Prevention and Treatment of Cytomegalovirus Infections in Solid Organ Transplant Recipients

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KEYWORDS

• CMV • Cytomegalovirus • Herpesvirus infection • Solid organ transplantation
• CMV prophylaxis • CMV treatment

KEY POINTS

- Cytomegalovirus (CMV) prophylaxis and preemptive monitoring have reduced the incidence of early CMV disease in solid organ transplantation, but late disease has emerged as a significant problem.
- CMV-specific cell-mediated immunity (CMI) is required to control CMV in the absence of antiviral therapy, and achieving strong CMI without coincident allograft rejection is the ultimate goal of CMV management strategies.
- Measurement of CMV-specific CMI may help refine CMV prophylaxis and preemptive monitoring strategies.
- Valganciclovir remains the mainstay of CMV treatment but comes at the cost of frequent myelosuppression.
- Letermovir is a newly approved antiviral with strong activity against CMV and minimal side effects and may change the landscape of CMV management.

Human cytomegalovirus (CMV) is a double-stranded DNA virus and member of the herpes virus family. Infection prevalence reaches 60% to 80% by adulthood in the United States and nearly 100% in many parts of the world.[1,2] First recognized as a major complication of solid organ transplantation (SOT) 50 years ago, it remains the most common viral infection encountered after SOT and can occur as a primary infection, secondary infection, or reactivation from a latent reservoir.[3] Although humans have evolved to live a lifetime with persistent asymptomatic infection, recipients of SOT

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are challenged to adapt to and control CMV infection while deliberately impairing immune recognition of their allograft.

CYTOMEGALOVIRUS INFECTION AND THE IMMUNE RESPONSE

Primary infection in immunocompetent individuals is most often asymptomatic and transmitted via secretions of an infected individual. CMV disseminates from the respiratory epithelium, most commonly via mononuclear cells and polymorphonuclear cells to endothelial, epithelial, and fibroblast of tissues and organs.[1] Prolonged shedding in saliva and urine after primary infection provides evidence for coincident chronic viral replication in some sites but emergence of latency elsewhere.

The innate immune system provides initial antiviral activity until the adaptive immune response can exert more definitive control of infection. Both CD4 and CD8 T-cell responses are instrumental for control of CMV and guard against replication and infection of new cells.[4,5] CMV establishes lifelong latency in endothelium, epithelium, smooth muscle, and fibroblasts by evading immune detection.[5,6] Infections with CMV variants and intermittent viral replication from latency expand the breadth of CMV recognition over a lifetime.[1,7] Although humoral immunity may restrict viral dissemination early in the primary infection and with reinfection, its role beyond this is debated.[4,8,9] CMV immunoglobulin G (IgG), however, is reflective of past infection.

Cytomegalovirus in Solid Organ Transplant Recipients

Immunologic recognition of acute CMV infection and control of latent infection require many of the same mechanisms that are disabled by the immunosuppression that prevents allograft rejection. **Fig. 1** depicts the evolution of CMV infection in the normal host and the impact of transplantation.

RISK FACTORS FOR CYTOMEGALOVIRUS DISEASE

Risk for CMV disease is associated with past CMV infection, new CMV exposure, the degree of T-cell impairment, and the type of organ being transplanted (**Table 1**).

Cytomegalovirus Immunoglobulin G Donor/Recipient Status

About 20% to 30% of adult transplant recipients are CMV IgG negative and are at greatest risk for primary infection. The donor organ is the most common source for primary infection, but it can also occur through blood products and community exposures (eg, healthy children with salivary shedding). CMV IgG results can be falsely positive or negative. Direct testing for CMV-specific cell-mediated immunity (CMI) is more sensitive and more specific than antibody testing at identifying those with latent infection but is not practical in the transplant donation process and is not currently recommended as a screening tool for recipients.[10] False-positive CMV IgG is most often due to passive antibodies via blood products, usually intravenous immunoglobulin (IVIG). False-negative CMV IgG testing can occur rarely from waning antibody over time or from insensitive testing methods.[10]

