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Review

The development and implementation of stewardship initiatives to optimize the prevention and treatment of cytomegalovirus infection in solid-organ transplant recipients

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Abstract

Classical stewardship efforts have targeted immunocompetent patients; however, appropriate use of antimicrobials in the immunocompromised host has become a target of interest. Cytomegalovirus (CMV) infection is one of the most common and significant complications after solid-organ transplant (SOT). The treatment of CMV requires a dual approach of antiviral drug therapy and reduction of immunosuppression for optimal outcomes. This dual approach to CMV management increases complexity and requires individualization of therapy to balance antiviral efficacy with the risk of allograft rejection. In this review, we focus on 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. These initiatives have the potential not only to improve judicious use of antivirals and prevent resistance but also to improve patient and graft survival given the interconnection between CMV infection and allograft function.

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Antimicrobial stewardship programs (ASPs) are a coordinated effort that improves patient outcomes through appropriate antimicrobial use, reduction of unnecessary exposure, and resistance mitigation.[1,2] Historically, stewardship efforts targeted immunocompetent patients due to lack of provider comfort, potential for more severe sequelae of infection, atypical clinical presentation, and lack of data in immunosuppressed patients. However, appropriate use of antimicrobials in the immunocompromised host has become a target of interest.[3,4] Antibiotic therapy in the immunocompromised host is a natural application of stewardship aims. However, initiatives targeting antiviral therapy, particularly as they pertain to the prophylaxis and treatment of cytomegalovirus (CMV) in abdominal solid-organ transplant (SOT) recipients, should not be overlooked. Response to antiviral therapy is dependent on the net immunosuppressive state.[5] Treatment of CMV requires a dual approach of antiviral drug therapy and reduction of immunosuppression for optimal outcomes. This dual approach to CMV management increases complexity and requires individualization of therapy to balance antiviral efficacy with rejection risk. Additionally, antiviral agents are not spared from the issues that resulted in the rise of ASPs; namely overuse, misuse and resultant resistance, toxicity, and poor outcomes. Although resistance to the drug of choice, ganciclovir (GCV) and its oral prodrug valganciclovir (VGC) has been historically low, it is now increasingly common and difficult to manage, and available alternatives and pipeline agents are minimal.[6,7] Finally, in the setting of SOT, success of treatment is not simply patient survival; the effects of disease and resultant immunosuppressive modulation on the functional longevity of the allograft are also paramount. In this review, we discuss the need for CMV stewardship initiatives within ASPs for the treatment and prevention of CMV, and we highlight unique aspects of CMV stewardship and reflects on insights gained from our experience with initiating and maintaining a CMV stewardship initiative at a large transplant center.

The health and economic burden of CMV disease

The negative impact of CMV infection on SOT outcomes has been well demonstrated. Despite improvement in antiviral drug therapies and implementation of universal prophylaxis strategies, CMV continues to negatively affect both short- and long-term graft and patient survival.[11,12] CMV is a ubiquitous herpes virus present in 40%–70% of the population.[13] After primary exposure, the virus enters lifelong latency via immunoevasion, with a predilection to myeloid cells.[14] In the setting of iatrogenic immunosuppression, viral reactivation and disease can occur. Response to CMV infection is highly dependent on cellular immunity, particularly CD4 and CD8 T cells.[15] Patients without previous exposure (seronegative, R−) who receive allografts from exposed donors

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Table 1. Recurrence Risk Factor Screening Protocol[a]

When CMV PCR is <LLOQ patients will be screened for transition to secondary prophylaxis (900 mg daily × 3 months, renally adjusted) vs discontinuation of therapy 1. Secondary prophylaxis WILL be given per protocol if a patient has at least one high risk factors for recurrence 2. Secondary prophylaxis will be considered if a patient has any of the moderate risk factors for recurrence. Plan should be discussed with provider
Strong predictors of recurrence
Multiple previous recurrences of CMV infection/disease (≥3 distinct episodes)
Concurrent treatment of rejection
Inability to effectively reduce maintenance immunosuppression
Moderate predictors of recurrence
Tissue invasive disease
Primary CMV infection in a seronegative recipient of a seronegative donor (D-/R-)
CMV infection in a pancreas transplant recipient with a functional pancreas allograft
High initial viral load (>100,000 IU/mL)
Slow reduction or persistent low level viremia on treatment
CMV D+/R− with lack of seroconversion at completion of therapy

Note. CMV, cytomegalovirus; PCR, polymerase chain reaction; LLOQ, lower limit of quantification.
[a]Adapted from Kotton et al[18] as well as expert opinion from the CMV Task Force at the University of Wisconsin Hospital and Clinics.

