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REVIEW

A call for cytomegalovirus stewardship initiatives in cardiothoracic transplant

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Despite the availability of potent antiviral therapy and increasingly long prophylaxis courses, cytomegalovirus (CMV) infection continues to negatively affect outcomes after cardiothoracic transplant (CT). CMV antiviral stewardship (AVS) represents an opportunity to implement organ-specific prophylaxis, treatment, and monitoring algorithms while optimizing care of the allograft and patient. Within the nuanced context of heart and lung transplant recipients, CMV prophylaxis, monitoring, and treatment strategies are reviewed for efficacy and safety. These insights highlight opportunities for CMV AVS programs to combine organ- and patient-specific data while implementing CMV guidelines, appropriately adopted to local context by local experts, with concurrent and retrospective evaluation for each patient and the transplant program. By applying concepts of CMV AVS currently practiced in abdominal transplant, CT programs can work to improve graft and patient outcomes related to CMV, including ongoing challenges such as atherosclerosis and impaired endothelial function in heart transplant recipients and chronic lung allograft dysfunction in lung transplant recipients. While implementation of CMV AVS is not without challenges, it also represents an opportunity for multidisciplinary teams to foster the development of CMV-specific cell-mediated immunity and improve long-term outcomes.

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Background

Cytomegalovirus (CMV) is a ubiquitous herpes virus. In immunocompetent hosts, CMV infection is typically mild. However, in the immunosuppressed population, such as those patients who have undergone solid organ transplantation (SOT), CMV is a serious complication with significant impacts on graft survival.[1,2] The virus's potential to cause significant disease in the immunocompromised host is closely tied to both the host's previous exposures as well as their net immunosuppressive state. Options for treatment of CMV are limited with ganciclovir (GCV) and its oral pro-drug, valganciclovir (VGC), serving as the guideline endorsed first line treatment agents.[1,2] Unfortunately, these agents are often subject to overuse and misuse with resultant resistance, toxicity, and poor outcomes. The prevalence of GCV-resistant CMV has been rising. When resistance develops, treatment options are limited, and rates of morbidity and mortality are high.[3] It is important to note that successful treatment of CMV infection in the immunocompromised host involves a complex interplay between antiviral drug therapy as well as development of immunity through immunosuppressive modulation, with subsequent antiviral freedom. Providers must be particularly alert to the interplay between both the host immune system, CMV replication and clearance, and rejection risk. Successful treatment of CMV in SOT recipients is not simply measured by disease clearance and patient survival, but allograft outcomes must also be considered.

Impact of CMV in cardiothoracic patients

Cardiothoracic transplant (CT) recipients are not excluded from the sequelae of complications related to CMV, and in fact, may be more sensitive than their abdominal transplant counterparts. In heart transplant (HT) recipients (HTR), CMV is associated with poor allograft and patient survival, as studies have shown CMV directly affects the transplanted heart by increasing the risk for rejection and atherosclerosis.[4] Additionally, CMV infection has been associated with impaired endothelial function as well as an increased incidence of cardiovascular-related events and death.[5] There are conflicting data regarding the association of CMV with cardiac allograft vasculopathy, and in the most recent era of antiviral prophylaxis, it is most associated with breakthrough CMV infections while on primary prophylaxis.[6] While use of antiviral prophylaxis reduces the incidence of CMV in the primary prophylaxis period, it does not eliminate development of CMV, particularly in CMV seronegative patients who have received CMV seropositive organs (D+/R-). In this high-risk HT patient population, rates of subsequent CMV disease following completion of 3 months of anti-CMV prophylaxis have ranged from 29% to 86%.[7] To ameliorate rates of post-transplant CMV following HT and theoretically subsequent negative allograft effects, alternatives to the standard preventative strategy have been explored, most notably extension of primary prophylaxis. However, while extension of primary prophylaxis from 6 to 12 months post-transplant delays the onset of CMV, it does not eliminate it. Indeed, the time from VGC discontinuation to onset of CMV infection does not change, with 95% of CMV infections in HTR occurring within 6 months after cessation of VGC.[8]

Lung transplant (LT) recipients (LTR) have similarly poor outcomes, and post-LT CMV is a leading contributor to morbidity and mortality in this population.[9] CMV infection has been suggested to be a major risk factor for chronic lung allograft dysfunction, which is a limiting factor to long-term survival after LT.[10] This has led many LT centers to pursue aggressive prophylaxis extension, upward of 18 months to "life-long" in attempt to improve outcomes.[11] However, as with HT, despite these extended anti-CMV prophylaxis durations there has not been great success in decreasing the incidence of post-transplant CMV. In one study, extension of primary prophylaxis from 6 to 9 months in high-risk patients resulted in a delay in CMV onset but did not significantly reduce the incidence of CMV infection (65% vs 64%, p = not significant).[12]

While the negative impact of CMV infections in CT recipients has been well documented, the risk conveyed by CMV serostatus is less clear in this population. A survival analysis of 620 HTR found that donor and recipient CMV serostatus independently did not impact 10-year survival after transplant.[13] A survival analysis of 652 LTR found that donor and recipient CMV serostatus independently did not impact 10-year survival after transplant.[14] Together this data suggest novel, patient-specific strategies beyond prophylaxis extension are needed to decrease the rates and complications of postprophylaxis CMV in CT recipients.

Antiviral stewardship programs

CMV antiviral stewardship (AVS) programs have been identified as an opportunity for improving prophylaxis and treatment of CMV in SOT recipients.[15] Like antimicrobial stewardship programs, CMV AVS promotes the appropriate use of antivirals to improve patient outcomes, prevent the misuse of antivirals, reduce the development of resistance and moderate health care resource utilization (Figure 1). When the CMV AVS program in abdominal transplant recipients was created at our center, the primary goal was to reduce the development of GCV resistance due to inappropriately dosed VGC. However, over time, the focus of the program shifted, as we found an approach focused only on VGC did not address the real issue, which is lack of CMV-specific cell-mediated immunity (CMI).[15] The methodology of CMV AVS now centers on proactive audit and feedback, relying heavily on early enrollment, monitoring, and surveillance of CMV high-risk patients to provide a targeted approach to intervention, including dose optimization, early detection of replication with preemptive treatment, and CMV-specific CMI target attainment. However, to date CT recipients have been excluded from these programs, due to a lack of provider comfort, the potential for more severe complications of infection to both recipient and transplanted graft, atypical clinical presentation and finally, lack of data regarding utilization of stewardship principles in this