Type and Degree of Immunosuppression

T-cell depleting agents are highly associated with CMV disease. High doses of steroids and higher levels of calcineurin inhibitors, mycophenolic acid, and azathioprine are also associated with CMV disease. CMV uses mammalian target of rapamycin (mTOR) pathways for viral replication, and the use of mTOR inhibitors have been associated with a lower risk for CMV infection and CMV syndrome (but not consistently

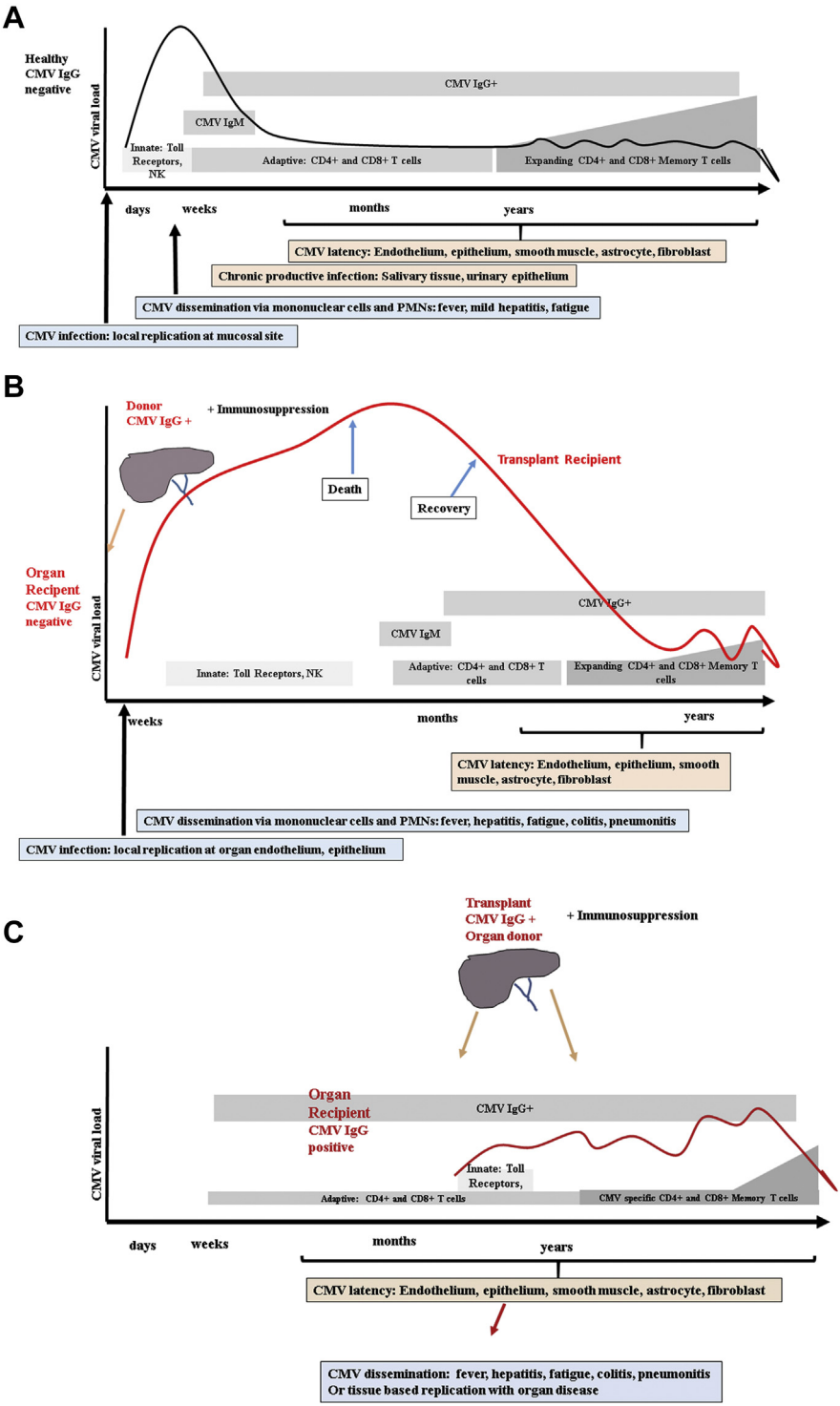

Fig. 1. (*A*) Immune response from CMV infection to latency in the healthy host. (*B*) Immunologic effects of typical immunosuppressive drugs and CMV infection after SOT in CMV D+/R− and (*C*) CMV D+/R+.

