovir, or valacyclovir Duration: 6 mo	Strong, high
		Preemptive therapy (if logistic support is available) Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after kidney transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] p.o. BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	Strong, high
	R+	Antiviral prophylaxis Drugs: valganciclovir (preferred), intravenous ganciclovir, or valacyclovir Duration: 3 mo	Strong, high
		Preemptive therapy (if logistic support is available) Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after kidney transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	Strong, high
Pancreas and kidney/ pancreas	D+/R−	Antiviral prophylaxis is preferred Drugs: valganciclovir (preferred) or intravenous ganciclovir Duration: 3-6 mo	Strong, high (3-month prophylaxis) Strong, moderate (6-month prophylaxis)
		Preemptive therapy is an option (if logistic support is available) Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after pancreas alone or kidney-pancreas transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	Strong, moderate
	R+	Antiviral prophylaxis Drugs: valganciclovir (preferred) or intravenous ganciclovir Duration: 3 mo	Strong, moderate
		Preemptive therapy (if logistic support is available). Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after pancreas alone or kidney-pancreas transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	Strong, moderate
Liver	D+/R−	Antiviral prophylaxis Drugs: valganciclovir (note FDA caution[a]) or intravenous ganciclovir Duration: 3-6 mo	Strong, high (3-month prophylaxis) Strong, moderate (6-month prophylaxis)
		Preemptive therapy (if logistic support is available) Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after liver transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	Strong, high
	R+	Antiviral prophylaxis Drugs: valganciclovir (note FDA caution[a]) or intravenous ganciclovir Duration: 3 mo	Strong, high
		Preemptive therapy (if logistic support is available) Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after liver transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	Strong, high

(Continues)

TABLE 4 (Continued)

Organ	Risk category	Recommendation/Options (see Table 3 for dose and text for special pediatric issues)	Level of evidence
Heart	D+/R−	Antiviral prophylaxis is preferred. Drugs: valganciclovir (preferred), or intravenous ganciclovir. Some centers add adjunctive CMV immune globulin. Duration: 3-6 mo	Strong, high (3-month prophylaxis) Strong, moderate (6-month prophylaxis) Weak, low (immune globulin)
		Preemptive therapy is an option (if logistic support is available), but not preferred. Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after heart transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	Weak, low
	R+	Antiviral prophylaxis Drugs: valganciclovir (preferred) or intravenous ganciclovir. Some centers add adjunctive CMV immune globulin. Duration: 3 mo	Strong, moderate Weak, low (immune globulin)
		Preemptive therapy Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after heart transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b]po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	Strong, moderate
Lung, heart-lung	D+/R−	Antiviral prophylaxis Drugs: valganciclovir or intravenous ganciclovir Duration: at least 6-12 mo. Some centers prolong prophylaxis beyond 12 mo. Some centers add CMV immune globulin.	Strong, high (12-month prophylaxis) Strong, low (6-month prophylaxis) Weak, low (>12 mo prophylaxis) Weak, low (immune globulin)
	R+	Antiviral prophylaxis Drugs: valganciclovir or intravenous ganciclovir Duration: 6-12 mo.	Strong, moderate
Intestinal	D+/R−, R+	Antiviral prophylaxis Drugs: valganciclovir or intravenous ganciclovir Duration: 3 mo for CMV R+; 6 mo for D+/R−.	Strong, low
Composite tissue allograft	D+/R−, R+	Antiviral prophylaxis Drugs: valganciclovir or intravenous ganciclovir Duration: 3 mo for CMV R+; 6 mo for D+/R−.	Strong, low

The above recommendations do not represent an exclusive course of action. Several factors influence the precise nature and duration of antiviral prophylaxis or preemptive therapy.Antiviral prophylaxis should be started within 10 d after transplantation (strong, high). Oral ganciclovir is no longer commercially available. Preemptive therapy is NOT recommended for lung and heart-lung recipients (strong, low). Preemptive therapy is less preferred for intestinal and composite tissue allograft transplantation (weak, low).

[a]The US FDA has cautioned against valganciclovir prophylaxis in liver recipients due to high rate of tissue-invasive disease compared to oral ganciclovir. However, many experts still recommend its use as prophylaxis in liver recipients (strong, moderate). CMV D−/R− SOT recipients do not require anti-CMV prophylaxis, but if they are HSV1- or HSV2-seropositive, they should receive anti-HSV prophylaxis during the early period after transplantation (strong, high; see separate HSV guidelines). If blood transfusion is required, CMV D−/R− patients should receive CMV-seronegative or leuko-reduced blood products (strong, high).

[b]Pediatric valganciclovir Dose is mg = 7 × BSA × Creatinine clearance.

Administration of intravenous ganciclovir prophylaxis was associated with lower incidence of CMV disease in kidney recipients receiving anti-lymphocyte antibodies.[105,106]

5.1.3 | Specific recommendations for antiviral prophylaxis

- Antiviral prophylaxis may be given to any "at-risk" SOT recipient to prevent CMV infection and disease after transplantation **(strong, high)**.
  - The antiviral drugs that can be used for prophylaxis are listed in Table 3.
  - Specific recommendations for various organ recipients are listed in Table 4.
- Valganciclovir is the preferred drug for antiviral prophylaxis in adults (level of evidence varies depending on transplant type; see Table 4). Alternative drug options for antiviral prophylaxis are intravenous ganciclovir (which entails the need for vascular access) and, for kidney recipients only, high-dose valacyclovir (2 g PO qid) (level of evidence varies depending on transplant type; see Table 4).