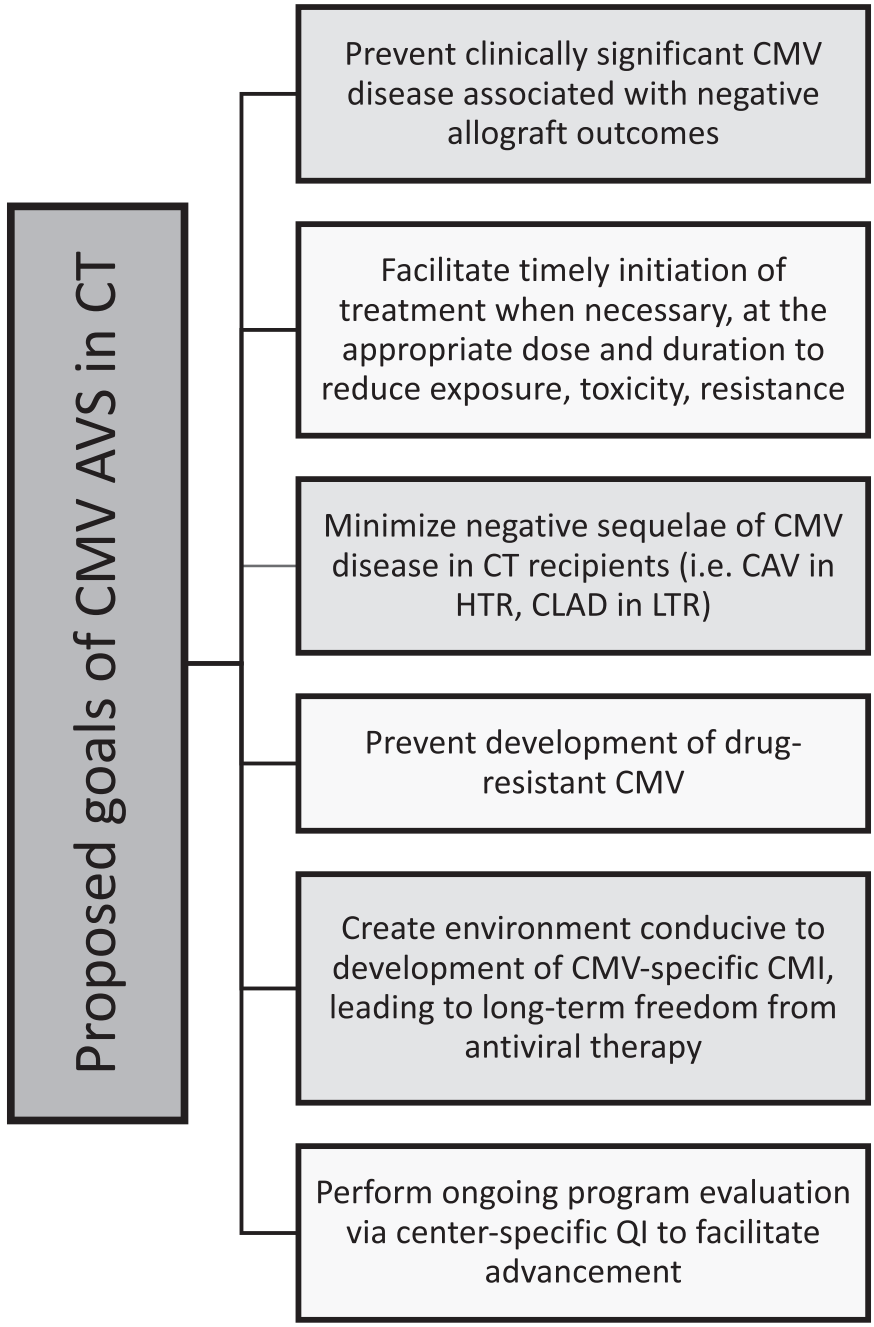

Figure 1 Hierarchy of CMV antiviral stewardship. AVS, antiviral stewardship; CAV, cardiac allograft vasculopathy; CLAD, chronic lung allograft dysfunction; CMI, cell-mediated immunity; CMV, cytomegalovirus; CT, cardiothoracic transplant; HTR, heart transplant recipients; LTR, lung transplant recipients; QI, quality improvement.

specific population. Yet, this patient population has perhaps the most to gain regarding improving the judicious use of antiviral therapy while decreasing the impact of viral complications on both the patient and the graft. Indeed, complications of antiviral therapy, including leukopenia and resistance disproportionately, affect the cardiothoracic transplant population.[16] Additionally, the use of alternative prophylaxis approaches do not seem to negate these risks as they do in other populations.[17] Furthermore, even judicious management of these complications do not seem to improve outcomes.[18]

To address this clinical gap, we propose an expansion of current AVS programs in abdominal transplant to CT recipients. Based on our center's experience in abdominal transplant, proposed programmatic elements for a CMV AVS program include involvement of multidisciplinary stakeholders, such as transplant clinicians specializing in each graft subtype, transplant infectious disease specialists, transplant pharmacists and nurse coordinators; support from transplant program and institutional leadership; incorporation of consensus guidelines, adapted to the local environment, and updated to newly available therapies; adequate time and resources; prospective audit and feedback concerning stewardship recommendations; measurement and accountability of the AVS program to its performance and outcomes; and ongoing education of practitioners executing and involved with AVS program.[15,19,20] Through implementation of organ-specific prophylaxis, treatment, and

