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REVIEW

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Cytomegalovirus antiviral stewardship in the COVID-19 Era: Increasing complexity of prophylaxis and treatment and potential mitigation strategies

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Abstract

Cytomegalovirus (CMV) infection is one of the most common and significant complications after solid organ transplant (SOT). Severe acute respiratory coronavirus 2 (SARS-CoV-2), which causes the novel betacoronavirus 2019 disease (COVID-19), has become the first global pandemic in 100 years. The world's attention has turned to address this unanticipated development; however, the viral infection that has long plagued outcomes after solid organ transplantation still requires vigilance. With physical distancing as the key intervention to reduce the healthcare burden, and the unease related to healthcare contact within the transplant population given the associated morbidity and mortality of COVID-19 in transplant recipients, providers have struggled to evaluate and streamline essential in-person healthcare contact, including laboratory visits. Owing to this, the COVID-19 pandemic has placed a significant strain on the delivery of CMV prophylaxis and treatment after solid organ transplantation. In this piece, we will describe issues our CMV antiviral stewardship service has encountered in the care of the transplant recipient with CMV during the this unprecedented time and share our expert opinion to approaches to providing optimal, evidenced based care during a pandemic associated with a seemingly unrelated viral infection.

KEYWORDS

infection and infectious agents, quality of care/care delivery, viral, viral: cytomegalovirus

1 | INTRODUCTION

Cytomegalovirus (CMV), or human herpesvirus 5 (HHV5), is a ubiquitous herpesvirus present in 40% to >70% of the general population. After primary exposure, the virus enters lifelong latency via immunoevasion, with a predilection to myeloid cells.[1] In the setting of immunosuppression, viral reactivation and disease can occur. CMV is one of the most common infections in transplant recipients and is an independent risk factor for graft loss and mortality.[2] Reactivation of latent infection occurs in >50% of seropositive recipients.[3] Pathogenesis relies on dysfunctional T cells which then results in uncontrolled CMV replication.[4] Without prophylaxis, onset is typically early after transplantation, ranging from the first 1-4 months to the highest risk in the first 5-13 weeks.[5] Given the association of CMV with graft loss and mortality, prophylaxis is recommended, and aggressive treatment is required in the setting of disease.[6] Both treatment and prophylaxis require close clinical monitoring to evaluate response and drug toxicity. Given this, there has been a recent

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push for the development and implementation of CMV stewardship initiatives, as a component of antimicrobial stewardship in the immunocompromised host, to optimize the management of prevention and treatment of CMV in SOT recipients.[7]

Severe acute respiratory coronavirus 2 (SARS-CoV-2), which causes the novel betacoronavirus 2019 disease (COVID-19), was first reported in Wuhan, China in December 2019. It is the third coronavirus identified in the last 18 years that is traced back to zoonotic origins along with SARS (2002 and 2003) and Middle East respiratory syndrome (MERS; 2012 to present).[8] Although SARS and MERS remained geographically contained, COVID-19 has become a global pandemic. This is attributed to the high infectivity of SARS-CoV-2, with an estimated R0 of 5.7, paired with lack of previous exposure in humans.[9] Disease manifestations can vary significantly, ranging from an asymptomatic carrier state to death.[10] Preliminary studies suggest patients with functional immunosuppression, including the elderly and those with preexisting respiratory or cardiac conditions to be at high risk for infection and negative outcomes.[11] Patients with a history of solid organ transplant population also appear to be at risk. Recent data have demonstrated increased hospitalization rates, ICU admission, and up to 25% mortality attributable to COVID-19 in this population.[12,13]

Given the virulence, lack of proven effective treatment or prophylaxis of COVID-19, and until recently, lack of vaccine, the main infectious containment measure to date has been government mandated physical distancing measures.[14–19] These have been pursued in attempts to reduce the rate of transmission and thereby reduce hospital volumes to avoid overwhelming the healthcare system. Reduced transmission rates would be expected to improve access to personal protective equipment and avoid rationing of COVID-specific therapies, such as ventilator support, to improve outcomes and reduce the overall risk to healthcare staff.[15] In response, healthcare institutions have canceled non-emergent, elective procedures to limit face-to-face contact with patients and focus hospital resources on patients with COVID-19.[20,21] Notably, extensive closures across the United States have led to significant strain in the economy, resulting in layoffs and mandatory furloughs in the public and private sector, including healthcare employees.[22]