- Despite US FDA caution, valganciclovir is the recommended drug for CMV prophylaxis in liver recipients **(strong, high).**
- The use of low-dose ("mini-dose") valganciclovir is not recommended, particularly in CMV D+/R− SOT recipients (**strong, high**).
- Unselected IVIg and CMV-Ig may be used, but only as an adjunct to antiviral therapy in lung, heart, and intestinal transplant recipients **(weak, low).**

- Antiviral prophylaxis should generally be started within the first 10 days after transplantation **(strong, high).**
- The duration of antiviral prophylaxis varies depending on the CMV donor and recipient serologies and the transplant types (level of evidence varies depending on serologies and transplant type; see Table 4).
  - CMV D+/R−: Antiviral prophylaxis for 6 months is recommended for CMV D+/R− kidney recipients **(strong, high)**, 3 months to 6 months for CMV D+/R− heart, liver, and pancreas recipients **(**level of evidence varies; see Table 4), 6-12 months for CMV D+/R− lung recipients **(strong, moderate to high)**, and 6 months for CMV D+/R− intestinal and composite tissue allograft recipients **(weak, low).**
  - CMV R+: Antiviral prophylaxis for 3 months is recommended for CMV R+ kidney, heart, liver, and pancreas recipients **(strong, high)**, 6-12 months for CMV R+ lung recipients **(strong, moderate to high)**, and 3-6 months for CMV R+ intestinal and composite tissue allograft transplant recipients **(weak, low)**.
  - The use of CMV-specific T-cell immune measures to guide the duration of antiviral prophylaxis has been suggested, but this remains investigational (**weak, low**).
- CMV-specific prophylaxis is not recommended for CMV D−/R− SOT recipients **(strong, high).**
  - HSV1- or HSV2-seropositive CMV D−/R− SOT recipients should receive antiviral prophylaxis for prevention of herpes simplex infection (eg, acyclovir, valacyclovir, famciclovir) **(strong, high).** Please refer to the HSV guidelines.
  - If blood transfusion is indicated, CMV D−/R− should receive CMV-negative blood or leuko-depleted blood products **(strong, high).**
- For the prevention of postprophylaxis delayed-onset CMV disease:
  - CMV QNAT at least once weekly for 3 months may be considered for surveillance to detect CMV replication after completion of antiviral prophylaxis **(strong, low).** Detection of CMV DNA above a predefined threshold should be preemptively treated with valganciclovir or intravenous ganciclovir.
  - Transplant recipients should be counseled of the risk of postprophylaxis delayed-onset CMV disease upon discontinuation of antiviral prophylaxis (**strong, low**). Close clinical follow-up is highly recommended **(strong, low).**
  - Measures of lymphopenia **(weak, low)** and impairment in global (nonspecific) and CMV-specific T-cell responses **(strong, moderate)** at the end of antiviral prophylaxis may be used to assess the risk of postprophylaxis delayed-onset CMV disease.
  - CMV serology at the end of antiviral prophylaxis has limited role in assessing the risk of postprophylaxis delayed-onset CMV disease and is not routinely recommended **(weak, low).**
- Antiviral prophylaxis with valganciclovir or intravenous ganciclovir should be given to patients receiving lymphocyte-depleting anti-lymphocyte antibodies for the treatment of rejection **(strong, high).**
  - The optimal duration of antiviral prophylaxis after treatment of rejection with lymphocyte-depleting drug is not known, but has been given for 1-3 months **(weak, moderate).**

5.2 | Preemptive therapy

An algorithm for CMV surveillance and preemptive therapy is depicted in Figure 1. Most studies have performed CMV surveillance at least once weekly after SOT to guide initiation of preemptive therapy.

CMV QNAT is the most common method for CMV surveillance to guide the initiation of preemptive therapy, although other centers may be using pp65 antigenemia. As discussed above (Laboratory Diagnosis section), there is no widely applicable viral load threshold to guide preemptive therapy.[50,59] Hence, site-specific and assay-specific viral load threshold values for initiation of preemptive therapy should be locally validated. It is likely that such viral load thresholds may be specific for various risk groups (eg, lower viral load threshold for CMV D+/R− compared to R+ patients) and patient populations (lung vs kidney recipients) and be immunosuppression-dependent (lymphocyte-depleting vs nondepleting regimens). In the absence of absolute viral load threshold to guide preemptive therapy, others have suggested viral kinetics as another approach to predicting the risk of CMV disease and the need for preemptive therapy,[54,107,108] although this requires more frequent viral load monitoring. There is a concern that the rapid viral kinetics in CMV D+/R− SOT patients may lead to failure to detect CMV replication early despite weekly CMV surveillance, and this may result in CMV disease.[53] Those studies were conducted at a time when CMV QNAT results are not available same day or in real time.[109,110] In the contemporary era when results of CMV QNAT are available on the same day of testing, this concern may no longer be valid. Indeed, data from recent studies conducted in kidney and liver recipients have shown that preemptive therapy was effective in preventing CMV disease, even in CMV D+/R− patients.[21] The results of a recent randomized controlled clinical trial reported a lower incidence of CMV disease among CMV D+/R− liver recipients who had CMV surveillance and preemptive therapy when compared to antiviral prophylaxis (ClinicalTrials.gov NCT01552369).[88]

Once CMV QNAT or pp65 reaches the predefined viral load threshold, treatment with oral valganciclovir (900 mg twice daily) or intravenous ganciclovir (5 mg/kg twice daily) should be initiated.[107,111] In a clinical trial, viral decay kinetics was similar between valganciclovir and intravenous ganciclovir for preemptive treatment of asymptomatic CMV reactivation.[111] Since preemptive therapy should treat low-level asymptomatic CMV replication, experts

recommend oral valganciclovir as preferable compared to intravenous ganciclovir for logistic issues.