(seropositive, D+) are at the highest risk of severe CMV infectious sequelae due to lack of learned immunity resultant of primary infection. The treatment of choice for CMV is intravenous ganciclovir (GVC) and/or its oral prodrug valganciclovir (VGC). VGC has significantly improved bioavailability over oral ganciclovir with comparable efficacy, and its market availability improved the efficiency of CMV prophylaxis after SOT.[16] However, VGC is associated with significant toxicity and high cost. Additionally, and most concerning, ganciclovir-resistant (GR)-CMV disease is emerging, with an overall incidence of 5%–12%.[6] GCV resistance is associated with significant morbidity and mortality, with literature describing rates of virologic failure and recurrence from 20% to 30%, 50% rejection incidence, 27% graft loss, and 20%–30% mortality following GR-CMV disease.[7] Treatment options for GR-CMV are limited and are associated with significant cost burden and toxicity. Indeed, a 10-fold increase in total hospital admission costs has been reported for GR-CMV–related infection and disease compared with wild-type CMV (US$200,000 vs US$20,000; $P < .01$).[17]

CMV stewardship need

Improvement is needed in the prophylaxis and treatment of CMV after SOT, making it a natural extension of the principles of antimicrobial stewardship to the immunocompromised host. The clinical issues and associated burden of CMV infection have been well described, and thr management of CMV after SOT is complex.[18–30] The drug of choice has a narrow therapeutic index, and alternatives require careful patient selection.[31–33] Adding complexity is the central role of cell-mediated immunity in successful treatment of CMV, requiring immunosuppressive modification and increasing risk of rejection.[5,7,34,36] Clinical suspicion for disease and timing after transplant also play an important roles.[37–42] The risk associated with inappropriate or mismanaged prophylaxis and treatment is significant and can have lasting impact on both patient and graft survival. Novel antiviral agents are few, and the incidence of CMV and GR-CMV continues to rise. Additionally, the population potentially impacted by CMV continues to expand as the number of patients receiving and living with SOTs grows daily.[43]

The following sections describe the elements that we feel are essential to the development of a CMV stewardship initiative as well as potential challenges, opportunities and future directions, based on our center-specific experience with the creation of a CMV stewardship program.

Essential elements of CMV stewardship initiative

Implementation of CMV guidelines adapted to local context by local experts

Consensus guidelines exist summarizing expert opinion and evidence-based treatment of CMV.[18,45] However, variations in patient populations and center-specific immunosuppressive protocols require local adaptation of these guidelines for a center-specific CMV stewardship protocol. Stakeholder and expert buy-in are paramount to providing consistent, evidence-based recommendations. Prophylaxis modalities must be selected to appropriately align with the patient population at each transplant center. For example, for centers with a local patient base, a central local laboratory, and a large seropositive population may be best suited for a preemptive monitoring (PEM)–based approach. In contrast, universal prophylaxis may be preferred at centers with an SOT population that is remote given the magnification of the challenges of PEM in this population. Another example highlighting local adaptation of consensus guidelines is the recent transition away from the use of secondary prophylaxis after treatment to a risk-based model. Our CMV stewardship team has been integral in incorporating this major shift in guideline-based practice through the creation of high-risk recurrence criteria (Table 1) and the implementation of these practices. Additionally, approaches to treatment thresholds, intravenous-to-oral transitions, the use of CMV cell-mediated immunity (CMI) assays and criteria for resistance testing should be outlined to avoid extraneous and expensive laboratory testing as well as potentially unnecessary drug utilization or hospital admission. These guidelines should be developed and intermittently reviewed for quality improvement opportunities by an identified champion group including transplant surgeons, medical transplant physicians, infectious disease physicians, and clinical pharmacists (ie, a CMV task force).

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Inclusion of institutional stakeholders

The CMV stewardship team should include a pharmacist and stewardship physician. The stewardship physician should be a transplant infectious disease physician, or physician team, with appropriate knowledge base and interest in the program and ability to respond quickly to the stewardship pharmacist for patient care guidance. This physician must receive adequate financial and protected worktime support to function in this role. Given the complexity of CMV stewardship, the pharmacist involved in the CMV stewardship initiative should have broad clinical knowledge of transplant pharmacology, including immunosuppressive medications and the care of the transplant population. Interest and experience in infectious disease are also needed because the interplay between immunosuppressive agents, antivirals, the immune system and viral replication kinetics is complex.