Table 1
Risk factors for cytomegalovirus disease

	High Risk	Intermediate Risk	Lower Risk	Comments
CMV serostatus	CMV IgG D+/R−	CMV IgG D+/R+, CMV IgG D−/R+	CMV IgG D−/R−	Falsely positive (blood products, IVIG) Falsely negative (loss of antibody, CVID) Equivocal results in donor: interpret as positive Equivocal results in recipient: interpret as negative Not all serologic testing products equivalent
Immunosuppression	Antilymphocyte antibodies (thymoglobulin, alemtuzumab, OKT3)	MMF, azathioprine, tacrolimus, cyclosporine, high-dose steroids	Maintenance steroids mTOR inhibitors	Increased risk for all agents, with higher doses
Organ transplanted	Lung Pancreas Intestine	Heart composite tissue	Liver Kidney	Burden of latently infected cells Higher levels of immunosuppression
CMV-specific cell-mediated immunity	Low	Intermediate	High	Data limited May be useful at guiding prophylaxis and preemptive prevention strategies

Abbreviations: CVID, common variable immunodeficiency; IVIG, intravenous immune globulin; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; OKT3, anti-CD3 antibody.

CMV disease).[11,12] Guidelines weakly recommend transition to mTOR inhibitors in patients with challenging CMV infection.[13]

Organ Transplanted

Lung, pancreas, and intestinal transplant recipients seem to be at greater risk for CMV disease than other organs. This circumstance may be, in part, due to the use of more aggressive immunosuppression for these transplants. CMV pneumonitis is particularly prevalent in the lung allograft and enteritis is particularly problematic in intestinal transplantation, suggesting a rich source of latent virus at risk for active infection[14–16]; the data are supported by murine models of CMV latency.[17]

CLINICAL MANIFESTATIONS

In the absence of prevention, CMV infection and disease typically occur in the first 3 months after transplantation, the peak period of immunosuppression.[3,18] CMV infection represents the period of CMV viral replication before the onset of significant symptoms (**Fig. 2**). CMV disease includes both CMV syndrome and tissue invasive disease. CMV syndrome is characterized by fever, malaise, leukopenia, and/or thrombocytopenia and is the most common presentation of symptomatic CMV infection.

Tissue-invasive CMV disease has a predilection for the allograft itself, a possible consequence of D+ allografts or disordered immune response within the allograft. Disease also occurs as colitis or enteritis, pneumonitis, hepatitis, and less commonly nephritis, myocarditis, pancreatitis, retinitis, meningoencephalitis, or polyneuritis. Because of the low incidence of retinitis, it not recommended to pursue retinal examination in the absence of visual symptoms.

CMV disease has been associated with a variety of secondary outcomes, including bacterial and fungal infections and posttransplant lymphoproliferative disorder.[19,20] An association with manifestations of chronic allograft rejection, including bronchiolitis

