

Cytomegalovirus Infection After Kidney Transplantation: From Recent Guidelines to Feasible Strategies in Resource-Limited Settings _____

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Abstract

Cytomegalovirus (CMV) remains one of the most frequent and clinically relevant opportunistic infections after kidney transplantation. Its importance is related not only to direct viral effects, including asymptomatic viremia, CMV syndrome and tissue-invasive disease, but also to indirect immunomodulatory effects that may contribute to acute rejection, graft dysfunction and other opportunistic infections. In recent years, CMV management has progressively moved toward a more individualized and risk-adapted approach, based on donor and recipient serostatus, net status of immunosuppressive therapy, recipient-related risk factors, quantitative viral-load monitoring and early recognition of refractory or resistant disease.

Current guidelines provide a detailed framework for prevention, diagnosis and treatment of CMV after solid organ transplantation. However, their application may be difficult in resource-limited settings, where access to standardized real-time quantitative PCR, repeated viral-load monitoring, rapid laboratory reporting, antiviral drugs and resistance testing may be limited. In this context, kidney transplant programs need feasible strategies able to translate guideline recommendations into daily clinical practice.

This review summarizes the clinical impact of CMV after kidney transplantation, focusing on risk stratification, diagnostic monitoring, prevention strategies, treatment of CMV infection and disease, antiviral resistance and toxicity. Particular attention is given to the practical management of CMV in resource-limited settings. In these contexts, CMV care should be based on a structured but adaptable approach, integrating donor-recipient serostatus, net state of immunosuppression, clinical presentation and locally available diagnostic resources. A practical risk-based algorithm may help clinicians identify patients who require universal prophylaxis, closer viral monitoring or early therapeutic intervention, improving CMV management while considering real-world limitations.

Key Words: *Cytomegalovirus Infection (CMV), Kidney Transplantation, Immunosuppressive therapy, CMV prophylaxis, resource limited-setting*

Introduction

Cytomegalovirus (CMV) is a double strand virus with widespread prevalence among the general population. It is estimated that around 60-90% of people get infected during their lives, with higher prevalence in developing countries (1,2).

CMV has different transmission routes including horizontal transmission through blood, saliva, urine, organ transplantation and vertical transmission through placenta and potentially breast-feeding.

In immunocompetent individuals first infection is characterized by self-limiting primary replication, which can be asymptomatic or associated with mild flu-like syndrome, followed by a latent, non replicating infection in CD34+ cells. As it represents a globally widespread infection most people result immunized with positive IgG; therefore previous exposure does not assure long-last protective immunity but can reduce the risk of reinfection and severe disease.

In immunodepressed patients, both reactivation and primary infection can be severe and lead to tissue invasive disease with life threatening complications.

In kidney transplant, CMV remains one of the most frequent and relevant viral infections associated with direct and indirect effects. It may present with asymptomatic viremia, general systemic manifestations such as fever, arthralgia, asthenia, or tissue invasive disease. In this case nearly every organ can be involved but most frequent complications are colitis, myocarditis, ground-glass pneumonia, encephalitis and uveitis (3,4). In addition to these direct effects there are some indirect effects of CMV mediated by its immunomodulatory properties which may contribute to acute rejection, rise of other opportunistic infections and Epstein-Barr virus (EBV) associated Post-Transplant-Lymphoproliferative Disease (PTLD)(3-5). For this reason CMV careful management represents a cornerstone in post-kidney transplant management.

Diagnostic evaluation of CMV in kidney transplant management is spread over two levels. Before kidney transplant it is crucial to define serological status of both donor and recipient in order to assess the associated risk. Based on donor/recipient immunological status there are two main strategies to prevent CMV infection or reactivation: universal prophylaxis with an antiviral drug used for a certain amount of time and pre-emptive therapy consisting in close monitoring of CMV replication and start of treatment after a certain threshold. After kidney transplant real time quantitative PCR for the determination of CMV DNA is the gold standard to monitor, diagnose and evaluate therapy's response to CMV disease. It is important to emphasize that since CMV is a virus with potential multiorgan tropism it may affect every organ posing an important diagnostic challenge in post-transplant management.

CMV therapy is based on modulation of immunosuppressive therapy and the use of antiviral drugs that inhibit viral replications. It may be used as prophylaxis or treatment of well established infection or disease but requires a careful balance between antiviral efficacy, nephrotoxicity and rejection risk.