The CMV stewardship initiative, which incorporates antivirals and immunosuppressive agents, is unique in its scope. Therefore, guidelines and monitoring protocols must be endorsed by the transplant division and by key transplant stakeholders. The inclusion of these key players as active members of the stewardship team is paramount because decisions that could improve CMV infectious outcomes must be weighed against the potential impact on the allograft. With all transplant subspecialties being involved in creation and approval of the guiding documents, awareness of the program is increased, and disparities and disagreements in care can be avoided.

Time commitment and allocation of dedicated resources

Current literature describing CMV stewardship initiatives have focused on either treatment or prophylaxis of CMV, and interventions mostly focus on appropriate dosing of GCV derivatives.[46,47] We believe that appropriate allotment of resources can expand the scope of CMV stewardship and thereby address the current clinical need.[48] When designing our center-specific initiative, we did not limit scope, which resulted in identification of a multitude of stewardship targets. As has been stressed in the creation of ASPs, allotment of dedicated resources is crucial to the success. Due to the complexity, time spent in pharmacist evaluation is significant, and previously conducted time studies of ASPs in immunocompetent patients may not be accurate or applicable.

Prospective audit and feedback and the EMR

Stewardship recommendations are best made at the time of patient assessment and ordering of the drug.[2] Prospective audit and feedback between care settings is challenging and requires mechanisms to track patients and to ensure therapeutic monitoring is present, timely, and includes key stakeholders. Utilization of the EMR for this function can streamline prospective audit and documentation in the medical record. At our institution, we have been able to successfully identify, enroll, and track patients with antiviral needs requiring stewardship by employing functionality provided in our base EMR. Through development of clear inclusion criteria for enrollment in the CMV stewardship program, transplant pharmacists in both the inpatient and outpatient setting can capture qualifying patients. An example of the inclusion–exclusion criteria used in our program can be found in Table 2. The pharmacist coordinates interventions using delegation protocols based on local guidelines and consults the transplant infectious disease physician for complex patients where the guideline and the protocol do not apply.

Interventions identified by the CMV stewardship pharmacist must be communicated to the care team in a timely fashion. Utilization of the EMR allows for rapid correspondence to the multidisciplinary care team while also allowing documentation in the patient chart. Challenges may arise at centers where transplant care is not centralized, and these should be addressed early in program development.

Dose optimization

A critical goal of CMV stewardship is ensuring appropriate dosing of VGC to avoid toxicity from overdosing, treatment failure, or viral resistance. Fluctuations in renal function early after transplant surgery make close monitoring and tracking of at-risk patients at regular intervals critically important.

Dose optimization goes beyond strict adherence to package insert dosing, which further highlights the need for a dedicated transplant pharmacist. Knowledge base and insight to anticipate ongoing changes in renal function, paired with overall risk of drug toxicity and risk of CMV infection are paramount. The pharmacist must be aware of potential limitations in manufacturer dose suggestions in patients of very large or small stature.

Finally, the risk–benefit of aggressive dosing must be weighed at important clinical transition points. Some studies suggest that rapid viral clearance kinetics are associated with improved outcomes of CMV infection and reduced rates of recurrence.[28] Brief periods of aggressive dosing paired with immunosuppressive reduction may result in rapid clearance of initial viral load and may help patients with persistent viremia clear the virus, thus improving CMV outcomes. Further research is needed in this area.

Measuring performance

The impact of the CMV stewardship must be assessed at regular intervals, with a focus on quality improvement. Given the longitudinal nature of CMV treatment, the creation of monitoring programs will provide further insight into the prevention and treatment of CMV after SOT. Members of a CMV stewardship team will be poised to study unique aspects of CMV care and address unanswered questions regarding management. When designing the CMV stewardship initiative, the creation of electronic tools to allow for retrospective evaluation of practices, quality review, and care efficiency should be individualized to optimize care at each transplant center. Additionally, measurable outcomes are necessary to demonstrate value and ongoing support for the program.