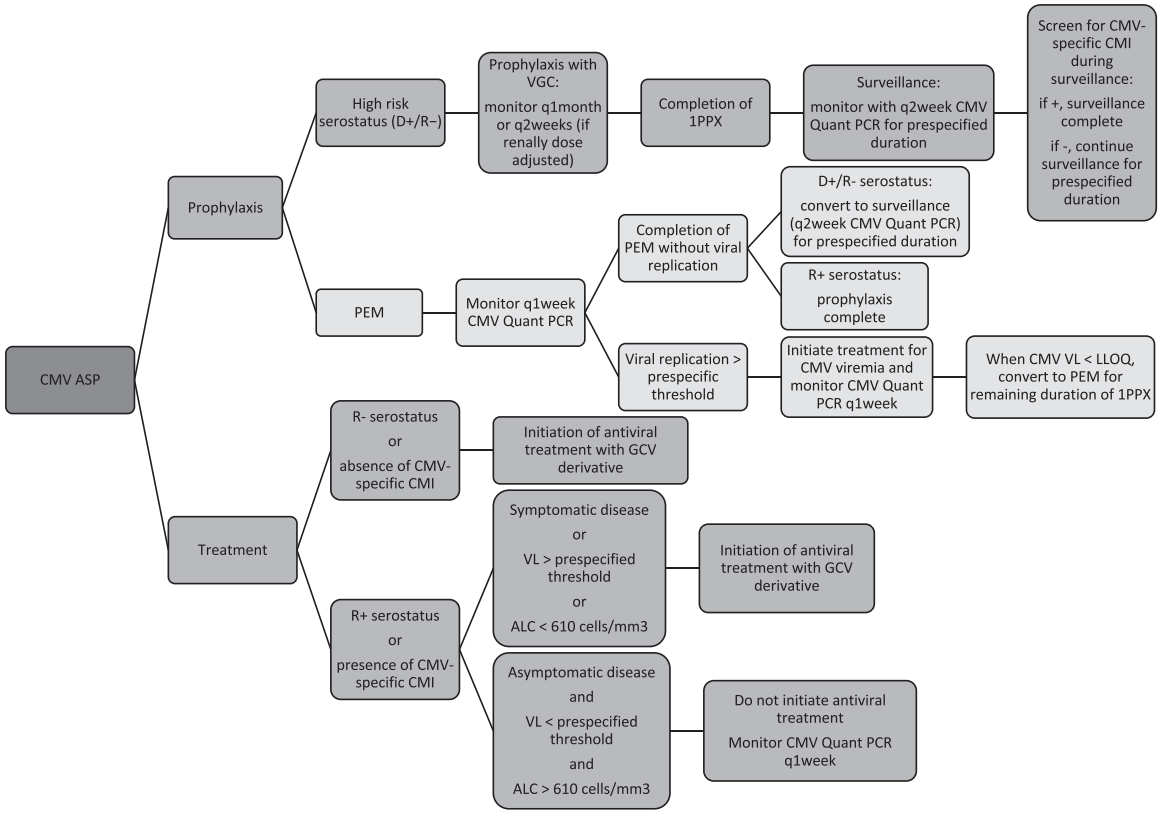

Figure 2 Proposed structure for management of cardiothoracic transplant recipients within CMV antiviral stewardship programs. ALC, absolute lymphocyte count; ASP, antimicrobial stewardship program; CMI, cell-mediated immunity; CMV, cytomegalovirus; GCV, ganciclovir; LLOQ, less than lower limit of quantification; LTV, letermovir; PEM, preemptive monitoring; PCR, polymerase chain reaction; q2week, every 2 weeks; VGC, valganciclovir; VL, viral load; 1PPX, primary prophylaxis. **Preemptive monitoring is not a preferred management strategy in lung transplant recipients due to the relatively high risk of tissue-invasive disease and chronic lung allograft dysfunction. Clinician discretion must be used to weigh the risks and benefits of this approach for each patient.

monitoring algorithms (Figure 2), the nuances of HTR and LTR can be addressed without compromising care of the graft or patient.

Essential elements of CMV stewardship initiatives

Essential elements of a CMV stewardship initiative in SOT recipients have been described previously.[15,19] Briefly the program in abdominal transplant is focused on optimization of both prophylaxis and treatment of CMV. Patients that are CMV high-risk (D+/R-) are enrolled prospectively at time of transplant and followed throughout prophylaxis with a protocolized postprophylaxis surveillance period to preemptively treat CMV replication. Allowing replication in this observed setting fosters the development of CMI without negative graft effects related to CMV disease. This is the most important element of the program. The program also enrolls patients who are utilizing the preemptive monitoring (PEM) prophylaxis approach, to ensure timely preemptive treatment and avoid prolonged or unnecessary antiviral exposure. Finally, the program enrolls patients who require treatment of CMV disease. This is the most complex and time-consuming aspect of the program, and therefore, the focus remains on proactive prevention and surveillance to minimize the need for treatment of CMV disease. Figure 2 outlines aspects of the current CMV AVS at our center. The focus of our review will be on the specific challenges and opportunities of CMV stewardship initiatives, as well as CMV therapy and management as they pertain to HTR and LTR. The overarching goal of the CMV AVS program is development of CMV-specific CMI via targeted interventions in the CMV high-risk subset, which have repeatedly been shown to be the population most negatively affected by CMV due to development of primary infection and disease.[21–23] These patients must be proactively identified prior to the development of complications for best efficacy of this approach.

Implementation of CMV guidelines adopted to local context by local experts

Consensus guidelines summarizing evidenced-based recommendations and expert opinions regarding the prevention and treatment of CMV are available.[1,2] These guidelines are, however, limited in that they provide broad recommendations for a large population. Additionally, HT and LT specific data are more limited than in the abdominal transplant population. In

this way, interpretation of such guidelines is not always consistent across centers. Variations in patient populations, as well as center-specific immunosuppressive practices, necessitate adaptation of national guidelines to meet center-specific needs via development of center-specific CMV AVS protocols. Development of such protocols requires inclusion of key stakeholders and clinical experts, including transplant infectious disease providers, transplant physicians, and transplant pharmacists. Additionally, buy in from each of these departments is of the utmost importance to ensure the AVS program provides consistent, evidence-based recommendations.

Programs must develop center-specific prophylaxis modalities that align with their specific patient population. Dedicated quality improvement (QI) related to these issues in the CT recipient to provide evidence-based approaches is paramount to improve outcomes, and the CMV stewardship task force is uniquely poised to spearhead these initiatives. The following paragraphs summarize CMV literature specific to the CT population, highlighting gaps and opportunities.

Role of immunosuppression

Immunosuppression plays an active role in the risk and management of CMV given the importance of immunity for control of viral replication. HTR often do not receive induction immunosuppression as it does not offer a survival benefit.[24] More LTR are now receiving induction immunosuppression, with interleukin-2 receptor antagonist basiliximab being the most common agent.[25] However, these trends may change with the increasing occurrence of immunologically high-risk CTs, which could result in mounting challenges managing CMV in patients that are more highly immunosuppressed after transplant and may have lost CMV-specific CMI developed before transplant. Different classes of maintenance immunosuppressive agents may impact the risk for CMV infection after CT as well. Compared to calcineurin inhibitor (CNI)-based regimens, mammalian target of rapamycin inhibitors (mTORi) may reduce the risk for CMV infections after HT and LT.[26,27] The antiviral properties of mTORi are likely due to the ability of mTORi to increase the quality, functionality, and efficacy of memory T cells in response to viral exposure.[28] With regards to antimetabolite agents, a randomized controlled trial in HTR demonstrated that end-organ CMV disease may be more common with mycophenolate compared to azathioprine.[29] While a CNI-based triple drug regimen remains standard for HTR and LTR at most transplant centers in the United States,[24,25] as these regimens are associated with reduced rates of rejection, the optimization of immunosuppression to reduce the risk of CMV infections or improve response to treatment remains an important consideration for the AVS program.