The duration of preemptive antiviral therapy should be guided by viral load monitoring. Generally, preemptive antiviral therapy is continued until virologic clearance (ie, the virus is no longer detectable by CMV QNAT or has reached levels below a predefined viral load threshold).[50] Two consecutive negative weekly CMV QNAT was previously suggested (in studies that used less sensitive CMV QNAT assays), but a single negative test may suffice if using a highly sensitive QNAT.[55,112] One study reported that CMV QNAT positivity persisted for about a week longer when monitored by a more sensitive assay,[112] or using a more sensitive specimen.[55]

The strategy of allowing subclinical CMV replication before preemptive treatment is started may allow for immune priming and generation of CMV-specific T cells; this could account for the low incidence of delayed-onset CMV disease (in contrast to antiviral prophylaxis). Hence, in addition to viral load, CMV immune monitoring has been proposed to guide the need for, and the duration of, antiviral therapy.[75] The presence of functional CMV-specific T-cell immunity at the onset of asymptomatic low-level CMV viremia may indicate potential for spontaneous resolution, without the need for antiviral therapy.[113] On the other hand, the lack of functional CMV-specific T cells at the time of virologic clearance may indicate a heightened risk of CMV relapse.[75] The failure to develop functional CMV-specific T cells during CMV replication suggests a highly suppressed immune system, and the potential need to reduce pharmacologic immunosuppression.

5.2.1 | Specific recommendations for preemptive therapy

- Preemptive therapy may be used for effective prevention of CMV disease in SOT recipients (**strong, moderate to high**).
  - Preemptive therapy is clinically useful for the prevention of CMV disease in CMV R+ kidney, liver, pancreas, and heart recipients (**strong, high**).
  - Preemptive therapy is effective for the prevention of CMV disease in CMV D+/R− liver and kidney patients, as long as personnel and logistics of close surveillance and follow-up (ie, CMV QNAT results are available on the same day of testing) are available (**strong, high**). If these are not available, antiviral prophylaxis is preferred for D+/R− liver and kidney recipients (**strong, high**).
  - Preemptive therapy is not recommended for prevention of CMV disease in CMV D+/R− and R+ lung (**strong, high**) and it is less preferred for CMV D+/R− heart recipients (**weak, low**). Antiviral prophylaxis is preferred over preemptive therapy for lung and heart recipients (**strong, moderate to high**). Preemptive therapy is less preferred after intestinal and composite tissue allograft transplantation (**weak, low**).
  - Preemptive therapy may be considered as alternative approach to CMV prevention in patients with acute rejection treated with anti-lymphocyte antibody **(weak, low)** or high-dose steroids **(weak, low).**
- The laboratory test recommended for CMV monitoring to guide preemptive therapy is CMV QNAT (preferred) or a pp65 antigenemia assay (**strong, high**).
  - The recommended monitoring frequency is at least once weekly and the duration is at least 12 weeks after transplantation (**strong, high**). The duration of CMV QNAT monitoring may be extended longer for patients considered at highly immune suppressed status, or CMV-specific T cell-deficient (**strong, low**).
  - There is no widely applicable viral load threshold for initiation of preemptive therapy, and this value should be assay-specific, center-specific, and risk-specific **(strong, moderate).** Future studies are needed to define clinically relevant viral load thresholds in IU/ml for the initiation of preemptive therapy. However, these thresholds will likely remain assay-specific and risk profile-dependent.
- The recommended antiviral drugs for preemptive therapy are valganciclovir (900 mg twice daily) and intravenous ganciclovir (5 mg/kg every 12 hours), adjusted based on renal function **(strong, high).**
- The duration of preemptive antiviral therapy should be individualized **(strong, high).**
  - CMV QNAT (or pp65 antigenemia) should be performed once weekly to monitor response to preemptive treatment **(strong, high).**
  - Antiviral therapy should be continued until CMV DNAemia or antigenemia is no longer detectable or has declined to levels below a predefined threshold **(strong, high).** When using less sensitive assays, CMV QNAT should be undetectable or below a predefined threshold for at least 2 consecutive weeks in the blood prior to stopping antiviral treatment **(strong, moderate)**. The duration may be reduced to a single negative result when using a highly sensitive CMV QNAT assay **(weak, moderate).**
  - There are data supporting the potential role of CMV-specific T-cell immune monitoring to guide the need and the duration of preemptive antiviral therapy **(weak, low).** However, further research is needed before this can be adapted widely in clinical practice.
- HSV1- or HSV2-seropositive SOT recipients who are undergoing CMV surveillance, and not actively receiving valganciclovir or intravenous ganciclovir, should receive herpes simplex virus-targeted antiviral prophylaxis with acyclovir, valacyclovir, or famciclovir **(strong, high).** Refer to the HSV guidance for specific recommendations.

6 | TREATMENT OF CMV DISEASE

The first-line antiviral drugs for treatment of CMV disease are intravenous ganciclovir and oral valganciclovir (Table 3).[114] Foscarnet and cidofovir are regarded as second-line agents due to the high risk of