Prophylactic use aims to prevent replication in high risk patients, particularly D+/R- status, patients treated with thymoglobuline for post-transplant induction, HIV+ patients, or those who underwent desensibilization or treatment for

acute rejection. In this context oral Valganciclovir is the preferred agent with close monitoring of CMV DNAemia, renal function and evaluation of gastrointestinal adverse effects. In the last years Letermovir has emerged as an alternative prophylactic agent, particularly in high-risk patients or in those with valganciclovir-related myelotoxicity.

Therapeutic use is required in clinically significant infection where oral Valganciclovir is preferred for mild to moderate disease while intravenous Ganciclovir is preferred in severe or invasive disease.

Antiviral resistance is present in 1-5% of cases and must be suspected in case of rising or persistence of CMV DNA despite appropriate dose therapy and adequate compliance. Risk factors for resistance are long-term exposure to low dose antiviral drugs, D+/R- status and high or repeated immunosuppressive treatment. It must be suspected if CMV replication starts during prophylaxis or CMV viremia persists after 6 weeks of treatment. When available it is possible to test for viral genetic mutations that induce drug resistance by inhibiting drug phosphorylation particularly in UL54 and UL97, which codes for two crucial proteins in viral replication.

In confirmed cases of antiviral resistance first is important to reassess immunosuppressive intensity, drug levels and compliance. In confirmed antiviral resistance to first line therapy, alternative agents such as Foscarnet, Cidofovir and Maribavir are available although their use is limited by high nephrotoxicity, elevated cost and availability.

Recent guidelines for CMV management in solid organ transplantation emphasizes a more individualized and risk-adapted approach based on serologic status, immunosuppressive intensity, standardized viral testing, personalized use of new antiviral agents as Letermovir and Maribavir for prophylaxis in patients with risk factors (6).

Although these guidelines provide a comprehensive and personalized framework for CMV management, their implementation in resource-limited setting remains challenging where access to molecular tests, frequent monitoring and use of new antiviral drugs isn't yet fully implemented.

Methods

This article is a narrative review prepared in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) criteria. PubMed/MEDLINE and Scopus were searched for English-language literature on cytomegalovirus in solid organ and kidney transplantation, combining the terms “cytomegalovirus,” “kidney/renal transplantation,” “prophylaxis,” “pre-emptive therapy,” “viral load / PCR monitoring,” “antiviral resistance,” and “resource-limited settings.” Priority

was given to current international consensus guidelines and recent studies, complemented by foundational references identified through citation tracking. Studies were selected and interpreted by the authors by consensus according to their relevance to risk stratification, diagnosis, prevention, treatment, and the feasibility of CMV care in resource-limited kidney transplant programs.

Clinical Impact of CMV after Kidney Transplantation

CMV burden in kidney transplant remains relevant despite advances in diagnosis, prevention and treatment. The wide spread of clinical manifestation associated with CMV is due to its capability to infect a large variety of cells thanks to a broad spectrum of surface proteins present in the viral envelope.

A key distinction is between CMV infection, which means the presence of viral replication, and CMV disease when viral infection is associated with systemic symptoms or tissue invasive disease. Nonspecific constitutional symptom may present as fever, malaise, fatigue, arthralgia, swollen lymph nodes, tonsillitis, splenomegaly often associated with hematological abnormalities such as leukopenia, thrombocytopenia and mild hepatic enzyme elevation (6,7)

Although tissue-invasive disease may involve nearly every organ system, in kidney transplant recipients, the most frequent clinical manifestation is gastrointestinal involvement. It may present as abdominal pain, dysphagia, diarrhea, vomiting and can be caused by esophagitis, enteritis and/or colitis. Diagnosis often requires endoscopic evaluation with histological confirmation since CMV viremia may be low (6,8).

Other tissue-invasive manifestations are less common but clinically relevant. CMV hepatitis is characterized by elevation in liver enzymes in absence of any other cause. CMV pneumonia may present with fever, cough, respiratory distress associated with ground-glass pattern on CT scan plus CMV detection in bronchoalveolar lavage fluid. Guillain-Barré syndrome may be the first manifestation of CMV encephalitis and anterior uveitis may also present in late stages. Myocarditis and pericarditis are rare but also potentially severe presentations(6,7). In addition a direct involvement of kidney allograft, also mentioned as CMV nephritis, has been described in the presence of histologic features, mostly as collapsing focal segmental glomerulonephritis, resulting in progressive deterioration of renal function (9,10).