The world's attention has turned to address the global COVID-19 pandemic; however, the viral infection that has long plagued outcomes after solid organ transplantation still requires vigilance. With physical distancing as the key intervention to reduce the healthcare burden, and the unease related to healthcare contact within the transplant population given the associated morbidity and mortality of COVID-19 in transplant recipients, providers have struggled to evaluate and streamline essential in-person healthcare contact, including laboratory visits. Owing to this, the COVID-19 pandemic has placed a significant strain on specialty practice including CMV prophylaxis and treatment after solid organ transplantation.[23] Although limited case reports exist in the literature describing the co-occurrence of CMV and COVID-19, there is currently no guidance on how to manage CMV in the COVID-era. In this piece, we will describe issues our CMV antiviral stewardship service has encountered in the care transplant recipients with CMV during the this unprecedented time and share our expert opinion to approaches to providing optimal, evidenced based care during a pandemic associated with a seemingly unrelated viral infection (Table 1).

TABLE 1 COVID-19 associated obstacles and mitigation strategies

Phase of care	Obstacle	Possible solution
Prophylaxis	Drug accessibility 1. Access	• PEM conversion • Screen for appropriateness of alternative agents
	2. Cost	• Manufacturer patient assistance program • Screen for appropriateness of alternative agents • PEM conversion
	Leukopenia	• CMV CMI testing to determine ongoing need for PPX • WBC > 2: monitor with at least Q2 week labs a. Screen for risk factors for leukopenia progression • WBC < 2: evaluate immunologic risk a. Adjust IS (MPA reduction, increase prednisone in tandem) b. Consider GCSF • WBC persistently < 2 a. PEM conversion b. LTV with Q2 week lab monitoring (if insurance approves)
	Laboratory delays in PEM	• CMV CMI testing to determine ongoing need for PPX • WBC > 2: Resume VGC universal PPX • WBC < 2: LTV with Q2 week lab monitoring (if insurance approves)
Treatment	Hospital admission 1. Avoidance	• Aggressive upfront IS adjustment (CNI trough goals) • Screen for clinical risk factors for progression with early aggressive treatment • Potential OPAT IV GCV
	2. Reduce LOS	• High dose GCV protocols • Use of adjuvant agents • Potential OPAT IV GCV

2 | COVID-19 AND CMV PROPHYLAXIS

2.1 | Universal prophylaxis

Universal prophylaxis refers to the administration of antiviral medication to all recipients, or a "at-risk' subset, starting in the immediate

post-transplant period.[24] For CMV prevention, the duration of universal prophylaxis depends upon the CMV serostatus of the donor (D) and the recipient (R) at the time of transplantation. Prophylaxis varies between 3 and 6 months based on the risk associated with the induction agent and other factors.[6] Valganciclovir (VGC) is the gold standard in transplant recipients at high-risk for the development of CMV post-transplant (D+/R-) and is recommended for moderate-risk recipients (R+), particularly in the setting in lymphocyte depleting induction.[6] Although some transplant centers temporarily suspended the use of lymphocyte depletion in the COVID-19 era because of concerns surrounding perioperative infection, many centers continue to use these agents. Universal prophylaxis with VGC is very effective, with breakthrough rates reported at <5%.[25] However, obstacles to the use of the prophylactic modality have arisen in the setting of the coronavirus pandemic.