CMV prophylaxis: Summary of cardiothoracic evidence

Given the negative impact of CMV on both graft and patient outcomes, prevention of CMV in the early post-operative period is of the utmost importance. Current guidelines endorse the use of GCV, or its oral pro-drug VGC, for the prevention of CMV following cardiothoracic transplantation.[1,2] The optimal duration of VGC in the CT population is unknown, and one must weigh the risk of CMV with the associated risk of ongoing drug exposure as well as underdosing in the setting of renal function fluctuation and risk for viral resistance. Several studies in both HT and LT have attempted to define the optimal duration of CMV prophylaxis.[30,31] While these studies have shown that the risk of CMV is low while receiving prophylaxis with VGC, extending the duration of prophylaxis does not appear to decrease the risk of CMV once therapy is stopped. Rather than a one-size-fits-all approach, a more tailored patient-specific approach is needed. AVS programs can provide a patient-centered approach to the prevention of CMV in high-risk CT recipients, incorporating available evidence (Table 1).

Antiviral use

While VGC has been recognized as the antiviral of choice for CMV prophylaxis following cardiothoracic transplantation, it is not without drawbacks. VGC suppresses the white blood cell count and can compound myelosuppressive effects of other drugs used post-transplant, such as antimetabolites. In turn providers may decrease antimetabolite doses to minimize bone marrow suppressive effects, which may increase the risk for rejection. Furthermore, it has been demonstrated that VGC administration facilitates a delay in CMV onset in high-risk recipients but does not allow development of CMV-specific CMI.[40] These factors combined have led to interest in alternative antiviral agents for CMV prophylaxis. Letermovir (LTV) is approved by the Food and Drug Administration for the prevention of CMV after hematopoietic stem cell transplant and after renal transplant in high risk (D+/R-) recipients, based on the results of a recent study demonstrated that LTV was effective and noninferior to VGC in preventing CMV following renal transplantation.[41] As its use in clinical practice expands, clinicians must be mindful that the spectrum of activity of LTV only includes CMV, so (val)acyclovir must be added to provide herpes simplex virus prophylaxis if the patient is transitioned to LTV within the first 1 to 3 months after transplant.[1,2]

LTV is not associated with myelosuppression, making the agent more favorable than VGC in recipients with leukopenia as it better allows for target antimetabolite dosing to be achieved. Additionally, LTV may facilitate CMV-specific CMI development.[42] It is important to note that LTV can cause drug interactions that may be clinically significant, including with CNIs, voriconazole, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Obtaining LTV through commercial insurance typically requires prior authorizations and/or appeals of denied claims, which necessitates additional resources from transplant centers and delays patient access to therapy. Involvement of the CMV AVS program is an ideal solution to these challenges, given the inclusion of the transplant pharmacist within the program. The pharmacist can avoid unintended consequences of drug interactions by

Table 1 CMV Prophylaxis in Cardiothoracic Transplant Recipients

Reference	Publication year	Design	*n*	Transplant type	Intervention	Primary efficacy endpoint	Primary efficacy endpoint measure	Conclusion
Alternative antiviral prophylaxis								
Golob et al[32]	2022	Case series	17	Heart	LTV for CMV prophylaxis after leukopenia on VGC	Tolerance of LTV	Able to tolerate LTV: $n = 13$ (76.5%) Unable to tolerate LTV: $n = 4$ (23.5%) Reasons for intolerance: 1. Clinically significant CMV viremia: $n = 1$ 2. Nonclinically significant CMV viremia: $n = 2$ 3. AE: $n = 1$	LTV is alternative CMV PPX agent in HTRs unable to tolerate VGC, though requires monitoring for breakthrough viral replication.
Saullo et al[33]	2022	Single-center retrospective study	41 with 42 PPX episodes	Heart and lung HTR: $n = 4$ LTR: $n = 37$	LTV for primary or secondary CMV prophylaxis	Tolerance of LTV	Able to tolerate LTV: $n = 28$ (66.7%) Early cessation of LTV: $n = 14$ (33.3%) Reasons for cessation: 1. Clinically significant CMV viremia: $n = 1$ 2. AE: $n = 5$ 3. Lack of insurance coverage: $n = 4$	LTV is well-tolerated and effective for PPX in CTRs.
Aryal et al[34]	2019	Case series	9	Heart and lung HTR: $n = 1$ LTR: $n = 8$	LTV for primary or secondary CMV prophylaxis	CMV DNAemia during prophylaxis	Clinical failure of LTV: $n = 1$ Low-level CMV DNAemia: $n = 1$	LTV is well-tolerated, though further study warranted to assess development of breakthrough viral replication.
Preemptive monitoring								
Potena et al[35]	2009	Longitudinal observational study	40 PEM: $n = 21$ PPX: $n = 19$	Heart	Primary PPX with VGC	1-year change in MIT assessed at 1 and 12 months post-transplant	1-year increase in MIT lower in patients receiving PPX vs PEM (0.15 ± 0.17 vs 0.31 ± 0.20 mm; $p = 0.01$)	PPX associated with less intimal thickening, as well as delayed onset of CMV infection, lower viral burden, reduced CMV disease/syndrome, compared to PEM.

(*continued on next page*)

Table 1 (*Continued*)

Reference	Publication year	Design	*n*	Transplant type	Intervention	Primary efficacy endpoint	Primary efficacy endpoint measure	Conclusion
Egan et al[36]	1995	Case series	32	Heart and lung HTR: *n* = 23 LTR: *n* = 9	CMV surveillance by CMV antigenemia	CMV infection and disease Accuracy of CMV antigenemia for CMV-related illness	CMV infection: *n* = 11 CMV disease: *n* = 5 CMV antigenemia: sensitivity = 100%, specificity = 93.7%, positive predictive value = 94.1%	CMV antigenemia can identify patients likely to develop CMV disease, which may allow for early treatment.
Kelly et al[37]	2000	Retrospective study	19	Lung	PEM with GCV, guided by CMV antigenemia	Incidence of CMV disease	Incidence of CMV disease: 26% (PEM) vs 38% (PPX) ($p = 0.51$)	PEM with GCV is as safe and effective as universal PPX in preventing CMV disease in LTRs and is less expensive.
Hybrid approach								
Bhorade et al[38]	2001	Prospective study	34	Lung	Hybrid capture system assay for detection of CMV infection and disease	Development of CMV disease/syndrome	CMV disease/syndrome: *n* = 10 Hybrid capture system assay: sensitivity, specificity, positive predictive value, and negative predictive value > 90%	HCS assay can be used to detect CMV disease earlier than other methods. Future studies needed to evaluate use in PEM to prevent morbidity associated with CMV disease.
Lin et al[39]	2012	Retrospective study	25	Heart (pediatric)	2-4 weeks of GCV followed by serial CMV VL monitoring	Development of CMV infection	CMV infection: *n* = 10 (38%) Median time to first viremia: 2.3 months (range, 9 days to 24.8 months) Median time to viral load clearance: 29 days (range, 4-233 days)	Pediatric HTRs at risk for CMV treated with hybrid strategy developed CMV infection, syndrome, and disease at rates similar rates with universal PPX found in literature.