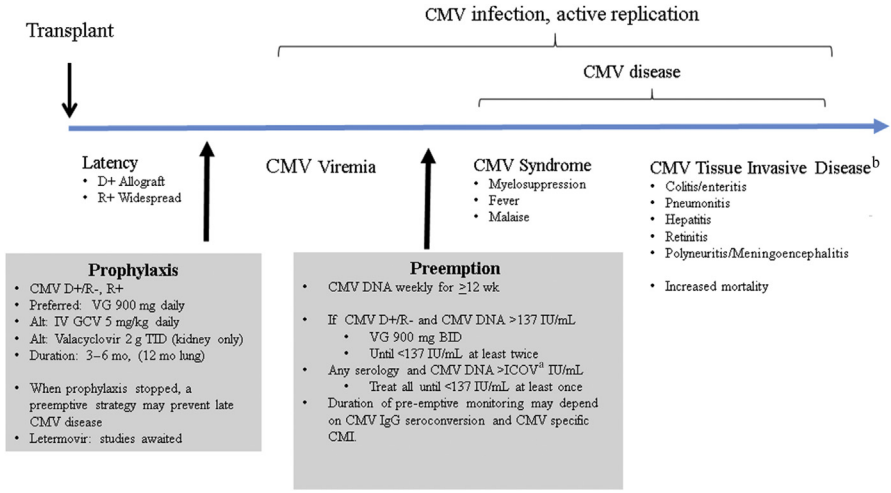

Fig. 2. The typical trajectory of CMV replication to tissue invasive disease in the organ transplant recipient. Insets depict the CMV prevention strategies available. Alt, alternative; GCV ganciclovir; ICOV, internal cutoff value; IV, intravenous; VG valganciclovir. [a] ICOV for initiating treatment decided at transplant program or center. [b] CMV tissue invasive disease can occur without CMV viremia. (*Courtesy of* Dr .Eric Cober.)

obliterans syndrome, chronic allograft vasculopathy, and vanishing bile duct syndrome, has also been made; but data are not consistent.[18,21,22] Most importantly, CMV infection has been associated with graft loss and increased mortality.[3,22,23]

DIAGNOSTICS

CMV infection is detected in blood by antigen detection with pp65 or with quantitative CMV DNA detection by polymerase chain reaction (PCR). Given the logistical limitations to performing antigen testing, most centers are now using CMV DNA detection by PCR. There are several commercial assays for CMV DNA detection, and many laboratories have developed their own home brew assays. Development of the World Health Organization's first CMV international standard based on international units, available since October 2010, allows laboratories to standardize results for comparison with those obtained at other laboratories using the same standard.[24] Not all laboratories use the standard (reported as international units per milliliter).

CMV syndrome is diagnosed by detecting CMV infection and having compatible clinical findings of malaise, and/or fever, leukopenia, and/or thrombocytopenia. CMV antibodies (IgG and IgM) are not typically used to diagnose acute infection in organ transplantation.

A definitive diagnosis of tissue-invasive CMV disease is made with histopathologic evidence of CMV (inclusion bodies or viral antigens by immunohistochemistry) with or without virus culture of the tissue. Diagnosis of tissue-invasive disease can be made presumptively in the setting of CMV viremia and compatible signs, symptoms (diarrhea, hepatitis, and so forth), and laboratory findings. If not appropriately responsive to antiviral therapy, a tissue diagnosis should be sought. Tissue-invasive disease can occur in the absence of CMV viremia, particularly in patients who are recipient CMV IgG positive (CMV R+), and requires tissue biopsy to diagnose.

PREVENTION

Preventive strategies are intended to avoid CMV disease as well as improve longer-term outcomes. **Fig. 2** highlights the different strategies used for CMV prevention.[25] Both strategies have greatly reduced the incidence of early CMV disease.[19] Many programs use a combined strategy for at-risk patients of prophylaxis followed by preemptive monitoring. An ongoing randomized, prospective, multicenter trial comparing prophylaxis with preemptive management in donor CMV IgG positive (CMV D+)/R− liver transplant recipients may help to answer many outlying questions (https://clinicaltrials.gov/ct2/show/study/NCT01552369?cond=CMV+liver+transplant+AND+%22Cytomegalovirus+Infections%22&rank=2). The ideal combination of these strategies has not been established.