It is unlikely that CMV stewardship will have the same immediate and significant impact in cost savings as the antibacterial efforts of ASPs in immunocompetent hosts.[49] Identification of issues may falsely skew outcome data to reflect increases in CMV infection after program initiation. However, this will also eliminate the "low-hanging fruit" conundrum many ASPs face when trying to demonstrate need for ongoing stewardship. Reduction in CMV complications will result in improvement in patient and graft survival, and it could even improve national transplant program ratings.

CMV therapy and management: Challenges and opportunities

Diagnostics

Improvement in interlaboratory variability in CMV viral load quantification are needed to improve comparability.[18] Despite

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Table 2. Cytomegalovirus (CMV) Antiviral Stewardship Pharmacist Monitoring and Interventions

Enrollment Criteria	Lab Test Monitoring	RPh Interventions
Weekly RPh review will occur for the following:		
Preemptive monitoring	• SCr/CrCL, WBC per SOC • CMV PCR weekly	If CMV PCR >500 IU/mL, start VGC treatment and contact provider. When CMV PCR <LLOQ stop VGC and resume preemptive monitoring for predetermined duration of therapy. If ppx period has closed, complete 3-PCR rule-out protocol
Every 2 weeks, RPh review will occur for the following:		
Leukopenia with WBC < 2 K/uL	• SCr/CrCL per SOC • WBC < 2 K/uL: CBC with differential weekly until WBC > 2 K/uL then every 2 weeks	If ANC < 1,000 cells/min^3: -Prophylaxis: evaluate marrow-suppressive medications including immunosuppression, patient-specific factors for potential switch to preemptive monitoring; discuss with provider -Treatment: contact the provider, consider addition of granulocyte colony stimulating factor and immunosuppressive adjustment
Active disease or infection	• SCr/CrCL per CrCl monitoring frequency • CMV PCR weekly • WBC monthly (or more frequently if WBC <2)	Treat until CMV PCR <LLOQ. At this point patient will be screened for secondary prophylaxis.
Lymphocyte-depleting induction with high-risk serostatus OR weight extremes	• SCr/CrCL & WBC every 2-4 weeks per SOC and stability	If weight>100 kg, doses should be aggressive for renal function. If weight <50 kg, doses should be conservative for renal function.
CrCl < 60 mL/min	• SCr/CrCL weekly every 2-4 weeks per SOC and stability WBC monthly (or more frequently if <2 K/uL)	Renal dose adjustments made for VGC 2 consecutive lab values at new dosing category required for dose adjustment
Monthly RPh review will occur for the following (unless patient meeting other stricter criteria):		
High-risk serostatus with lymphocyte depleting induction OR weight extremes OR secondary prophylaxis with VGC following active disease or infection	• SCr/CrCL, WBC per SOC	Adjust to weekly monitoring if indicated by lab results
RPh monitoring will be discontinued:		
Active disease or infection	Once patient has completed secondary prophylaxis OR if CMV PCR <250 for 3 weeks after discontinuation of VGC treatment and no secondary prophylaxis	
Leukopenia	Once WBC is >2 K/uL for >2 consecutive readings & not meeting other enrollment criteria	
Lymphocyte depleting induction with high risk serostatus OR high-risk serostatus with weight extremes OR preemptive monitoring	Once prophylaxis /preemptive monitoring duration is completed	
CrCl <60 mL/min	Once prophylaxis duration is completed OR CrCl stably > 60 mL/min for 3 weeks OR dose is unchanged for at least 8 weeks and not meeting other enrollment criteria	

Note. RPh, pharmacist; WBC, white blood cell count; SOC, standard of care; LLOQ, lower limit of quantification; ANC absolute neutrophil count.

the introduction of the World Health Organization (WHO) international standard, PCR results can vary significantly between laboratories due to a number of factors including amplification target, extraction methods, probe, amplicon size, and other factors.[50,51] This variation results in diagnostic and clinical management challenges, particularly as they pertain to initiation and discontinuation of antiviral treatment. The CMV stewardship team can aid in the delineation of appropriate treatment and/or the need for repeat testing based on concomitant clinical factors. Additionally, the sensitivity of currently available molecular diagnostics assays varies. Laboratories have, with increasing frequency, highly sensitive assays with the ability to quantify CMV viral loads to 35 IU/mL. The clinical significance of these low-level values is unknown, and clinical concern varies based on specific patient factors such as serostatus at transplant, current immunosuppressive regimen, indication for testing and the presence of symptoms. These highly sensitive assays also complicate duration of treatment, particularly in light of guideline recommendations to end therapy at the achievement of a viral load less than the lower limit of quantification (<LLOQ). This change to a relatively nonspecific therapy transition point can lead to vast differences in treatment duration. These inconsistencies in practice can be improved with a CMV stewardship initiative.