Accordingly, CMV should always be considered whenever aspecific systemic symptoms or organ dysfunction occur in the presence of the rise of active viral replication.

TABLE 1. CMV effects and clinical manifestations after kidney transplantation [3–10].

Effect / category	Clinical features
Direct — viremia / CMV syndrome	Asymptomatic viremia; fever, malaise, fatigue, arthralgia, lymphadenopathy, tonsillitis, splenomegaly; leukopenia, thrombocytopenia, mild hepatic enzyme elevation
Direct — tissue-invasive, gastrointestinal (most frequent)	Esophagitis, enteritis, colitis: abdominal pain, dysphagia, diarrhea, vomiting; often requires endoscopy with histological confirmation
Direct — other organs	Hepatitis; pneumonia (ground-glass pattern + BAL detection); encephalitis (may present as Guillain-Barré); uveitis; myocarditis/pericarditis (rare); CMV nephritis (collapsing FSGS)
Indirect (immunomodulatory)	Acute rejection and graft dysfunction; increased risk of other opportunistic infections; EBV-associated PTLD

Risk Stratification: Serostatus, Immunosuppression, and Host Factors

Risk stratification represents the first step in CMV management after kidney transplant and should guide the choice between prophylaxis and a pre-emptive approach.

It is based on immunologic status of both donor and recipient, the intensity of immunosuppressive therapy and the presence of secondary host factors such as concomitant transplant or infections.

Immunological status of both donor and recipient represent the strongest predictor of CMV infection and must be defined before kidney transplant through serology in order to assess the risk of transmission and reactivation. The most risky case is when the donor is positive for CMV-IgG while the recipient is negative (D+/R-) as the transplant procedure itself may become a new route of transmission with primary disease in the immediate post-transplant time (6,11).

The overall state of immunosuppression is also an important aspect of risk stratification and relies on type, intensity and frequency of induction and maintenance therapy used during transplant. In induction therapy lymphocytes T depleting agents such as rabbit anti-thymocyte globulin (rAtg) or Alemtuzumab induces a strong and prolonged lymphocyte depletion, thereby increasing susceptibility to CMV complications compared to non-depleting agents such as antiCD25 monoclonal antibody known as Basiliximab(6,12). Long-term maintenance therapy also plays an important role in CMV risk after kidney transplant. Widely used combination of prednisone, calcineurine-inhibitor and Mofetil Mycophenolate may increase susceptibility to CMV replication. Conversely, several evidences suggest that mTOR inhibitors may be associated with a lower risk of CMV infection which may reflect a direct effect on host-cell

pathways resulting in a less permissive environment for CMV replication and a lower impact of these drugs on antiviral cellular immune responses(13,15).

Host-related factors are also important in defining risk stratification. First of all impaired cellular immunity is central to CMV susceptibility therefore older recipient age, comorbidity, frailty, and long dialytic treatment before kidney transplant are considered important contributing factors. Transplant-related factors may also contribute as happens in second/third or multiorgan transplant.

TABLE 2. Determinants of CMV risk after kidney transplantation [6,11–15]

Risk domain	Higher risk	Lower risk
Donor–recipient serostatus	D+/R– (primary infection via graft)	R+ (pre-existing immunity); D–/R–
Induction therapy	Lymphocyte-depleting agents (rATG, alemtuzumab)	Non-depleting agents (basiliximab)
Maintenance therapy	Prednisone + calcineurin inhibitor + mycophenolate mofetil	mTOR inhibitor–based regimens
Host / transplant factors	Older age, comorbidity, frailty, long pre-transplant dialysis, re-/multi-organ transplant	—

Diagnosis and Monitoring: From Guidelines to Real-World Constraints

Diagnosis and monitoring of CMV in kidney transplant is evolving to a multilevel and personalized approach. It is important to distinguish between CMV infection, determined by the presence of CMV viremia without systemic signs or tissue invasive disease and CMV disease characterized by increasing viremia and symptoms/signs of organ involvement.

Gold standard for diagnosis and monitoring is made by real time PCR performed on whole blood or plasma samples; both methods are accepted but they must not be used interchangeably(6,17). Indeed whole blood CMV viremia reflects circulating and intracellular viremia resulting in more sensitive tests; on the other hand plasma viremia may offer greater clinical specificity for active viral replication(6,16). Real time PCR for CMV can be quantitative or qualitative: qualitative assays can just detect the presence of CMV viremia but are unable to differentiate the grade of replication, which is important to predict the risk of CMV disease and response to therapy; consequently quantitative assays are the most diffused test as they can measure viral load distinguishing low from high-level replication allowing treatment to be started promptly when necessary.