Prophylaxis entails giving antivirals (intravenous ganciclovir, oral valganciclovir or, in select kidney transplant recipients, high dose valacyclovir) during the peak period of immunosuppression. Data support at least 3 months of prophylaxis for most organs.[26] Longer courses (6 months) have been shown to be more effective at preventing CMV, particularly in high-risk (CMV IgG D+/R−) recipients.[20] Prophylaxis with 12 months compared with 3 months in lung transplant recipients seems to be even more effective in these patients.[27,28] Prophylaxis is also associated with reduced incidence of opportunistic infections, graft loss, and mortality.[20,27] Consensus guidelines recommended prophylaxis for most at-risk recipients for most organs.[14,23] There are particular concerns for valganciclovir prophylaxis in liver transplant recipients due to data that indicate inferior efficacy to oral ganciclovir.[29]

Longer courses of prophylaxis may be attractive, but there are costs to the strategy. One concern is that prophylaxis delays effective immunologic control. Late CMV infection (beyond 6 months) has emerged as a significant cause of morbidity and mortality in transplantation.[30] Other concerns include myelosuppression, antiviral resistance, and the high cost of antivirals. It is acknowledged that in studies supporting the benefits of prophylaxis, many randomized effectively, the comparator group is not a concurrent preemptive monitoring group.

Preemptive monitoring entails testing blood routinely for early CMV replication and treating the infection before it progresses to symptomatic disease. There is no established threshold of CMV DNA viral load at which one should treat with antiviral agents and no established lower threshold at which one should stop this treatment. Each center is currently responsible for establishing its own practice. However, lower thresholds for initiating and stopping treatment would be appropriate for those at greatest risk for progression to CMV disease (CMV D+/R− with recent exposure to lymphocyte depleting antibody). Those with CMV R+ and no lymphocyte depletion may warrant higher thresholds. Antiviral therapy is continued until the viral load reaches the lower limit threshold measured once or twice separated by a week. Preemptive prevention of CMV disease requires the resources for obtaining and responding to laboratory results in a rapid fashion. It also requires that patients be adherent to laboratory testing and available to start treatment. Preemptive monitoring has been evaluated by multiple studies and in retrospective meta-analyses and has been shown to reduce the risk for CMV disease but does not seem to have the same beneficial effects on allograft outcomes and patient mortality as universal prophylaxis.[31]

TREATMENT

Treatment of CMV early after transplant is challenging. Assessing the immunosuppression strategy for each patient is important to predicting the duration and intensity of T-cell impairment. It is unlikely that adaptive immunity will occur in the setting of recent lymphocyte-depleting agents. Consideration can sometimes be given to reducing tacrolimus trough concentration, reducing or stopping mycophenolate mofetil, and lowering prednisone dosing when appropriate. Changes, when done, to immunosuppressive medications should be made *only* by the transplant team to avoid rejection, as therapy for rejection will invariably make CMV management even more challenging while having deleterious effects on graft function.

Ganciclovir, valganciclovir, foscarnet, and cidofovir target viral replication at the step of DNA polymerization. The drug letermovir is the first drug approved for CMV that acts at the level of viral packaging. Dosing and indications for the available antivirals are listed in **Table 2**. Treatment is generally recommended for at least 2 weeks for tissue-invasive disease and until CMV DNA is less than the lowest limit of detection on 2 separate measurements separated by at least 1 week. Continuing a maintenance (or secondary prophylaxis) dose for weeks to a few months (until adaptive immune response improves) may be warranted depending on the risk for recurrent infection (CMV D+/R−, recent lymphocyte-depleting agent).

Ganciclovir and valganciclovir are the recommended first-line antivirals for CMV infection and disease. Valganciclovir is converted to ganciclovir by hydrolysis before reaching the systemic circulation and can provide drug exposure similar to that of intravenous ganciclovir. Although Asberg and colleagues demonstrated noninferior treatment outcomes with valganciclovir compared with intravenous ganciclovir, their study comprised mostly kidney transplant recipients with non–life-threatening CMV disease.[32] Thus, when drug absorption is uncertain or disease severity warrants,

Table 2
Antivirals available for treatment of cytomegalovirus infection or disease