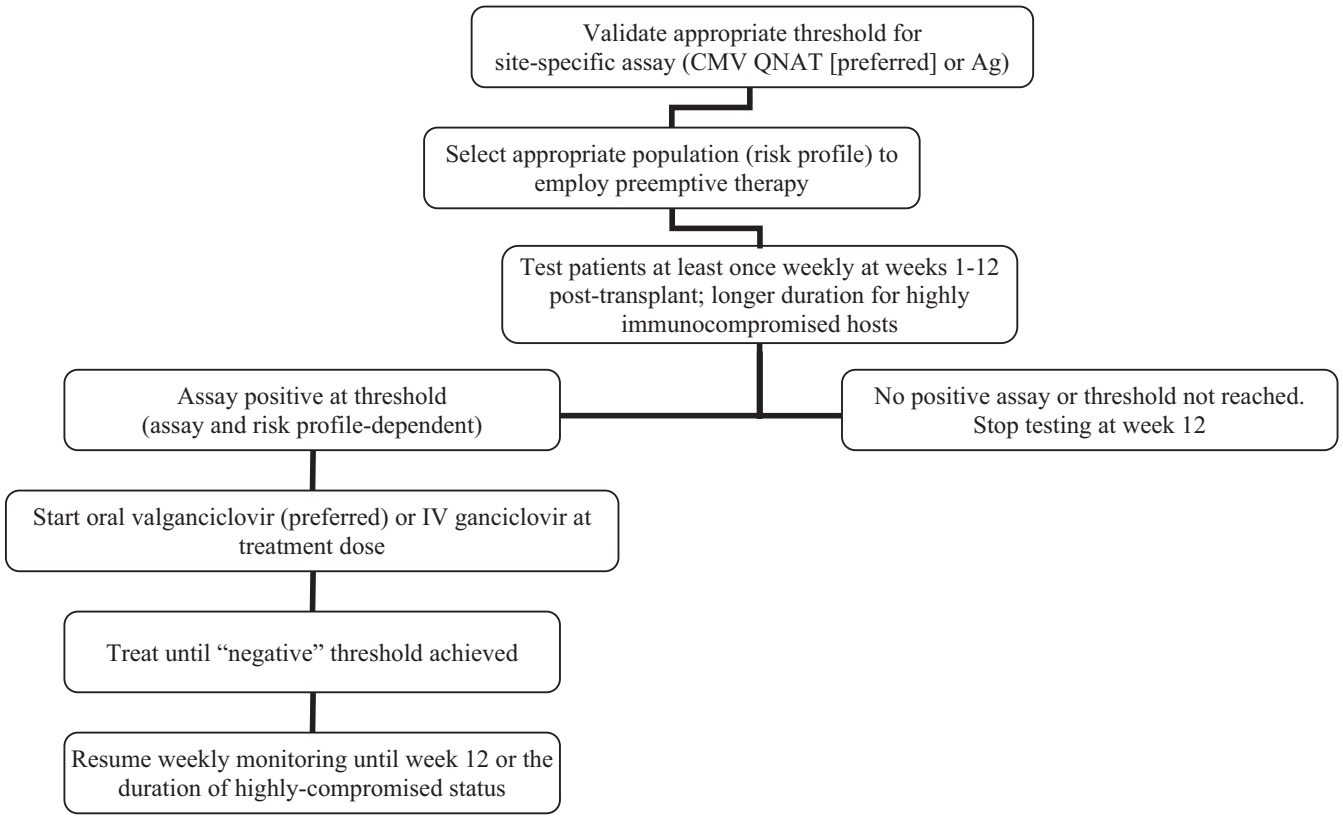

FIGURE 1 Suggested algorithm for preemptive therapy. CMV monitoring may be extended beyond the first 12 wk after transplantation in patients who remain severely immunocompromised, as assessed by the clinician. A clinically relevant "negative" threshold should be defined for every CMV quantitative nucleic acid test, depending on its lowest limit of detection and quantitation. This algorithm may be followed for solid organ transplant recipients who receive lymphocyte-depleting anti-lymphocyte antibodies, when CMV surveillance and preemptive therapy is chosen as the CMV prevention strategy

nephrotoxicity.[115] Letermovir has been used off-label in few cases of SOT recipients with CMV disease, but the drug is not approved for treatment indication.[116,117] Because durable control of CMV infection relies on a functional immune system, cautious reduction in immunosuppression should be considered in SOT patients with CMV disease, especially if the disease is moderate to severe.

The efficacy of intravenous ganciclovir for treatment of CMV disease has been demonstrated in numerous trials.[114,118,119] Routine measurement of serum ganciclovir levels during ganciclovir treatment has not been significantly associated with improved clinical response.[120] Because valganciclovir achieves blood levels that are comparable to intravenous ganciclovir, it has been used for treatment of mild-to-moderate CMV disease. In a randomized clinical trial that compared 3 weeks of oral valganciclovir to intravenous ganciclovir for treatment of CMV disease in 321 SOT recipients with mild-to-moderate CMV disease, both drugs had similar efficacy.[114] Notably, many patients remained viremic at day 21 (end of induction treatment), suggesting that longer courses of antiviral therapy are needed.[114]

Indeed, the duration of antiviral therapy should be individualized based on resolution of clinical symptoms and virologic clearance.[114,118,119,121] Generally, SOT recipients with CMV disease should be monitored once weekly using CMV QNAT or pp65 antigenemia to assess virologic response. CMV relapse is higher among patients with detectable CMV viral load at the end of antiviral therapy.[118,119,121] Patients with CMV disease should receive full therapeutic dose of antiviral therapy until CMV DNAemia or antigenemia has declined to undetectable levels or below a predefined viral load threshold. Accordingly, the duration of antiviral treatment is dependent on the sensitivity of the assay being used. Theoretically, use of a highly sensitive assay may lead to longer treatment duration when compared to less sensitive assays.[55] However, one study demonstrated that the overall duration of treatment was not significantly different between cases monitored by an older less sensitive vs a newer more sensitive CMV QNAT.[112] The use of CMV-specific T-cell immune monitoring may further guide the duration of antiviral therapy.[75] However, further research in this area is encouraged before this is widely implemented in clinical practice.