Antiviral use

Transplant practitioners are acutely aware of the negative impact of CMV on patient and graft outcomes; therefore, they are often quick to treat a positive result. However, the risk of antiviral toxicity and exposure predisposing to resistance should factor into the

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treatment decision. Isolation of bacteria in culture should not result in reflex antimicrobial use, and detectable CMV replication does not always necessitate antiviral therapy. Reduction in unnecessary testing and surveillance outside guideline-endorsed practice could reduce inappropriate antiviral use and its consequences. Utilizing prospective audit, CMV stewardship initiatives can preemptively assess results of molecular diagnostic testing and provide guidance.

Immunosuppressive management

CMV infection after SOT is a result of the immunosuppressed state required to support the allograft. However, there is minimal literature describing how best to modify immunosuppression in the setting of CMV infection. Although some small studies have evaluated the effect of immunosuppressive reduction at time of infection,[5,34] no guidance is available on titration after infection resolution. CMV stewardship initiatives should focus on this aspect of CMV treatment and bridging current knowledge gaps.

Emerging developments and future directions

The future of CMV therapy will likely focus on measurement and enhancement of the CMV-specific immune response. Recent literature suggests that the major outcome driver in CMV infection is CMV-specific immunity and reconstitution of these responses, not antiviral therapy.[52] As the pathogenesis of CMV infection relies on dysfunctional T cells, a number of assays designed to measure the degree of CMV cell-mediated immunity (CMI) have developed. The literature suggests that these assays could be used in risk stratification protocols to provide targeted therapy. This strategy could reduce antiviral exposure, and thus, toxicity and resistance. To date, the lack of a test with adequate predictive potential has limited this approach.[53,54] However, recent prospective multicenter studies utilizing newer enzyme-linked immunosorbent spot (ELI-Spot)–releasing assays have been successful in predicting future CMV risk in the prophylactic setting.[55,56] How these assays can be used in treatment and the transition from treatment to secondary prophylaxis has yet to be established.

Passive immunity utilizing intravenous immunoglobulin has been a longstanding component of the treatment of CMV infection.[57] Monoclonal antibodies active against CMV are also actively being explored.[58] While immunity via vaccination has been investigated, inherent limitations in immunostimulation in the transplant population has resulted in minimal success to date.[59] Given the success of chimeric antigen receptor T cell (CAR-T) therapy in treatment of malignancy, there has been increasing interest in a similar model of adoptive transfer of immunity utilizing engineered CMV specific T cells to treat CMV infection. This therapy has been successful in the stem cell transplant population and is being actively investigated in SOT recipients, with positive outcomes to date.[60,61]

These immune-dependent monitoring strategies and immunomodulatory treatment modalities will only further complicate the prevention and treatment of CMV after SOT. The CMV AVS will be integral in successful utilization of these new clinical tools and in measuring their impact on patient outcomes.

In conclusion, development and implementation of a CMV stewardship initiative has the potential not only to improve judicious use of antivirals but also to improve patient and graft survival. Given the interconnection between CMV infection and graft survival, the limited nature of the donor pool, and the lack of potent antivirals either clinically available or in the pipeline, CMV stewardship is an important extension of antimicrobial stewardship practices within the immunocompromised host. Institutional variation in transplant immunosuppressive protocols, laboratory differences in testing methods, as well as regional variance of recipient CMV serostatus all necessitate adaptation of guideline based practice to center-specific transplant populations. Adequate allocation of staffing resources is essential given the increased complexity of CMV stewardship. Input and buy-in from key stakeholders in infectious disease and transplant is necessary throughout the development of the stewardship initiative. Based on our experience, a successful CMV stewardship initiative is highly dependent on an orchestrated effort requiring engagement from a multidisciplinary team as well as end-user consensus. In addition, an effective method of tracking patients and documenting interventions is needed to ensure timely management. An integrated method is preferred given the increased transparency over external tracking and documentation systems. Finally, demonstration of value to hospital administrators through reduction in healthcare costs will help justify the initiative; however, improvement in patient and graft outcomes is the ultimate goal.

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