	Indication	Dosage	Side Effects	Comments
Valganciclovir Oral High dose	CMV infection • CMV DNA <1 × 10^5 IU/mL[a] CMV disease GCV resistance (<5× GCV EC50)	900 mg twice daily 1350–1800 mg twice daily	Leukopenia Anemia Thrombocytopenia	Dose adjust for renal impairment Consider adequacy of GI absorption Oral option after initial therapy with IV ganciclovir
Ganciclovir Intravenous High dose	CMV infection • CMV DNA >l × l0^5 IU/mL[a] CMV disease requiring hospital admit[a] GCV resistance (<5 × GCV EC50)	5 mg/kg every 12 h 7.5–10.0 mg/kg every 12 h	Leukopenia Anemia Thrombocytopenia	Dose adjust for renal impairment Can change to oral valganciclovir to complete course
Foscarnet Intravenous	CMV infection or disease with GCV resistance (≥5× GCV EC50)	90 mg/kg every 12 h	Nephrotoxicity Electrolyte wasting Cytopenias	Dose adjust for renal impairment Hospital admission usually required for hydration, initial monitoring of renal function, K, Mg, Ca, P
Cidofovir Intravenous	CMV infection or disease refractory and resistant to GCV and FOS	5 mg/kg weekly ×2 then every 2 wk	Highly nephrotoxic	Alternative lower doses used
Letermovir Oral Intravenous	Primary CMV infection? Secondary CMV infection? CMV disease? CMV with GCV and/or FOS resistance	480 mg daily (240 mg daily with CSA)	Peripheral edema Headache Nausea Diarrhea	CYP3A4 inhibitor Increases concentration of CSA Increased concentration by CSA May increase concentration of tacrolimus Not active against HSV or VZV

Abbreviations: Ca, calcium; CSA, cyclosporine; EC50, 50% effective concentration; FOS, foscarnet; GCV, ganciclovir; GI, gastrointestinal; HSV, herpes simplex virus; IV, intravenous; K, potassium; Mg, magnesium; P, phosphorus; VZV, varicella zoster virus.

[a] Valganciclovir may suffice for less severe infection, clinically assessed, but with stronger consideration only when CMV DNA <1 × 10^5 IU/mL. Otherwise intravenous ganciclovir may be more reliable. There is no established cutoff.

intravenous ganciclovir is recommended.[33] Dose reductions are recommended for reduced creatinine clearance. Because of fluctuations in creatinine concentrations with acute illness and volume depletion, it may be preferred to err on the higher side of dosing early when disease severity warrants rather than trying to catch up, because late eradication of CMV DNA is associated with antiviral resistance.[34] Judicious use of granulocyte colony-stimulating factor may be required to allow for fully effective therapy.[22]

Foscarnet is the second-line agent for CMV disease or infection that is refractory or resistant to ganciclovir therapy.[35] It is active against ganciclovir-resistant strains harboring only UL97 mutations. Foscarnet generally requires hospital admission to initiate intravenous therapy (with insertion of a central venous catheter) for adequate hydration and initial monitoring of creatinine and electrolytes. Most patients will require planned oral electrolyte repletion before discharge on intravenous foscarnet.

Cidofovir is an intravenous antiviral agent with activity against CMV, other herpes viruses, adenovirus, and polyoma viruses. Its use is limited by frequent and possibly severe nephrotoxicity particularly in the setting of calcineurin inhibitor therapy. There is also the potential for cross-resistance to ganciclovir with certain UL54/pol gene mutations, so it may not be an option for some patients failing ganciclovir. Cidofovir has been used successfully in SOT recipients with refractory CMV disease, with high rates of renal injury or failure.[36,37]

Letermovir blocks the terminase complex of CMV, preventing cleavage and packaging of viral DNA.[38] It has high potency and is active against strains resistant to ganciclovir, cidofovir, and foscarnet. It has no activity against herpes simplex virus or varicella zoster virus and, thus, may require coadministration with an acyclovir derivative.[39] In clinical trials, the safety profile of letermovir is excellent with no myelosuppression or nephrotoxicity.[40,41] It was FDA approved in November 2017 for CMV prophylaxis in stem cell transplant recipients.[42] It is unclear how it will be used in the SOT setting; but given its favorable safety profile, it has the potential to significantly change CMV management strategies. In a phase 2b clinical trial of preemptive management of CMV infection in 27 kidney or kidney pancreas transplant recipients in Germany, letermovir demonstrated similar outcomes to valganciclovir.[43] It has been used successfully under compassionate provision for a lung transplant recipient with drug-resistant CMV refractory to other available antivirals.[44] Because of metabolism by CYP3A4, dose adjustments are required in the setting of calcineurin inhibitors.[45] For both treatment and prevention, it was observed that, although effective, the rate of viral load decline was slower than expected for letermovir possibly reflecting its mechanism of action and should be considered with future use.