Abbreviations: AE, adverse effect(s); CMV, cytomegalovirus; CTR, cardiothoracic transplant recipient; GCV, ganciclovir; HTR, heart transplant recipient; LTR, lung transplant recipient; LTV, letermovir; MIT, maximal intimal thickening; PEM, preemptive monitoring; PPX, prophylaxis; VGC, valganciclovir.

completing a thorough medication review and providing recommendations for dosage adjustments of impacted medications prior to starting or when discontinuing LTV. The pharmacist can also navigate common insurance challenges and assist in the appeal process. Due to its reassuring clinical data and current market availability, LTV is being adopted into practice for CMV prophylaxis in both abdominal[41] and cardiothoracic transplantation.

In the HT population, LTV has been studied for primary CMV prophylaxis in high-risk recipients. In a small case series in 17 HTR (15 patients with CMV D+/R- serostatus) switched from VGC to LTV for leukopenia, LTV was well-tolerated.[32] At end of follow up, 9 patients (52.9%) remained on LTV; 4 patients (23.5%) had completed the prophylaxis window and were transitioned to surveillance monitoring. During surveillance, 2 patients developed low-level CMV viremia and received treatment with VGC, possibly suggesting similar rates of postprophylaxis CMV with VGC and LTV in HTR. Two additional single-center retrospective reviews of LTV for primary and secondary CMV prophylaxis among HTR and LTR found LTV to be well-tolerated and effective.[33,34] However, in a single-center case series, 3 patients (37.5%) developed CMV viremia within 2 months of initiating LTV, with viral loads ranging from 1,910 to 33,392 IU/ml.[34] Notably, all 3 patients had high-risk CMV serostatuses (D+/R-), suggesting a period of surveillance monitoring may be necessary in these patients, though additional monitoring did not appear to be required in high-risk kidney transplant recipients in the recently published phase 3 noninferiority trial.[41]

The occurrence of transient viremia shortly after initiating LTV may be inherent to the drug's mechanism of action as a CMV DNA terminase complex inhibitor and should be anticipated as this does not necessarily represent pathogenic replication or antiviral failure. The involvement of a CMV AVS pharmacist who is comfortable evaluating and managing these low-level viremias is imperative to minimize unnecessary discontinuation of LTV. Presence of significant breakthrough viral replication on LTV, particularly in high-risk patients, warrants further investigation in both abdominal and CT populations.

Preemptive monitoring

A PEM approach for CMV prophylaxis is not well-studied in high-risk HTR and LTR, and avoidance is suggested in consensus guidelines.[1,2] In LTR, PEM is not a preferred management strategy due to the relatively high risk of tissue-invasive disease and chronic lung allograft dysfunction, namely bronchiolitis obliterans.[43] However, it may be necessary in select patients as pancytopenia in LTR is often exacerbated by concurrent disorders more prevalent in this patient population, such as hypogammaglobulinemia and short telomere syndrome.[44] Cytopenias often persists despite dose reduction or discontinuation of contributing post-transplant medications, including antimetabolites and sulfamethoxazole-trimethoprim. PEM has been shown to be a useful strategy to manage leukopenia in kidney and pancreas transplant recipients.[45]

Additionally, the risk associated with PEM conversion is not consistent between serostatuses. Centers that serve a primarily local patient base, utilize a central laboratory and service a predominantly CMV seropositive population might be well equipped for utilization of this approach. Conversely, centers whose population is widely dispersed, with patients who require laboratory tests be shipped with long turnaround times may do best to avoid PEM and instead focus on alternative universal prophylaxis strategies. The AVS program and its protocols can help delineate patients who may benefit from antiviral withdrawal and conversion to PEM in the setting of significant bone marrow suppression, drug-induced leukopenia or those unable to afford universal prophylaxis and study this approach in dedicated QI initiatives. Additionally, the CMV AVS program can set forth specific guidelines for treatment, such as when to initiate and when to stop treatment, and when to stop monitoring in a stable patient.

There is a paucity of evidence for PEM in both HT and LT. One longitudinal observational study in HTR found that patients who received VGC prophylaxis ($n = 19$) experienced significantly lower 1-year change in maximal intimal thickening compared with HTR undergoing PEM ($n = 21$).[35] Patients receiving prophylaxis also experienced later onset of CMV infection ($p = 0.01$), lower peak CMV viral load ($p < 0.01$), and reduced incidence of CMV disease ($p = 0.04$). On the contrary, there is also data to suggest efficacy of this approach in both HT and LT.[36,37] One case-controlled study found PEM to be as effective as universal prophylaxis and more cost-effective.[37] The greatest risk to PEM in the CT population is in the setting of missed laboratory monitoring due to patient or laboratory error, or delayed response to laboratory results due to prolonged result turnaround time, resulting in progression to high-level, symptomatic disease. This again highlights the pivotal role of the AVS program to ensure ongoing appropriate monitoring and suitability of alternative approaches based on patient-specific risk factors.

Hybrid approach

A hybrid approach to CMV prophylaxis involves initial use of universal antiviral prophylaxis followed by antiviral discontinuation and surveillance. The hybrid approach is not specifically endorsed by consensus guidelines, but noted that if pursued, is likely to have the greatest yield in the first 12 weeks after antiviral discontinuation.[1,2] However, the hybrid approach is commonly used in the setting of CT, likely due to the potentially severe ramifications of CMV disease in this population. This strategy has been shown to be effective in preventing progression of early replication to symptomatic disease in LT[38] and was noninferior to standard duration universal prophylaxis in pediatric HTR.[39] The hybrid approach in the setting of CMV AVS is referred to as postprophylaxis surveillance and is the cornerstone of optimization through utilization of a proactive approach focused on the patients at highest risk. In this way, CMV AVS programs dovetail well with what is considered standard of care in CT and can provide further risk stratification

and QI through prevention of and prompt remediation of missed monitoring intervals that could allow progression to symptomatic disease and negative outcomes, as well as develop center-specific protocols to determine optimal duration of prophylaxis and surveillance.