The clinical value of quantitative testing, however, depends heavily on the reliability and comparability of viral-load measurements. Until the introduction of Who International Standard for CMV DNA quantification, viral load results were commonly reported in assay-specific units, making comparison across laboratories

highly problematic. In 2010 Who introduced an International standard for CMV DNA quantification, allowing viral-load results to be reported in IU/mL and improving comparability across PCR assays (18,19). Even if Who standardization has reduced results variability different pre-analytic factors influence viral load such as: type of assay, specimen use (whole blood vs plasma), storage conditions, amplification targets, serostatus of both donor and recipient, organ transplanted and type of immunosuppression.

Although these advances in standardization of CMV viral load have improved sensitivity and comparability, no universal CMV viremia cut-off has been established across all transplant settings. Clinically relevant thresholds vary according to analytic and pre-analytic factors mentioned before; therefore most recent guidelines suggest that CMV viremia should still be interpreted using institution-specific thresholds and, more importantly, viral-load kinetics rather than isolated absolute values (6,17,20)..

When a CMV tissue invasive disease is suspected, histologic examination may be needed. Cultural tests for CMV are commonly used but their sensitivity is not ideal because body fluid can contaminate tissue and viral shedding can occur in the absence of clinical disease. For this reason the preferred method is by the identification of CMV inclusions or a positive immunohistochemistry for CMV. This technique is preferred to usual histology because tissue can be contaminated with body fluid and viral shedding can occur from some sites in the absence of clinical disease. However, the absence of viral inclusion does not exclude tissue invasive disease especially in lung, gastrointestinal and retinal involvement where the inclusion detection can be missed.

Viral load assays are also used for monitoring the load during CMV treatment. Since the differences between test type and assays is essential to use the same assay and specimen type to evaluate viral kinetic during treatment.

Although uncommon antiviral resistance is an important complication of CMV disease. It must be suspected in patients who take longer than six weeks to test negative or who show ongoing viral replication during prophylaxis. Risk factors for antiviral resistance include suboptimal or prolonged exposure to antivirals, inadequate dose adjustment based on renal function, D+/R- immune status, lymphopenia, induction therapy based on lymphocyte-depleting agents or repeated rejection treatment.

The latest guidelines distinguish between refractory and resistance to CMV therapy; refractory is when the viral load does not decrease adequately after at least 2 weeks of therapy while resistance requires the demonstration of viral mutations associated with drug resistance. In this setting, mutations generally involve viral genes encoding proteins crucial for viral DNA replication and antiviral drug activation, such as UL97 phosphotransferase, which is mainly associated with ganciclovir/valganciclovir resistance, and, less frequently, UL54 DNA polymerase, which may confer broader cross-resistance to ganciclovir/valganciclovir, cidofovir,

and/or foscarnet. When suspected, genotypic sequencing of viral genes can be performed; testing requires sufficient viral DNA so it results most informative in patients with persistent or clinically significant DNAemi (6,21,22).

Given the complex distinction between CMV infection and disease, the extent organ tropism, the absence of specific clinical manifestations and the risk of recurrence in IgG positive patients CMV diagnosis in transplant recipients relies primarily on quantitative real-time PCR requiring sequential monitoring performed where its reliability depends on sequential monitoring using the same specimen type, assay platform and laboratory, with rapid response in order to allow timely interpretation and appropriate therapeutic decisions.

For these reasons, in resource-limited settings, CMV diagnosis and monitoring in transplant recipients may be very challenging. Updated recommendations are largely based on the availability of real time quantitative PCR, standardized assay platforms, consistent sample processing, and rapid turnaround times. However, in many developing transplant systems these conditions may be difficult to guarantee. Real time quantitative PCR for CMV may be limited by cost, restricted laboratory capacity, delayed reporting, lack of assay harmonization, and fragmented follow-up between transplant centres and peripheral hospitals.

These limitations are especially relevant for pre-emptive strategies, which depend on frequent viral-load monitoring and prompt initiation of therapy when clinically significant DNAemia is detected. The same diagnostic constraints also affect post-treatment and long-term post-transplant management. After antiviral therapy has been started, serial quantitative PCR is essential to assess virological response, guide treatment duration, detect recurrent CMV DNAemia, and identify patients with refractory or resistant infection.