2.1.1 | Drug accessibility

Universal prophylaxis is dependent on the patient's ability to obtain and consistently take preventative medication. VGC is currently available from several manufacturers, making it less vulnerable to disruptions in the supply chain. However, given the global extent of the COVID-19 pandemic, particularly in China and India, there has been concern for medication shortages as the US primarily relies on overseas manufacturing of pharmaceutical ingredients.[26,27] The pharmaceutical supply chain is made up of numerous independent steps leading to end products that are used by consumers. Any disruption of the process can have a detrimental effect on drug availability. To combat this, the US Center for Drug Evaluation and Research (CDER) has instituted several measures including regulatory flexibility for imports and monitoring of the drug supply chain and working with industry to prevent and alleviate shortages. However, the etiology of supply chain disruption is not always clear, so the full extent of the COVID-19 pandemic on distribution of medicines within the US continues to remain uncertain.

Government-issued orders to shelter in place and limit work to essential businesses because of the COVID pandemic threaten both drug availability and accessibility. Medication transport has experienced longer transit times as companies work to meet demands while functioning with fewer employees, either owing to sickness or state mandates. Additionally, the order has resulted in many pharmacies closing to walk-in customers to prevent risk to employees, leading to increased demand for home-delivery, and mail-order services.[28] Paired with increased mail volume because of stay-at-home orders, this has led to significant delivery-related delays.[29] Concern for drug availability because of hoarding or stockpiling of medications by patients, in light of CDC endorsed recommendations to maintain an adequate supply, has also been raised.[30] Finally, affordability of medications threatens universal prophylaxis as business closures lead to rising unemployment rates. Given the high cost of VGC, transplant recipients who already struggle to afford high-cost copays may find themselves unable to obtain their medications. In this instance, these patients may qualify for access to medication through the Genentech Access to Care Foundation (https://www.genentech-access.com/hcp.html). If they do not qualify, they may require transition to an alternative approach.

2.1.2 | Monitoring and toxicity

Ensuring appropriate dosing of VGC to avoid toxicity from overdosing, treatment failure, or antiviral drug resistance is a critical goal of CMV stewardship initiatives.[7] Evaluation of relatively frequent laboratory data, including renal function and hematologic labs, is needed to achieve this goal. Leukopenia has always been a major issue with the use of ganciclovir derivatives. The pandemic has simply magnified these issues with the risk of associated laboratory and hospital exposures amplified dramatically and in difficult to characterize ways. In the current setting of the COVID pandemic, avoidance of leukopenia is paramount as limited data suggest leukopenia is a risk factor for adverse COVID-19 disease outcomes.[31]

In the setting of persistent leukopenia, immunosuppressive (IS) modification may be necessary, focusing on the reduction of antimetabolites such as azathioprine and mycophenolic acid derivatives (MPA), given their myelosuppressive potential.[32] The addition of prednisone to dual therapy regimens consisting of MPA and CNI, as are commonly found in steroid avoidance protocols,[33] can allow temporary dose reduction or discontinuation of MPA and recovery of leukocytes. If leukopenia persists, administration of granulocyte-colony-stimulating factor (GCSF) may be warranted. Immunologic risk assessment of the recipient is necessary when modifying IS regimens. Additionally, concerns have been raised regarding the immunostimulatory effects of GCSF. However, these are mostly theoretical in nature and literature exists demonstrating the value of GCSF in this role.[34]

If none of the above measures are successful at improving leukopenia, transition from universal prophylaxis to preemptive monitoring may be necessary. However, this approach is not spared from COVID-19-related issues, and there is no literature to guide prophylaxis conversion in the setting of leukopenia.

2.2 | Preemptive monitoring

The preemptive monitoring approach (PEM) is a form of targeted prophylaxis utilizing surveillance via molecular diagnostic testing (CMV PCR) to provide antiviral therapy to transplant recipients with asymptomatic viral replication above a predefined threshold. De novo PEM after transplant is considered non-inferior to universal prophylaxis with VGC in kidney and liver transplant recipients when adherence to the weekly monitoring frequency is upheld, and this approach is endorsed by consensus guidelines.[6,35] Studies have shown less frequent monitoring frequencies result in viral replication and symptomatic CMV disease.[36] This is particularly important in high-risk serostatus (D+/R-), given rapid viral replication rates in

this population.[37,38] Indeed, it is suggested a 24-hour turn-around is required to ensure equivalent efficacy.[35] Although PEM avoids toxicity associated with VGC, it is a labor intense strategy requiring close monitoring by the CMV stewardship team to detect low-level replication before it progresses to symptomatic disease.