CMV treatment: Summary of cardiothoracic evidence

Limited literature is available describing the treatment of CMV in CT recipients (Table 2). Historically, GCV has been shown to be tolerable and improve outcomes after CMV infection in heart and heart-lung transplant recipients.[46] However, the tolerability issues are intensified with the more aggressive treatment doses. More recently maribavir, a benzimidazole riboside, was FDA approved for treatment of resistant and refractory CMV infection.[47] This is an attractive agent given its lack of myelosuppressive toxicity and nephrotoxicity when compared with VGC/GCV/foscarnet; however, evidence exists suggesting a lower genetic barrier to resistance, particularly at higher viral loads and potential cross resistance with GCV-derivatives.[48] Additionally, despite the positive findings in the clinical trial on clearance rates and symptom resolution when examining the entire study population, subgroup analysis of SOT patients including kidney, heart, and lung recipients did not demonstrate the same benefit.[47] Furthermore, a recently published real world case series described breakthrough CMV viremia on maribavir in 4 patients, 2 of whom were LT recipients.[49] While further data are certainly forthcoming, maribavir represents a new, orally available CMV active antiviral that can avoid toxicities related to available antiviral therapies ([val]ganciclovir, foscarnet, cidofovir), such as acute kidney injury and neutropenia,[47] and may reduce hospitalizations and lengths of stay by minimizing the need for intravenous antiviral treatment. The CMV AVS program can guide patient selection and address drug interactions to increase successful utilization of this agent in cardiothoracic transplant recipients (CTRs).

Much of the more recent data on CMV treatment in CT recipients involves the use of alternative or adjunctive therapies. A small case series ($n = 3$) demonstrated that the addition of CMV immunoglobulin (CMVIg) may be beneficial in HTR with CMV disease and concurrent hypogammaglobulinemia.[50] A single-center retrospective study of 23 LTR and 12 HTR described the addition of CMVIg to standard antiviral regimens for the treatment of CMV infection or disease.[51] After a median of 2 doses of CMVIg, a majority of patients (73%) had undetectable viral loads at 4 weeks. A case report published in 2019 described the successful management of a single LTR with severe, bilateral, GCV-resistant CMV retinitis treated with standard antiviral treatment, adjunctive leflunomide, CMVIg, and intravitreal antiviral therapy.[52] Most recently, a case series described 6 LTR and 1 HTR with genotypically-confirmed GCV-resistant CMV infections managed with CMVIg monotherapy or with adjunctive leflunomide.[53] The majority of these patients had high-risk CMV serostatuses (CMV D+/R-; 71.4%). Patients were transitioned to a regimen of CMVIg with or without leflunomide after failing to tolerate standard treatment due to declining renal function, myelosuppression or symptomatic pleural effusions. Five patients achieved undetectable viral loads, though the number of CMVIg doses (median 10 doses; range 1-21 doses) and time (median 25 weeks; range 4-50 weeks) were highly variable.

A novel approach to treating viral infections involves the use of virus-specific T-cell therapy. Eight LTR and 1 HTR were included and received treatment in a single-arm, open-label phase 1 trial investigating autologous adoptive T-cell therapy for recurrent or drug-resistant CMV infections.[54] This study found CMV-specific adoptive T-cell therapy was safe in SOT recipients and offers a potential therapeutic benefit based on the demonstrated ability to generate CMV-specific T cells from immunosuppressed individuals, which resulted in viral control after T-cell therapy in most treated patients. Though the use of cellular therapy for the treatment of viral infections remains in its infancy, and many considerations remain in SOT recipients such as the impact of immunosuppressive regimens on the performance of cellular therapies, it remains an exciting area of research given the challenges of currently available antiviral therapies for CMV.

Recent developments and future directions

Future direction for management of CMV in CT recipients will likely focus on fostering development of the CMV-specific cellular immune response, as this frees the patient from the burden of ongoing antivirals. Immune functional assays can be used to identify CMV-specific CMI by using a stimulant to trigger immune cells, primarily T cells, and quantify the cytokine response to stimulation.[55] Several classes of immune functional assays are available to determine a patient's CMV-specific CMI: enzyme-linked immunosorbent spot (ELISpot) assays T-SPOT.CMV and T-TRACK.CMV; enzyme-linked immunosorbent assay (ELISA) QuantiFERON-CMV; and flow cytometry assay CMV insight T Cell Immunity Panel.[54] There are differences amongst these assays, including immune cells targeted by stimulation and whether the response of different types of immune cells are distinguished in results, which can create difficulties in comparing the results of one assay to another. The results of these assays can be used to help guide patient-specific therapy and reduce antiviral therapy duration and associated toxicities in patients who demonstrate CMI against CMV.

Evidence is available for the use of immune functional assays in CT (Table 3). A single-center study of 44 CMV-seropositive HTR showed that patients with CMV-specific CMI by QuantiFERON-CMV assay had significantly fewer (66.7% vs 14.3%, $p = 0.036$) CMV infections after withdrawal of prophylaxis compared to patients without CMV-specific CMI.[56] Patients with CMV-specific CMI also had lower median peak CMV viral loads and controlled viral replication without initiation of antiviral therapy. Patients who did not develop CMV-specific CMI after infection were significantly more likely to experience recurrent

Table 2 CMV Treatment in Cardiothoracic Transplant Recipients

Reference	Publication year	Design	*n*	Transplant type	Intervention	Primary efficacy endpoint	Primary efficacy endpoint measure	Conclusion
Keay et al[46]	1988	Multicenter retrospective review	22	Heart and heart-lung	GCV treatment	Survival of initial therapy	Survival: *n* = 18 (82%) Recurrent CMV: *n* = 6 (33%)	GCV well-tolerated and improved outcomes in CTRs with life- or sight-threatening CMV infections.
Avery et al[47]	2021	Randomized phase 3 OL study	352 MARI: *n* = 235 IAT: *n* = 117	Kidney, lung, heart, liver, pancreas, intestine, multiorgan	MARI vs IAT	Confirmed CMV viremia clearance at 8 weeks	Overall: 55.6% (MARI) vs 26.1% (IAT) Lung: 47.5% (MARI) vs 13.6% (IAT) [adjusted difference 38.2; 95% CI 16.89-59.53)	A benefit trend for MARI vs IAT observed in subgroup analysis of LTRs.
Sabatino et al[49]	2023	Case series	4	Lung and kidney	MARI	Breakthrough CMV viremia	Breakthrough viremia in 4 patients on MARI (2 LTRs)	Antimicrobial stewardship needed to guide appropriate use of maribavir given observed breakthrough infections in SOT recipients.
Sarmiento et al[50]	2005	Case series	5	Heart	IVIG	Detection of CMV antigens	Detection of CMV antigens negative: *n* = 5 (100%)	In HTRs with hypogammaglobulinemia and CMV disease, adding IVIG to antiviral therapy may improve outcomes.
Santhanakrishnan et al[51]	2019	Single-center retrospective study	35	Heart and lung	CMVIg	Reduction in CMV VL	Undetectable CMV VL at 4 weeks: 73%	CMVIg rescue therapy well tolerated and effective at controlling viral replication in CTRs.
Fu et al[52]	2020	Case series	7	Lung	Antiviral therapy (foscarnet, GCV), intravitreal antiviral therapy, leflunomide, CMVIg	Loss of GCV resistance	Loss of GCV resistance: 100%	LTRs with severe, progressive CMV retinitis refractory to other treatment modalities (intravitreal foscarnet, systemic leflunomide) may benefit from multimodal treatment approach including CMVIg.