Recurrence of CMV viremia occurs in up to 35% of high-risk SOT recipients with CMV infection and disease.[118,119] In an attempt to reduce CMV recurrence, some programs provide secondary valganciclovir prophylaxis for 1-3 months after clinical and virologic response.[61,122,123] However, the efficacy of this approach is not proven. In observational studies, the incidence of CMV relapse was not significantly different between patients who did and did not receive secondary prophylaxis.[61,122,123] The risk of CMV relapse

after treatment of CMV disease may be predicted by persistent viral load[118,119,124] or deficiency in the quantity (lymphopenia)[33,34] and function of T cells.[75] Lack of CMV-specific T-cell response at the time of virologic clearance was associated with higher rate of CMV relapse.[75] However, the optimal approach to preventing CMV relapse is not defined, but may involve strategies to allow for CMV-specific T-cell immune reconstitution.

6.1 | Specific recommendations for treatment of CMV disease

- CMV disease should be treated with intravenous ganciclovir (5 mg/kg every 12 hours) or oral valganciclovir (900 mg twice daily), adjusted based on renal function **(strong, high).**
  - Intravenous ganciclovir is the recommended initial treatment for severe or life-threatening CMV disease **(strong, high)**, those with very high viral load **(strong, moderate)**, and those with questionable gastrointestinal absorption **(strong, moderate).**
  - Oral valganciclovir and intravenous ganciclovir are equally effective initial therapy for mild-to-moderate CMV disease **(strong, high).**
  - Because of the risk of nephrotoxicity, foscarnet and cidofovir are considered second-line alternative drugs for SOT recipients unable to tolerate valganciclovir or intravenous ganciclovir **(strong, moderate).**
  - Until clinical trials demonstrate its efficacy and safety in the SOT population, letermovir is not recommended for treatment of CMV disease after SOT (**strong, low**).
- Antiviral treatment of CMV disease should be continued until the following criteria are met **(strong, high):**
  - Resolution of clinical symptoms, AND
  - Virologic clearance below a threshold negative value (test specific; see text) based on laboratory monitoring with CMV QNAT or pp65 antigenemia once a week, AND
  - Minimum 2 weeks of antiviral treatment
- Transplant recipients with CMV disease treated initially with intravenous ganciclovir may be switched to oral valganciclovir once there is adequate clinical and virologic control, based on the clinical assessment of the treating provider **(strong, high).**
- Acyclovir, valacyclovir, and oral ganciclovir (no longer commercially available in the United States) should NOT be used for treating CMV disease **(strong, high).**
- The addition of IVIg or CMV-Ig to antiviral treatment of CMV disease may be considered for patients with life-threatening disease, CMV pneumonitis and possibly other severe forms of disease, drug-resistant virus, and those with hypogammaglobulinemia **(weak, low).**
- CMV QNAT (or pp65 antigenemia) should be performed once weekly to assess virologic response to treatment **(strong, high).**
  - Only one type of CMV QNAT assay and one sample type (plasma or whole blood) should be used to assess virologic response over the course of CMV disease **(strong, high).**
  - CMV QNAT should decline to a level below a predefined threshold or to undetectable level prior to stopping antiviral treatment of CMV disease **(strong, high).** When using less sensitive assays, CMV QNAT should be undetectable or below the predefined threshold for at least two consecutive weeks in the blood prior to stopping antiviral treatment **(strong, moderate).** The duration may be reduced to a single negative result when using a highly sensitive CMV QNAT assay **(weak, moderate).**
- Complete blood count (with differential) and serum creatinine should be monitored once weekly to assess for potential drug toxicity **(strong, high).**
  - Antiviral drug dosing should not be adjusted down due to leukopenia or pancytopenia **(strong, high).**
  - Antiviral drug dosing should be adjusted based on renal function **(strong, high).**
- Serum ganciclovir level monitoring (therapeutic drug monitoring) is not recommended for routine clinical use **(strong, moderate).**
- After completion of full-dose antiviral treatment, secondary prophylaxis intended to prevent CMV relapse is not recommended as a routine practice for all patients **(strong, moderate)**, but may be considered in subsets of high-risk patients **(weak, low).**
  - Patients should have clinical and virologic follow-up after discontinuation of antiviral treatment to assess the risk of CMV relapse **(strong, moderate).**
  - Lymphopenia may be used to assess the risk of CMV relapse **(weak, low).**
  - CMV-specific (and nonspecific) T-cell immune monitoring may be used to determine a patient's risk of CMV relapse **(weak, low).**
  - The approach to preventing CMV relapse in high-risk T cell-deficient patients is not known, but approaches such as secondary prophylaxis (**weak, low**) and further reduction in immunosuppression to allow for T-cell immune reconstitution, if feasible (**weak, low**), are suggested.
- If feasible, cautious reduction in immunosuppression should be considered in SOT patients presenting with CMV disease, especially if moderate to severe (**strong, moderate**).
  - Reduction in immunosuppression may not be feasible in patients with recent rejection or at heightened risk of rejection episodes.
  - Reduction in immunosuppression should be strongly considered in SOT patients with severe lymphopenia and those with deficient nonspecific or CMV-specific T-cell function **(weak, low).**

7 | REFRACTORY AND RESISTANT CMV

A one-log decline in CMV viral load is the anticipated outcome after at least 2 weeks of appropriately dosed antiviral therapy. CMV infection is considered refractory if CMV DNAemia, or antigenemia increases after at least 2 weeks of appropriately dosed antiviral therapy (ie, >1 log10 increase between baseline value and viral load at 2 weeks or more).[12] It is defined as probable refractory CMV infection if the viral load persists (at the same level or increases <1 log10

over baseline viral load) after at least 2 weeks of appropriately dosed antiviral therapy.[12] Nonresolution or lack of improvement in the clinical symptoms after two weeks of appropriately dosed antiviral therapy is suggestive of refractory CMV disease (Table 1). Potential reasons for refractory CMV infection are (a) an over-immunosuppressed status, including absence or deficiency in CMV-specific T-cell immunity,[125,126] (b) subtherapeutic antiviral drug concentrations,[127] or (c) resistance to ganciclovir or other antiviral drugs.[128,129]

The incidence of ganciclovir-resistant CMV infection after SOT is 0%-3%.[128,131,132] Risk factors for drug resistance are prolonged subtherapeutic dose of antiviral drugs (eg, mini-dosing), D+/R− serostatus, intense immunosuppression, and lung transplantation.[126,127,133,134] Drug resistance should be suspected in patients with refractory CMV infection or disease and possess any of these aforementioned risk factors.