Given the rapid progression of COVID-19 and the need to control disease transmission, we are facing a challenging clinical care situation in the provision of PEM. CDC recommendations and state mandated physical distancing, as well as the pressures placed on procurement of molecular diagnostics for SARS-CoV2 testing, have become significant obstacles in obtaining weekly labs and timely CMV PCR results in the COVID-19 era.

2.2.1 | Laboratory challenges

Given the urgency for characterization of disease epidemiology and infection control, there is a demand for laboratories to expanded capacity of COVID-19 molecular diagnostic testing. Two of the largest commercial laboratories, LabCorp and Quest Diagnostics, which also process other molecular diagnostic tests including CMV PCR, have taken on this task.[39] However, because of the demand for COVID-19 testing, these laboratories have been significantly burdened, which has resulted in delays.[40] These delays are not limited to SARS-CoV-2-related results. In our institution's experience, CMV PCRs from COVID-19 testing centers have been delayed by up to 2 weeks as compared to their test information which notes availability of results in 1-2 days.[41] Additionally, concern among the transplant population regarding risk of nosocomial spread, although largely unfounded,[42] has resulted in reduced laboratory compliance in attempts to "medically distance," further aggravating this issue.[43] This is clearly at odds with consensus recommendations regarding time to result, and functionally undermines the efficacy of PEM as a prophylaxis modality.

2.3 | Alternative prophylaxis modalities

To avoid the leukopenia associated with the use of GCV derivatives, alternative antiviral agents have been studied in this role. These agents are also less expensive than VGC and could mitigate issues with drug availability and PEM. Unfortunately, most have been found to be inferior to VGC, particularly in the high-risk population. Valacyclovir was found to be efficacious for the prevention of CMV in renal transplant recipients.[44] However, high dosing is required, which increases risk of neurotoxicity and theoretically puts SOT recipients at risk for acyclovir-associated crystal nephropathy. Additionally, follow-up studies suggest a higher risk of biopsy-proven rejection in recipients receiving this agent as compared to VGC.[44,45] High dose acyclovir studied specifically in the moderate-risk population (R+) was found to have a significant rate of viral breakthrough and subsequent negative effects on graft survival.[46]

Studies have investigated prophylaxis regimens utilizing reduced doses of VGC, commonly referred to as "mini-dose" VGC. In a systematic review and meta-analysis of low-dose (450 mg) and standard dose (900 mg) VGC for CMV prophylaxis in renal transplant recipients, the incidence of CMV (95% CI, 0.352-0.967; $P = .036$) and leukopenia (95% CI, 0.264-0.523; $P = .001$) decreased in the low-dose group, suggesting this as a safe and effective practice.[47] Therefore, a possible approach to mitigation of both associated leukopenia and potential supply chain issues could include VGC dose reduction. However, studies did not include a significant number of high-risk CMV (D+/R-) patients or high-risk populations such as lung transplant recipients or those that were highly sensitized on aggressive immunosuppression. Therefore, low dose VGC strategies cannot be generalized to the highest risk populations.[48] In addition, literature exists linking underdosing of VGC to development of antiviral resistance, thereby cautioning against utilization of mini-dose VGC for CMV prophylaxis.[49,50]

Letermovir (LTV) is currently approved for CMV prophylaxis for HSCT patients and was found in phase III clinical trials to be both efficacious and safe, without associated myelotoxicity.[51] Literature exists demonstrating efficacy in the solid organ transplant population, and there is currently an ongoing clinical trial for CMV prevention in kidney transplant recipients.[52,53] However, a breakthrough rate approaching 30% was reported in the clinical trials.[51] Although there is no robust data available yet to support LTV prophylaxis in the SOT population and breakthrough rates are not insignificant, there is substantial literature describing the negative outcomes associated with CMV infection on both graft and patient survival and the importance of weekly CMV PCR monitoring to prevent CMV infection in the PEM population.[54]