As a result, clinicians may need to adapt guideline-based recommendations to local resources, combining donor–recipient serostatus, intensity of immunosuppression, clinical presentation, and feasible PCR monitoring schedules. In such settings, improving CMV care requires not only access to antiviral drugs, but also investment in standardized diagnostic pathways, laboratory continuity, and national protocols for post-transplant viral surveillance.

TABLE 3. Key diagnostic definitions in CMV after kidney transplantation. Whole blood is more sensitive and plasma more specific; the two are not interchangeable. Use the same specimen, assay and laboratory over time, report in IU/mL (WHO standard) and interpret viral-load kinetics rather than isolated cut-offs [6,16–22].

Term	Definition
CMV infection	Viral replication (viremia) without systemic symptoms or tissue-invasive disease
CMV disease	Viremia with systemic symptoms (CMV syndrome) or tissue-invasive organ involvement
Refractory	Viral load that does not decrease adequately after at least 2 weeks of appropriate therapy
Resistant	Refractoriness with a demonstrated resistance mutation (UL97, less often UL54)

Prevention Strategies: Universal and Pre-emptive Approaches

CMV is one of the most clinically relevant opportunistic infections in kidney transplantation due to its extensive seroprevalence in the general population, ability to establish lifelong latency, and strong dependence on T-cell immune control. Under immunosuppression the risk of primary disease or reactivation of CMV after kidney transplant is very high, leading not only to direct viral disease but also to indirect effects on graft function, rejection risk, and susceptibility to other infections. Because CMV is associated with considerable morbidity and mortality and has been identified as a risk factor for rejection in kidney transplant recipients, it is crucial to define a correct prevention strategy in order to reduce CMV burden in this group of patients. Two approaches are generally accepted in post-transplant management: antiviral prophylaxis, which consist in the administration of antiviral drug in the first post-transplant months when immunosuppression is the highest or pre-emptive therapy, which consist in sequential monitoring of viral load with prompt start of therapy if significant increase is detected (6,23,34)

The choice between them depends on several aspects taking into account the patient's related factors such as serological status, net state of immunosuppression, concomitant infection, and local feasibility of virological monitoring. International guidelines do not define one preferred approach except in the case of high risk patients with D+/R- status where antiviral prophylaxis is highly recommended since the risk of a transplant transmitted primary disease is very high and potentially fatal (6,25).

Antiviral prophylaxis is generally started from day 10 to 3-6 months with Valganciclovir as the most common agent while intravenous ganciclovir can be used in severe disease and letermovir as an emerging alternative in patients at risk of myelotoxicity(25,26). Antiviral prophylaxis, however, may be associated with myelotoxicity, gastrointestinal intolerance and neurological symptoms, elevated costs, late-onset CMV after discontinuation, and potential resistance. In the last years Letermovir has emerged as an alternative prophylactic agent, particularly in high-risk patients or in those with valganciclovir-related myelotoxicity, because it inhibits the CMV terminase complex and has a more favourable hematological safety profile(27).

Pre-emptive therapy is based on close monitoring, usually on a weekly basis, of viral kinetics in the first 4-6 months thereby reducing unnecessary drug exposure but requiring strict laboratory and clinical follow-up in order to assure a prompt initiation of therapy if active viral replication is detected. Therefore, CMV prevention represents a dynamic, risk-adapted strategy that integrates virological risk, immunosuppressive burden, drug safety but must be adapted to real-world diagnostic capacity.

TABLE 4. Risk stratification and recommended CMV prevention strategy after kidney transplantation. *Additional risk factors: lymphocyte-depleting induction (rATG/alemtuzumab), mycophenolate mofetil–based maintenance, lymphopenia, re-/multi-organ transplant, HIV infection [6,11,12,25].

Donor–recipient serostatus	Risk	Recommended prevention strategy	Monitoring
D+/R–	Very high	Universal prophylaxis (strongly recommended)	CMV PCR after prophylaxis (late-onset disease)
D+/R+ or D–/R+	Intermediate	Universal prophylaxis or pre-emptive	Weekly CMV PCR for 4–6 months if pre-emptive
D–/R– with additional risk factors*	Intermediate	Universal prophylaxis 3–6 months (especially if reliable monitoring is not available)	According to locally available resources
D–/R– without additional factors	Low	Pre-emptive	Weekly CMV PCR for 4–6 months

TABLE 5. Universal prophylaxis versus pre-emptive therapy for CMV prevention [6,23–27].