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Table 2 (*Continued*)

Reference	Publication year	Design	*n*	Transplant type	Intervention	Primary efficacy endpoint	Primary efficacy endpoint measure	Conclusion
Santhanakrishnan et al[53]	2022	Case series	7	Heart and lung	CMVIg ± leflunomide	Reduction in CMV VL	Undetectable CMV VL: *n* = 5 (71.4%)	CTRs with GCV-resistant CMV may benefit from addition of CMVIg with or without leflunomide to guideline-recommended antiviral therapy.
Smith et al[54]	2019	Single-arm, phase I OL study	20	Kidney, lung, heart	In vitro-expanded autologous CMV-specific T cells	Improvement in symptoms, including complete resolution or reduction in VL and CMV-associated end-organ disease and/or the cessation or reduced use of antiviral drugs	Improvement in symptoms: *n* = 11 (84%)	CMV-specific adoptive T-cell therapy safe and may offer therapeutic benefit for SOT recipients with recurrent and/or drug-resistant CMV infection or disease, including CTRs.

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; CMVIg, CMV hyperimmune globulin; CTR, cardiothoracic transplant recipient; GCV, ganciclovir; HTR, heart transplant recipient; IAT, investigator-assigned therapy; IVIG, intravenous immune globulin; LTR, lung transplant recipient; MARI, maribavir; OL, open-label; SOT, solid organ transplant; VL, viral load.

Table 3 Use of CMV-Specific Cell-Mediated Immunity Assays in Cardiothoracic Transplant Recipients

Reference	Publication year	Design	n	Transplant type	Intervention	Primary efficacy endpoint	Primary efficacy endpoint measure	Conclusion
Chiereghin et al[56]	2018	Prospective cohort study	47	Heart	Serial QFN-CMV testing post-transplant	CMV infections after withdrawal of PPX	14.3% (demonstrated CMV CMI) 66.7% (without CMV CMI) [$p = 0.036$]	QFN-CMV assay may be to identify HTRs at increased risk of developing postprophylaxis infection, late-onset CMV and recurrent infections.
Poglajen et al[57]	2020	Prospective cohort study	93	Heart	QFN-CMV-guided PPX	Late-onset CMV infections	7% (PPX continued until CMV CMI achieved) vs 26% (SOC) [$p < 0.05$]	Individualization of CMV PPX, guided by the development of CMV CMI, may reduce post-PPX CMV infections in HTRs.
Westall et al[58]	2019	Prospective cohort study	118	Lung	QFN-CMV-guided PPX	Incidence of CMV infection in allograft within 18 months of LT	37% (PPX continued 5-11 months post-LT if QFN-CMV negative) vs 58% (SOC) [$p = 0.03$]	CMV immune monitoring can be used to individualized CMV PPX, which may reduce late-onset CMV infection within lung allograft
Veit et al[59]	2021	Retrospective review	50	Lung	CMV CMI by ELISpot assay (CMV-IE1, CMV-pp65)	Incidence of late-onset CMV infection	5.3% (positive CMV CMI) vs 35.7% (negative CMV CMI) [OR = 0.05, $p = 0.01$]	Identification of CMV CMI may be used in high-risk LTRs to identify patients at increased risk of CMV infections after LT.
Altaf et al[60]	2021	Prospective study	39	Lung	Pretransplant QFN-CMV	CMV reactivation post-LT	Cumulative risk of CMV reactivation: CMV immune vs non-immune (HR = 4.28; 95% CI, 1.16-15.76; $p = 0.01$).	CMV CMI status can be used to identify LTRs at increased risk of viral reactivation after transplant and guide PPX strategies and monitoring.
Donadeu et al[61]	2021	Retrospective study	60	Lung	CMV CMI by ELISpot assay (CMV-IE1, CMV-pp65)	CMV CMI by ELISpot assay response in patients with late-onset CMV infection	LTRs with late-onset CMV infections had lower (IE-1)CMV and (pp65)CMV responses vs patients without infection ($p = 0.045$; $p = 0.078$)	CMV CMI assays may be useful to categorize risk for late-onset CMV infections after LT.

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Table 3 (*Continued*)

Reference	Publication year	Design	n	Transplant type	Intervention	Primary efficacy endpoint	Primary efficacy endpoint measure	Conclusion
Kumar et al[62]	2017	Prospective study	27	Kidney, liver, lung, multiorgan	QFN-CMV after clearance of CMV viremia	Recurrence	69.2% (negative CMV CMI) vs 7.1% (positive CMV CMI) [$p = 0.001$]	Demonstration of CMV CMI after treatment for CMV viremia conveys lower risk for recurrent infection, highlighting patients without CMV CMI may gain more benefit from secondary prophylaxis after treatment compared to patients with CMV CMI.
Li et al[63]	2023	Prospective study	23	Lung	QFN-CMV and T-Track	CMV replication in serum and bronchoalveolar lavage fluid	28% discordance between QFN-CMV and T-Track QFN-CMV and T-Track were unable to predict viral replication in lung allograft	CMV-specific CMI assays be unreliable for assessment of risk for allograft tissue-invasive disease in LTRs.

Abbreviations: CI, confidence interval; CMI, cell-mediated immunity; CMV, cytomegalovirus; ELISpot, enzyme-linked immunosorbent spot; HR, hazard ratio; HTR, heart transplant recipient; LT, lung transplant; OR, odds ratio; PPX, prophylaxis; QFN-CMV, QuantiFERON-CMV assay; SOC, standard-of-care.

infection. Another single-center study compared 47 HTR who received standard-of-care CMV prophylaxis to 46 HTR who received CMV prophylaxis guided by QuantiFERON-CMV assay.[57] All patients received the center's standard-of-care, 100 days of VGC prophylaxis; patients in the experimental group continued prophylaxis until a positive QuantiFERON-CMV was achieved. The group who received standard-of-care had significantly more late CMV infections (26% vs 7%, $p < 0.05$).