Therefore, in the setting of reduced lab frequency, the potential benefit of LTV on suppression of CMV replication may outweigh any potential associated risks, particularly in the high-risk serostatus patient at risk of rapid viral replication and may be preferable to PEM without appropriate monitoring or resuming VGC in the setting of leukopenia. However, this has not been specifically studied. Additionally, ongoing surveillance of CMV PCRs, with at least every 2-week lab monitoring, in SOT recipients receiving LTV may be prudent given the breakthrough replication noted in the clinical trials.[51] If utilizing this approach, calcineurin inhibitor (CNI) dosing should be empirically adjusted because of a potential drug interaction with LTV which has been reported to increase CNI Cmax by 37%-70% and AUC by 70%-78%.[55] In our experience, a empiric dose reduction of at least 50% is prudent, particularly in the setting of reduced monitoring because of social distancing practices. Payor coverage in this setting is the major limitation on use of this agent.

2.3.1 | The role of CMV cell-mediated immunity testing

T cell-mediated responses are essential to immune control of CMV.[4] Interferon-gamma releasing assays (IGRAs) that measure patient-specific CMV cell-medicated immunity (CMV CMI) exist. These including enzyme-linked immunosorbent based (ELISA)

assays which measure CD8 T cell responses, enzyme-linked immunosorbent spot (ELI-Spot) assays which measure composite CD8 and CD4 T cell responses, and intracellular cytokine staining assays which use flow cytometry (ICS) to measure multiple cytokines and cell surface molecules in real time. Data exist supporting their predictive potential in the setting of CMV treatment and prophylaxis.[56–58] Utilization of these tests in the COVID-19 era could be crucial to avoiding the aforementioned issues related to prophylaxis. In transplant recipients considered low risk based on reconstituted cell mediated immunity, early discontinuation and avoidance of ongoing prophylaxis and monitoring may be possible.[59–61] However, the presence of clinical risk factors should also be factored into this decision as part of a multimodal assessment.[62] In our experience, laboratory test accessibility is a significant limitation to this approach.

3 | COVID-19 AND CMV TREATMENT

Currently, three drugs are approved by the United States Food and Drug Administration for the treatment of CMV disease: GCV derivatives (IV GCV and PO VGC), foscarnet (IV), and cidofovir (IV). When severe symptomatic disease resulting in questionable gastrointestinal absorption and/or high viral load/confirmed end organ disease is present, intravenous (IV) GCV is the drug of choice.[6,35] GCV IV typically requires hospital admission for initiation given community access issues. The alternative medications are also limited by the need for intravenous administration and are typically only used in the setting of GCV resistance because of associated toxicity.[63] However, in the settinof the pandemic, the impetus on avoidance of hospital admission to avoid resource strain is intensified. For this reason, we believe avoidance of hospitalization during the COVID-era is a priority for CMV stewardship teams.

3.1 | Hospitalization avoidance strategies

3.1.1 | Immunosuppressive modulation

Treatment of CMV infection is a dual pronged approach of effective antiviral therapy and immunosuppressive modification. Studies exist suggesting that immunosuppressive modification is as efficacious as antiviral therapy and when done judiciously, does not result in negative allograft effects.[64,65] Additionally, there is evidence to support that a lack of immunosuppressive modification in the setting of severe infection can result in treatment failure, the development of resistance, and recurrence.[50,65] Given the importance of the development of CMV-specific T cell-mediated immunity in the control and suppression of CMV infection, adjustment of T cell-specific agents, particularly adjustment of CNI trough goals is paramount.[66,67] However, this must be titrated to effect as part of a multidisciplinary effort between the CMV stewardship team and the primary transplant provider, as the negative ramifications of allograft rejection are substantial at baseline, and further compounded in the setting of concomitant CMV infection.[68] More aggressive upfront adjustments in the first 2 weeks of therapy, along with use of adjuvant agents such as intravenous immunoglobulin, with titration back to goal once reassuring CMV viral clearance kinetics have been demonstrated may improve response to oral therapy and avoid hospital admission/intravenous therapy, although this tactic has not been specifically studied.