When drug-resistant CMV infection is suspected, genotypic resistance testing should be obtained to detect specific mutations in *UL97* and *UL54* genes. CMV *UL97* is the gene that encodes for a viral kinase that catalyzes the initial mono-phosphorylation and activation of ganciclovir. Subsequent phosphorylation by human cellular enzymes leads to the active ganciclovir-triphosphate (a nucleoside analogue), which serves as a competitive substrate for incorporation into the elongating CMV DNA chain, a process that is catalyzed by CMV DNA polymerase (an enzyme encoded by CMV *UL54* gene). Genotypic assays, which are preferred over culture-based phenotypic assays, are performed on viral sequences that are directly amplified from blood (whole blood, plasma, or leukocytes), body fluids (urine, CSF, BALF, vitreous fluid), or tissue specimens. The degree of resistance to ganciclovir conferred by CMV *UL97* genetic mutants depends on the site of mutation, which could confer either a low-level or high-level resistance.[71,128,130] The most common *UL97* genetic mutations that confer high-level ganciclovir resistance are M460V/I, H520Q, C592G, A594V, L595S, and C603W.[69] Less commonly observed causes of ganciclovir resistance are mutations in *UL54* (which encode CMV DNA polymerase).[128] Since foscarnet and cidofovir also act to inhibit *UL54*-encoded CMV DNA polymerase, mutations in *UL54* gene may confer cross-resistance to ganciclovir, foscarnet, and cidofovir.[69] While letermovir is not yet approved clinically for use after SOT, genetic mutations have already been reported.[116] Based on experimental models and early clinical experience, letermovir resistance correlates with genetic mutations in *UL56* and less commonly *UL51* and *UL89*, which encode for viral terminase complex.[69,135]

The options for the treatment of refractory and resistant CMV are limited. Because an over-immunosuppressed status may account for the occurrence of refractory and resistant CMV, it is highly recommended, as a first-line strategy, to cautiously reduce the degree of immunosuppression. However, the specific approach to reducing immunosuppression is not defined or standardized.

There are no controlled clinical trials to guide the optimal choice for antiviral treatment of resistant CMV infection. Generally, ganciclovir-resistant CMV isolates with*UL97*-only mutations remain susceptible to foscarnet and cidofovir. Based on observational studies, foscarnet is the first-line drug for the treatment of *UL97*-mutant ganciclovir-resistant CMV.[115,127,136] There are only a few observational studies of foscarnet and cidofovir use in SOT recipients, but they support its efficacy.[136,137] The major problem with foscarnet and cidofovir is nephrotoxicity, which is worrisome for transplant patients who are already be receiving potentially nephrotoxic drugs.[136,137] Ocular complications (eg, uveitis) have been reported with cidofovir.[140]

Since ganciclovir, foscarnet, and cidofovir act by competitively inhibiting*UL54*-encoded CMV DNA polymerase, mutations in *UL54* gene may confer mono- or cross-resistance to any of these drugs depending on the site of the mutation. A ganciclovir-resistant CMV with *UL54* mutation is more likely to be cross-resistant to cidofovir; hence, foscarnet is the empiric choice for treatment of ganciclovir-resistant CMV infection. However, definitive antiviral drug choice should be guided by the results of the genotypic assays.[128] Because of the complexity in the management of drug-resistant CMV disease, referral to transplant infectious diseases experts for guidance is highly recommended. An algorithm for evaluation and management of ganciclovir-refractory or ganciclovir-resistant CMV infection or disease is presented in Figure 2.

Adjunctive intravenous immunoglobulin infusion has been given anecdotally to supplement the management of resistant CMV infection.[99,127,134,136,141,142] Several investigational and off-label drugs have also been used for the treating resistant CMV disease. Letermovir, which is approved as CMV prophylaxis in allogeneic hematopoietic stem cell transplant recipients,[89] has been used anecdotally for treatment of a lung recipient with CMV disease that was resistant to ganciclovir, foscarnet, and cidofovir.[117] Since its approval for clinical use, there have been reports related to the off-label use of letermovir for management of ganciclovir-resistant CMV. The off-label use of letermovir for treatment of ganciclovir-resistant CMV in SOT was complicated by emergence of *UL56*-mutant letermovir-resistant virus.[116] Maribavir has been used in a case series of transplant patients with refractory and resistant CMV,[143,144] and in a phase 2 study conducted in 120 transplant patients (ClinicalTrials.gov NCT01611974).[144] Maribavir is currently undergoing phase 3 clinical trials for the treatment of resistant and refractory CMV (ClinicalTrials.gov NCT02931539). The clinical development of brincidofovir, an oral formulation of cidofovir, is on hold due to its failure to prevent CMV infection in a phase 3 clinical trial in allogeneic hematopoietic stem cell transplant recipients (ClinicalTrials.gov NCT01769170).[145,146] Leflunomide and artesunate have been used off-label for treatment of a few cases of drug-resistant CMV disease, but their role is controversial.[147,148] Finally, sirolimus and mTOR inhibitors have been associated with a lower risk of CMV disease and may be a useful adjunct in the immunosuppressive management of SOT recipients with resistant CMV disease.[40,149,150]