Use of CMV hyperimmune globulin and IVIG preparations as part of CMV prophylaxis and therapy remain controversial and only weakly recommended in clinical guidelines.[14,22,46] Nevertheless, it remains widely used for prophylaxis in intestinal transplantation and for salvage therapy for CMV-refractory disease.[16,37] Data remain inconclusive for its clinical benefits in the era of more potent direct antiviral agents. Randomized data from the 1990s provide evidence for its role in prophylaxis for D+/R− cardiac transplant recipients.[46,47] Data for its purported benefit in the setting of severe CMV pneumonitis have not consistently been demonstrated.[48,49] Secondary hypogammaglobulinemia in the posttransplant setting has been associated with CMV disease, but it is unclear that this is a direct effect of low antibody and not a downstream effect of cell-mediated immune impairment.[50]

Leflunomide is a disease-modifying drug used to treat rheumatoid arthritis that has coincident anti-CMV activity. Cases and case series have been reported, and it may improve CMV disease in the setting of resistance to standard antivirals; but outcomes

are varied, and it has not been formally studied.[51–53] It takes several weeks to achieve the target blood level, has a very long half-life, and has the potential for hepatotoxicity and irreversible peripheral neuropathy, particularly at the higher doses used to treat CMV and is not recommended unless other more proven therapies are not available.[13,22]

The last option for managing severe CMV disease, open only to intestinal and kidney transplant recipients, is stopping immunosuppression completely and allowing for allograft failure, often with allograft removal.

The investigational drugs brincidofovir, an oral lipid conjugate of cidofovir, and maribavir, an oral benzimidazole L-riboside that inhibits the UL97 viral protein kinase of CMV, hold some promise as alternative agents of CMV prophylaxis and treatment of refractory/resistant CMV. Neither is currently approved for use in the United States.

One published case[53] reported efficacy of the antimalarial drug artesunate in treating ganciclovir- and foscarnet-resistant CMV, but a subsequent case report[54] did not corroborate this experience.

CYTOMEGALOVIRUS-SPECIFIC CELL-MEDIATED IMMUNITY

The CMV-specific immunity may be the most direct measure of CMV infection risk and may help stratify the risk for CMV recurrence after therapy and in prophylaxis and preemptive strategies. There are now several assays to measure CMV-specific CMI, some of which are commercially available. These assays measure gamma-interferon or other cytokine markers in response to CMV-specific peptides.[23,55] A recent study demonstrated the feasibility of using CMV-specific CMI (QuantiFERON-CMV, Qiagen, Hilden, Germany) to guide the use of antiviral secondary prophylaxis in 27 SOT recipients completing treatment of CMV viremia and disease.[56] Those with evidence of CMV CMI at the end of treatment had antivirals successfully stopped without significant viremia on follow-up. Additional validated studies to determine the optimal use of these assays is required but will, it is hoped, help limit prophylaxis and CMV DNA monitoring only to those who benefit the most.

There is no way to restore CMV-specific immunity other than delicate reduction of immunosuppression as able. Adoptive immunotherapy (stimulating donor T lymphocytes in vitro with CMV peptides and infusing into patients) has been used successfully in hematopoietic stem cell transplantation recipients but is not available for widespread use and has not been performed in SOT recipients.[57]

ANTIVIRAL RESISTANCE

Resistance mutations in CMV UL97 protein kinase and UL54 DNA polymerase genes confer varied degrees of resistance to ganciclovir, foscarnet, and cidofovir. **Table 3** highlights the common mutations associated with antiviral resistance. Genotypic testing is currently the method of choice for determining antiviral resistance. Phenotypic resistance testing has been available but can take weeks to result and may be affected by fitness characteristics of drug-resistant viral strains.[58]