3.1.2 | Outpatient parenteral antiviral therapy

Although IV GCV is typically initiated in the inpatient setting, a relatively stable patient in the outpatient setting can receive IV GCV via home infusion, with effort on the part of the CMV stewardship team. This begins with coordination of insurance coverage. Our institution collaborates with a home health agency (HHA), which also provides assessments while inpatient. This first step is extremely important in determining whether a patient is a candidate for home IV therapy, in terms of physical ability to manipulate pumps and out of pocket costs for home care or infusion center care. Additionally, this step confirms ability of the HHA to provide GCV. Given its high cost and designation as a hazardous drug by the National Institute for Occupational Safety and Health (NIOSH) with the requirement for a chemotherapy hood to compound, some HHAs will not be willing/able to provide this agent.[69] After these barriers are negotiated, the next step is coordinating the placement of an intravenous catheter for use at home, such as peripherally inserted central catheter (PICC) or Hickman. The CMV stewardship pharmacist must work with nursing staff and the clinic to write appropriate orders for medication adjustment as well as the laboratory monitoring and line cares. Weekly laboratory monitoring is necessary in this setting to evaluate response and toxicity.

In contrast to GCV, which, while complex in set up and drug procurement, can be safely administered at home, there are more administration and monitoring challenges that arise with foscarnet and cidofovir, in addition to their significant toxicity. Foscarnet has very short stability when diluted for administration and typically is not able to be provided in a home infusion setting. Additionally, frequent electrolyte supplementation is required.[70] Cidofovir is ideal for an infusion center setting because of the weekly administration of this medication. However, given requirements for pre and post hydration, patients will spend several hours each week receiving this medication at the infusion center. Additionally, it is associated with increased rate of adverse effects making this agent less desirable overall.[71]

3.1.3 | Reevaluation of “severe disease” criteria

Tolerance of viral loads that would result in admission prior to the COVID-19 era could be considered in those transplant recipients

who are relatively asymptomatic, particularly if GI symptoms are not present or mild and when paired with aggressive immunosuppressive adjustment. Typically, a viral load of approximately 2000 international units/mL has been correlated with symptomatic disease; however, a universal threshold for what is considered clinically significant replication has not been established.[72] Early evaluation of patient risk factors, paired with CMV CMI testing to assess risk of rapid viral replication in the setting of lower viral loads, may be warranted in the COVID-19 era to avoid replication requiring hospital admission.

3.1.4 | Timing of disease and post prophylaxis surveillance

Awareness of the timing of CMV infection after transplant is helpful in preventing negative outcomes.[73] CMV infection in the first year, particularly after discontinuation of prophylaxis, is anticipated. Expert opinion has suggested the utility of surveillance monitoring after completion of prophylaxis in the setting of high-risk factors, although supporting literature is lacking.[6,74] Late-onset CMV disease, or disease occurring >1 year after transplant, is less predictable and the utility of surveillance is less clear. Screening of transplant recipients using CMV CMI testing and clinical risk factor screening tools[68] to determine CMV disease risk after prophylaxis completion could identify a high-risk group in which surveillance monitoring, along with standard transplant labs, could prevent symptomatic presentation.

3.2 | Strategies for rapid viral clearance if hospitalized

If admission is unavoidable because of severe or life-threatening disease or failure of hospital avoidance tactics, strategies to reduce duration of admission are crucial.

3.2.1 | High dose GCV

Standard dosing of GCV is 5 mg/kg every 12 hours, adjusted for renal dysfunction.[75] The manufacturer package insert recommends a single 5 mg/kg loading dose, regardless of renal function. However, doses up to 10 mg/kg are recommended by consensus guidelines in the setting of viral resistance.[6] There is literature supporting viral replication kinetics as a defining parameter of CMV infectious outcomes. More rapid viral clearance kinetics have been tied to improved outcomes and reduced risk of recurrence.[36] Brief periods of aggressive dosing paired with immunosuppressive reduction may result in rapid clearance of initial viral load and prevent persistent viremia, thus improving CMV outcomes. However, this strategy has not been specifically investigated. Additionally, the risk of additive myelosuppressive toxicity associated with this tactic must be considered and may not be appropriate in those who present with significant leukopenia.