Adoptive transfer of CMV-specific T cells, derived from autologous and allogeneic (organ donor or third party donors) sources, has been used in experimental settings for the treatment of resistant and refractory CMV after transplantation, especially

allogeneic hematopoietic stem cell transplantation.[153,154] Only sporadic reports have suggested its clinical utility in SOT recipients.[157,158] In a pilot trial, adoptive transfer of in vitro-expanded autologous CMV-specific T cells was effective in 11 of 13 SOT patients with recurrent or ganciclovir-resistant CMV infection, as indicated by improvement in symptoms, clearance or reduction in CMV DNAemia, or cessation in use of antiviral drugs.[159]

7.1 | Specific recommendations for ganciclovir-resistant CMV

- Patients who develop refractory CMV infection or disease after prolonged antiviral drug exposures and those failing to respond after at least two weeks of appropriately dosed antiviral treatment should be suspected of having drug-resistant virus **(strong, moderate).**
- Genotypic assays to detect *UL97* mutation should be performed among patients suspected to have resistance to ganciclovir, and *UL54* mutation analysis should be performed among patients suspected to have resistance to ganciclovir, foscarnet, and cidofovir, and this is preferred over phenotypic resistance testing **(strong, moderate to high).**
  - Genotypic assay to detect mutations in *UL56* and less commonly in *UL51/UL89* should be performed when resistance to letermovir is suspected (**strong, low**).
- Cautious reduction in immunosuppression is recommended for patients with refractory or resistant CMV infection and disease **(strong, moderate).**
  - A switch to sirolimus-containing regimen may be an option due to the reportedly lower risk of CMV disease in patients receiving mTOR inhibitors **(weak, moderate).**
- Options for empiric treatment of suspected resistant CMV disease include high-dose intravenous ganciclovir (up to 10 mg/kg q 12 hours, renally adjusted) or foscarnet (**weak, low to moderate**). Definitive antiviral treatment should be guided by results of genotypic testing **(strong, moderate to high).**
  - Other therapeutic options are cidofovir (**weak, low**), participation clinical trials (eg, maribavir treatment of refractory and resistant CMV) (**strong, low**), and off-label letermovir **(weak, very low).**
- CMV immunoglobulin or IVIg may be used as an adjunct to antiviral drugs in transplant recipients with resistant CMV disease **(weak, low).**
- If available, adoptive transfer of CMV-specific T cells may be considered for the treatment of refractory and resistant CMV **(weak, low),** but this will need to be investigated further in controlled clinical trials.

8 | PEDIATRIC ISSUES

The basic principles in prevention and management of CMV infection and disease in the pediatric SOT population are generally similar to adults, but there are unique characteristics in children that warrant emphasis.

First, there are considerably fewer studies to support recommendations for CMV prevention and treatment in pediatric SOT populations. Hence, most recommendations for CMV prevention and treatment in children are extrapolated from studies conducted in adult SOT recipients.

Second, the estimate of the burden of CMV disease in pediatric SOT recipients is based on limited number of pediatric cohort studies.[160] These cohort studies suggest that there are more CMV-seronegative pediatric SOT patients (compared to adults), and therefore, a relatively larger cohort are at increased risk of primary and potentially severe CMV disease. Even if the CMV-seronegative pediatric SOT recipient receives an organ from CMV-seronegative donor (CMV D−/R−), there is risk of acquiring de novo CMV infection as a result of exposures in the community, such as day care facilities.

Third, transplacental transfer of maternal CMV-IgG antibodies makes for a difficult interpretation of CMV serology in pediatric SOT patients less than 18 months of age. In this context, detection of CMV shedding in urine or saliva by CMV QNAT or culture may be used to confirm CMV infection status in infants and children less than 18 months of age.[32] Even if viral shedding in the urine and saliva is intermittent, studies have shown that this test is clinically useful to determine baseline CMV infection status in infants and young children.[68] Detection of CMV-specific T cells is another measure that could indicate baseline CMV status in children awaiting organ transplantation, when interpretation of CMV serology is confounded by transplacental transfer of maternal IgG antibodies.[32]

8.1 | Pretransplant screening in children

In pediatric SOT candidates <18 months of age who may have passively acquired maternal CMV IgG antibody, CMV QNAT or culture of urine specimen may be performed to determine baseline CMV status **(strong, moderate).**

- If urine CMV QNAT or culture is positive, the transplant candidate is considered CMV-infected (**strong, high**).
- If urine CMV QNAT or culture is negative, the assignment of CMV status should be based on the highest-risk level for the purposes of CMV prevention, and will take into account the CMV status of the donor **(strong, moderate).** For donors <18 months age, if the CMV serology is positive, the donor should be assumed as truly seropositive **(strong, moderate).**

8.2 | Prevention and treatment of CMV in children

The recommendations for antiviral prophylaxis and preemptive therapy in adult recipients are generally applicable to pediatric SOT recipients, with the following qualifying statements:

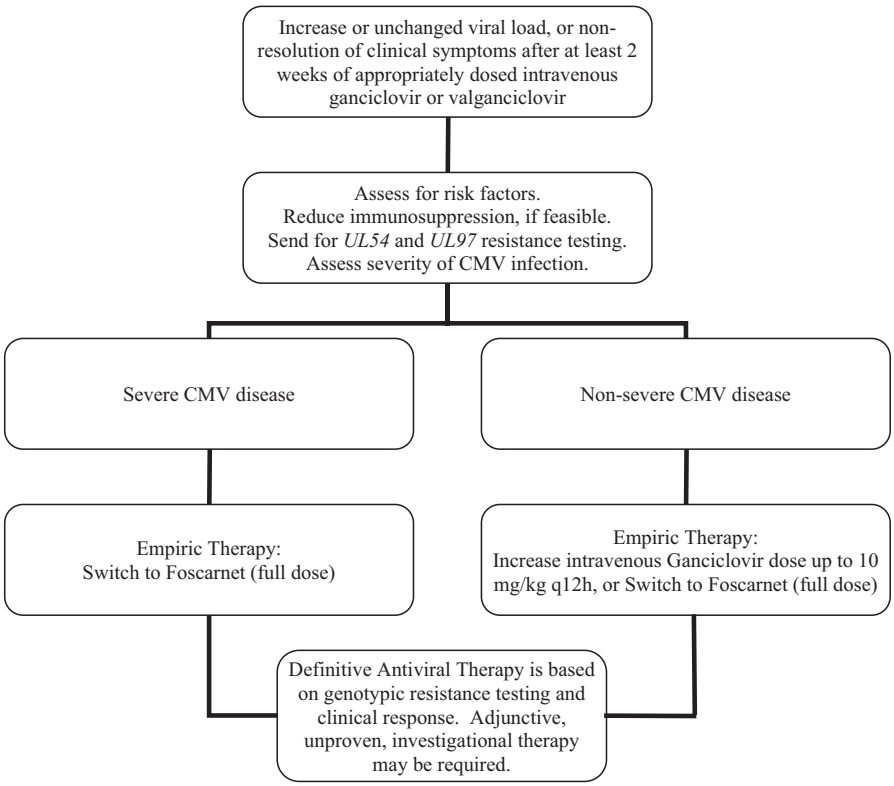

FIGURE 2 Algorithm for evaluation and management of refractory and resistant cytomegalovirus infection and disease

- Antiviral prophylaxis, preemptive therapy, and hybrid approach are effective for prevention of CMV disease in pediatric SOT patients (**strong, moderate**).
- Intravenous ganciclovir and oral valganciclovir are recommended for CMV prophylaxis, preemptive treatment of asymptomatic infection, and treatment of established CMV disease. Dosing of valganciclovir in children should be based on body surface area and renal function (**strong, moderate**).
- There is no single standard recommendation for the optimal duration of antiviral prophylaxis. The duration of intravenous ganciclovir prophylaxis varies from a minimum of 14 days to 3 months. Other centers prolong antiviral prophylaxis to 6 months after transplantation **(weak, moderate).**
- The risk of postprophylaxis delayed-onset CMV disease is highest during the first 3 months after cessation of antiviral prophylaxis, and pediatric SOT patients should undergo CMV QNAT surveillance during this at-risk period (**strong, moderate**).
- For pediatric patients undergoing the strategy of preemptive therapy, CMV QNAT is recommended once weekly for at least 12 weeks (**strong, high**).
- Oral valganciclovir is recommended for treatment of asymptomatic CMV DNAemia (**strong, low**).
- Treatment of mild-to-moderate CMV disease is with intravenous ganciclovir (**strong, moderate**) or oral valganciclovir (**strong, low**).
- Intravenous ganciclovir is recommended as first-line therapy for severe CMV disease (**strong, moderate**).
- CMV-Ig or intravenous Ig is generally not recommended (**weak, low**) but may be considered in combination with intravenous ganciclovir for the treatment of CMV disease in young infants and for treatment of more severe forms of CMV disease (**weak, low**).
- Intravenous ganciclovir treatment of CMV disease in pediatric SOT recipients may be transitioned to oral valganciclovir in clinically stable patients with declining and well-controlled viremia and resolved or resolving clinical symptoms (**strong, low**).

9 | FUTURE RESEARCH DIRECTIONS

There are a number of areas that are being actively explored in basic, translational and clinical research fields related to CMV disease diagnosis, prevention, and treatment. Despite widespread adaption of the WHO International Reference Standard for calibration, there remains clinically significant variability in viral load values. Hence, the search continues to define widely applicable viral load thresholds that should guide risk stratification, preemptive therapy, and therapeutic assessments. Clinical and commercial laboratories are encouraged not only to calibrate CMV QNAT assays based on the recently available WHO International Reference Standard, but also to work further to standardize the other steps in CMV QNAT. In the meantime, transplant providers should develop center-specific/assay-specific and patient population-specific viral load thresholds for different CMV QNAT clinical applications.

Numerous in-house (laboratory-developed) and commercial assays for the assessment of CMV-specific T-cell immunity are available to predict the risk of CMV disease in adults.[82,113,161] However, studies to assess the validity and utility of CMV immune assays in

pediatric SOT recipients will need to be completed. In addition, interventional studies to assess the potential clinical uses of CMV-specific T-cell assays beyond merely risk stratification are needed. In particular, the utility of these assays in determining duration of antiviral prophylaxis, the need for preemptive treatment, and guide the duration of treating CMV disease, and assess the risk of relapse after treatment.

There are novel preventive and therapeutic options in the horizon. Several CMV vaccine candidates are being tested, although results of recent clinical trials performed in CMV D+/R− kidney recipients have been disappointing.[162,163] Several novel antiviral drugs are in various stages of clinical development, including letermovir, maribavir, and brincidofovir. While letermovir has recently been approved for CMV prophylaxis in allogeneic hematopoietic stem cell transplant recipients, it remains investigational in SOT recipients. Letermovir is currently being compared with valganciclovir in a randomized controlled trial involving CMV D+/R− kidney transplant recipients. The role of letermovir for treatment of CMV disease is not known. Maribavir, on the other hand, is undergoing clinical trials for the treatment of refractory and resistant CMV infection. The clinical fate of brincidofovir, which had disappointing results in the recently concluded prophylaxis trial in allogeneic hematopoietic stem cell transplant recipients, is not known. Finally, studies should advance the potential for adoptive transfer of CMV-specific T cells as immunotherapy in SOT recipients with refractory, recurrent, and resistant CMV infection.[117,143,164]

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CONFLICT OF INTEREST

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