CMV resistance should be suspected when CMV viremia or disease persist or worsen despite appropriate therapeutic doses of ganciclovir or valganciclovir for greater than 2 weeks. One should expect at least a 0.5 to 1.0 log reduction from baseline of CMV DNA viral load in 2 weeks. However, of those with suspected drug resistance, only one-quarter have genotypic resistance.[59] Therefore, concern should prompt an evaluation of drug dosing in the context of renal function and drug absorption. Oral valganciclovir can be changed to intravenous ganciclovir, and higher dosing could be considered (up to 10 mg/kg every 12 hours) or combining ganciclovir and

Table 3
Cytomegalovirus resistance mutations

	Ganciclovir High-Level Resistance >5× EC50	Ganciclovir Low-Level Resistance <5× EC50	Foscarnet	Cidofovir	Letermovir[a]
UL97 Frequent	M460VI H520Q A594V L595S C603W	C592G	—	—	—
UL97 Infrequent	M460T A594G 595del L595FW E596Y K599T Del601–3 C603R C607Y	L405P V466G A594ET E596G L600del C603S C607F I610T A613V	—	—	—

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Table 3
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	Ganciclovir High-Level Resistance >5× EC50	Ganciclovir Low-Level Resistance <5× EC50			Foscarnet		Cidofovir		Letermovir[a]
UL54	V526L	D301N N408DKS N410K F412CV D413EAN L501I T503I A505V K513ENR L516R I521T P522AS	C524delV526L C539G D542E L545S Q578L D588N I726TV E756K L773V L776M V781I	V787L L802M A809V V812L T813S T821I A834P G841AS L957F Del981–2 L987G	N495K V526L Q578L D588EN T700A V715 AM E756DKQ L773V L776M V781I	V787L L802M A809V V812L T813S T821I A834P T838A G841AS Del981–2	D301N N408DKS N410K F412CV D413EAN L501I T503I A505V K513ENR L516R I521T P522AS C524del	V526L C539G D542E L545S I726TV L773V K805Q V812L T813S A834P G841A Del981–2 L987G	—
UL56	—	—			—		—		Codons 231–369 V236M E237D C325F/R

Abbreviation: EC50, 50% effective concentration.
[a] More data required to identify clinically significant resistance mutations.
Data from Refs.[63–66]

foscarnet while awaiting genotypic drug resistance testing.[60,61] Persisting CMV infection should also prompt a review of immunosuppressive therapy with reductions as able. Consideration to switching to an mTOR inhibitor-based regimen can be given.[13]

Risk factors for CMV drug resistance include D+/R− serostatus, high peak viral load (>10^5 IU/mL), increased duration of antiviral exposure (including >6 months CMV prophylaxis), and suboptimal antiviral drug concentrations. Lung, intestinal, and kidney/pancreas transplant recipients seem to be at higher risk for antiviral drug resistance.[15,62] Most patients with ganciclovir resistance have mutations in UL97 that confer high- or low-grade resistance. Mutations in the UL54 polymerase gene can increase the degree of ganciclovir resistance and confer coincident cidofovir or foscarnet resistance, even without prior exposure to cidofovir or foscarnet.

Treatment of low-level ganciclovir-resistant virus (<5-fold increase in 50% effective concentration [EC50]) includes increasing the dose of ganciclovir to 7.5 to 10.0 mg/kg every 12 hours or combined ganciclovir/foscarnet.[60,61] Treatment of high-level ganciclovir-resistant virus (>5-fold increase in EC50) includes foscarnet or cidofovir, assuming no cross-resistance. There have traditionally been no available drugs for multidrug-resistant CMV infection, but letermovir may successfully change that.

SUMMARY

Prevention and management of CMV infection and disease has been a major advance in SOT. Given the goals of immunosuppressive therapies, it is unlikely that organ transplantation will soon be free of CMV disease risk. Optimizing prevention and treatment strategies remains the responsibility of each transplant center. Newer monitoring assays and available antivirals may help reduce the toxicities of existing therapies and create more opportunities for patients to adapt to lifelong CMV latency.

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