Comparatively more evidence for the use of immune functional assays is available for LTR. A randomized trial of 118 LTR compared 5 months of CMV prophylaxis to variable length (5-11 months) prophylaxis, with duration guided by QuantiFERON-CMV assay results.[58] Patients whose CMV prophylaxis duration was guided by presence of CMV-specific CMI had significantly lower rates of CMV infections (58% vs 37%, $p = 0.03$) and severe viremia (> 10,000 copies/ml; 50% vs 3%, $p < 0.001$). Another study included 50 LTR with high-risk CMV serostatuses (D +/R-).[59] Over half ($n = 31/50$, 62%) of patients developed early-onset CMV infections; after resolution of infection 13 patients developed CMV-specific CMI by ELISpot assay, indicating the infection served as an immune priming event. As patients were followed further after transplant, the development of CMV-specific CMI was found to be protective against late-onset CMV infections (OR = 0.05, $p = 0.01$). A prospective study of 39 LTR highlighted the importance of pretransplant CMV-specific CMI testing alongside IgG serostatus to adequately assess risk of reactivation and disease after transplant.[60] Among seropositive patients, patients without CMV-specific CMI by QuantiFERON-CMV assay had a significantly higher risk of reactivation post-transplant compared to patients with CMV-specific CMI ((hazard ratio) HR = 4.28; 95% (confidence interval) CI, 1.16-15.76; $p = 0.01$). Patients without CMV-specific CMI also had significantly higher peak viral loads ($p = 0.03$). A retrospective study including 60 CMV seropositive LTR evaluated CMV-specific CMI by ELISpot assay.[61] Patients with the lowest levels of viral replication demonstrated numerically higher responses to IE-1 and pp65 antigens. Patients with late-onset CMV infections or high viral loads had significantly lower responses to IE-1 and pp65 antigens. LTR were also included in an interventional study of 27 SOT recipients with CMV viremia who underwent CMV-specific CMI testing after clearance of viremia.[62] Patients with negative CMV-specific CMI response received secondary prophylaxis for 2 months. However, patients without CMV-specific CMI had higher rates of recurrence compared to patients with CMV-specific CMI (69.2% vs 7.1%, $p = 0.001$). Notably, recent literature suggests that CMV-specific immunity assays may be limited to predicting viremia and not accurately convey risk for viral replication within the transplant lung(s).[63]

This evidence in CT recipients suggests that immune functional assays can be highly impactful clinical tools to identify patients at higher risk of developing postprophylaxis, late or recurrent infections, as well as patients who are at lower risk of CMV infections and may not require prolonged primary and/or secondary prophylaxis. Additional data in LTR are expected

from the ongoing CYTOCOR STUDY, a noninferiority trial in which a reduced duration of prophylaxis coupled with CMV-specific immunological monitoring will be compared to standard-of-care (prophylaxis then preemptive therapy) in 150 CMV-seropositive LTR.[64] This study will offer valuable insights to guide the adoption of a hybrid CMV prophylaxis model utilizing CMV-specific CMI testing in cardiothoracic and all SOT recipients.

Underlying the utilization of immune functional assays and the detection of CMV-specific CMI is the ability to develop such an immune response. A myriad of factors play a role in determining whether a patient cultivates CMV-specific CMI. Hematologic conditions, such as neutropenia and leukopenia, convey an increased risk of infection; an absolute lymphocyte count over 610 cells/ul has been proposed to convey protection against CMV,[65] which may be due to the ability to mount and maintain CMV-specific CMI. Older age (> 50 years) may reduce the ability to develop CMV-specific CMI,[66] possibly due to immunosenescence of advancing age. Patients must have sufficient T cell activity despite ongoing therapy with multidrug immunosuppressive regimens including drugs that target T-cell function, such as CNI. An immune priming event is required to develop CMV-specific CMI, which can occur pre- or post-transplant. Antiviral exposure is also a crucial element for formation of CMV-specific CMI. GCV derivatives are highly effective at preventing CMV replication, but do not facilitate the development of CMV-specific CMI due to additional immunosuppressive properties and complete prevention of replication.[67] This has been corroborated in CT by a real-world experience of LTR that observed seronegative patients were unlikely to develop CMV-specific CMI while on a GCV-based prophylaxis regimen.[68] On the contrary, LTV may facilitate CMV-specific CMI development by creating an immune priming event with late-stage inhibition of viral replication through the terminase complex and absence of myelosuppressive effects, as demonstrated in abdominal transplant recipients.[42] These factors must be taken into account and optimized as able to improve the patient's ability to develop CMV-specific CMI, which is vital for the control of viral replication without antiviral therapy.

Limitations to implementation

While CMV AVS programs have been shown to be effective in improving the prophylaxis and treatment of CMV in SOT, centers wishing to implement such programs must be aware of possible barriers and limitations.[15] Among these, availability of resources, management support of dedicated AVS time and buy-in from key stakeholders remain the most significant. Addressing these obstacles during program initiation will help set the AVS program up for success and prevent interruptions in services as the program grows and expands.

Implementation and ongoing management of a CMV AVS program require dedicated resources to be successful. As the CMV AVS program enlarges, so must its support structure of dedicated personnel. The CMV AVS initiative requires prospective audit and feedback to impact prescribing, as use of GCV derivatives is typically not restricted. Review and management of patients enrolled in the AVS program must be timely to maximize patient benefits. Anticipation and identification of high-risk patients are crucial to a program's success. Studies have demonstrated that initiating CMV treatment early with lower viral loads is correlated with quicker clearance of viremia and lower chance of CMV-related complications.[69] This may be especially true in CT recipients who are at increased risk for poor outcomes. The CMV AVS pharmacist must be able to review labs, determine if treatment is necessary, and initiate treatment quickly to prevent delays in therapy. In rural settings, the importance of timely therapy initiation may be heightened due to lag times in CMV viral load reporting which can be up to 1 week, depending on the laboratory and location.

This ideal CMV AVS would have sufficient staffing to meet the prospective nature of the program's needs, with the opportunity for an increase in dedicated time as the program expands. Consistently scheduled, dedicated time to AVS tasks must be approved and supported by management to maximize the benefit of the program. While it can be difficult to demonstrate the true value of a CMV AVS program, frequent review of QI processes and protocol evaluation can help ensure program goals are being met. This is particularly true in the CT population, where the impact of the CMV AVS is not as well defined.

Finally, a successful CMV AVS program requires buy-in from key stake holders, particularly the CT providers. The CMV AVS program should by multidisciplinary and include experts in transplant infectious diseases, transplant pharmacy, transplant medicine, and transplant surgery. Collaboration among these specialties during development of protocols and center-specific guidelines can help identify and address concerns preemptively. Consistent practices among the CMV AVS program allow for easier review of program outcomes and clearer identification of program benefits, which should be reviewed frequently. The CMV AVS program is uniquely poised to spearhead both these reviews and lead changes in protocols if goals are not being met or areas for improvement are identified.

Conclusions

Based on the allograft-specific effects of CMV in the setting of cardiothoracic transplantation, this population likely will benefit more than abdominal transplant recipients with the use of CMV AVS initiatives to improve judicious use of antiviral therapy thus decreasing the impact of viral complications on both the patient and the graft. Through implementation of organ-specific prophylactic, treatment, and monitoring algorithms, the nuances of HT and LT can be addressed without compromising care of the transplanted organs or patient and the focus can be shifted from antiviral therapy, to fostering the development of CMV-specific CMI and improving long-term outcomes.

Disclosure statement

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