3.2.2 | Adjuvant therapies

The use of additional, less toxic agents to augment GCV for treatment of CMV is a well-studied concept. Passive immunity utilizing intravenous immunoglobulin has been a longstanding component of the treatment of CMV infection.[76] CMV hyperimmune globulin (CMVIg) has been the most extensively studied in this role but because of cost and the prevalence of CMV in the general population, standard IVIG is frequently used interchangeably, as no literature exists supporting clinical superiority of either product. However, given the lack of rigorously designed studies, it is difficult to tease apart the direct effects of IVIG on CMV treatment, thus recent consensus guidelines do not give a strong recommendation for or against its use beyond stating it may have a role in some clinical scenarios.[6] At our institution we typically utilize IVIG for its immunomodulating effect to provide additional protection against rejection in the setting of aggressive immunosuppressive reduction for CMV, as has been previously described for other opportunistic infections,[77] as well as its potential benefit in enhancing viral clearance.

It is also possible that the addition of LTV could augment GCV given its alternate mechanism of action and result in synergistic or additive activity. Although this has been shown in the in vitro environment[78] it has not been demonstrated in vivo, and the low genetic barrier to resistance and resultant risk of rapid resistance development, particularly at high viral loads, is a limitation to its use in this manner.[52]

4 | OTHER COVID-19-RELATED ISSUES

4.1 | Personnel shortages

In addition to the numerous issues described above, personnel shortages because of COVID-19-related furloughs of healthcare staff may be the most difficult challenge faced when managing CMV in transplant recipients. Management of CMV prophylaxis and treatment requires a team of interdisciplinary providers and pharmacist services dedicated to the management of CMV in transplant recipients.[7] Lack of dedicated resources because of reallocation of trained CMV stewardship personnel to other roles will result in delayed follow-up, and the loss of prospective audit and feedback. Lack of prospective audit and feedback will significantly affect the quality of care, as this is has been suggested as a key aspect influencing the impact of stewardship initiatives.[79] Lack of resources could lead to failure to respond to rising PCRs, inappropriately dosed antivirals following improved renal function, and delayed response to adverse effects. These may negatively impact transplant recipients previously benefiting from services provided by an interdisciplinary CMV stewardship initiative.

5 | CONCLUSION

The global pandemic caused by COVID-19 has led to drastic changes in how we function as a society, and in turn, how we provide healthcare. Given the overall lack of highly effective therapies to treat SARS-COV-2, and concern for the safety of healthcare workers and the general population, healthcare systems have significantly modified standard practices to reserve healthcare resources and alleviate care burdens on personnel. Preliminary antibody testing results have demonstrated low rates of positivity in the population, suggesting herd-immunity is unlikely to be achieved without large-scale vaccination.[80] To date, two vaccines have become available via early use authorization from the US Food and Drug Administration. However, despite this positive development, many have criticized the current vaccination pace in the US as it has not met previously set benchmarks because of a variety of obstacles, suggesting a more protracted course to the return to the pre-pandemic state.[81] Therefore, management of CMV in the setting of COVID-19 will be an ongoing challenge. Center-specific critical review and adaptation of consensus guidelines to the current era and creation of a toolkit to address identified issues will be critical to ensuring the safe and effective management of CMV and the prevention of associated negative allograft outcomes.

CONFLICT OF INTEREST

None.

DISCLOSURE

None.

AUTHOR CONTRIBUTIONS

MRJ: original concept, design, manuscript preparation, analysis, editing. CW, JRS: manuscript preparation, JLD, SP, JPR, RRR, JAS, DAM, CMS: manuscript preparation, editing.

DATA AVAILABILITY STATEMENT

No datasets were generated or analyzed during the current study.

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