Feature	Universal prophylaxis	Pre-emptive therapy
Approach	Antiviral from the early post-transplant period	Monitor viral load; treat on significant rise
Typical timing	From day ~10, 3–6 months	Weekly CMV PCR during first 4–6 months
Preferred when	High risk (D+/R–) or reliable monitoring not feasible	Lower risk with reliable laboratory follow-up
Main agent	Valganciclovir (letermovir if myelotoxicity)	Valganciclovir started on trigger
Advantages	Prevents early disease and indirect effects	Less drug exposure and toxicity
Limitations	Myelotoxicity, cost, late-onset CMV, resistance	Requires strict laboratory organization and rapid response

Treatment, Refractory Disease and Antiviral Toxicity

The treatment of CMV viremia or disease in kidney transplant is based on two major cornerstones: immunosuppressive modulation and antiviral drugs. It should be modulated based on viral load kinetics, severity of clinically symptomatic disease, net state of immunosuppression, graft function and risk of rejection. Asymptomatic viremia, defined as a progressive increase in viral load, is usually targeted for treatment because it can rapidly evolve in CMV syndrome or disease and to prevent its indirect effects on graft and immune system. In this case, if viral load is low, the first step is to modulate immunosuppressive therapy by stopping anti-metabolite (Mofetil Mycophenolate or Azathioprine) followed by close monitoring of viral load in order to assess the need of adding antiviral therapy. Evidence on the long-term impact of antimetabolite discontinuation after asymptomatic CMV viremia remains limited: in a retrospective study of 52

kidney transplant recipients, antimetabolite withdrawal led to CMV clearance in 98% of patients, but 10% subsequently developed biopsy-proven acute rejection, mostly low-grade T-cell-mediated rejection. Since rejection occurred more than one year after discontinuation, causality remains uncertain; therefore, long-term antimetabolite withdrawal cannot currently be routinely recommended and personalized strategy must be assessed.

If the viral load shows rapid increase, or if it persists despite stopping antimetabolite, antiviral therapy must be started at full dose. The most used agent is oral Valganciclovir at the dose of 900 mg twice a day which must be continued until viral replication is no longer detectable (28).

In case of symptomatic infection, whether manifested as CMV syndrome or tissue invasive disease both immunosuppressive reduction and start of antiviral treatment must be initiated promptly. In this case, given that CMV symptomatic disease suggests an excessive state of immunosuppression most centres opt for a long-term anti-metabolite suspension; in high risk context of rejection antimetabolite reinitiation must be balanced and can be restored at low dose after CMV treatment conclusion.

The choice of antiviral therapy is based on initial viral load, severity of illness, adequate gastrointestinal absorption and tolerance of oral therapy. For patients with mild to moderate disease (rapid increase in viral kinetic, CMV syndrome without organ involvement) oral Valganciclovir is preferred as first line agent at the dose of 900 mg twice daily, adjusted for renal function as it is better tolerated and avoid hospitalization and need for central venous access. In a trial of more than 300 solid organ recipients with mild/moderate CMV disease oral Valganciclovir resulted comparable to intravenous Ganciclovir in viraemia eradication and treatment success(28).

In case of severe manifestation with tissue invasive disease, intravenous Ganciclovir at 5 mg/kg twice daily is the treatment of choice with possible transition to oral Valganciclovir after clinical improvement (6,28).

Treatment duration is typically 21 days but it depends on severity and is guided by clinical and virological courses. Generally antiviral therapy is continued until symptoms resolution and viral replication become undetectable .

In some cases there is a persistence or progression of CMV infection despite correct reduction of immunosuppressive therapy and appropriate and tolerated antiviral treatment. If after six weeks of treatment there is no clear viral response refractory or drug resistance must be suspected. In this case resistance mutations can be confirmed by genotypic sequencing of viral genes giving a useful tool in selecting second line agents.

There are three available agents approved for CMV disease with confirmed resistance but their use must be guided by disease severity, resistance mutations, kidney function and drug availability. Foscarnet, an intravenous pyrophosphate

analogue that inhibits CMV DNA polymerase, is active against UL 54 and UL97 mutations. Its use is limited by elevated nephrotoxicity requiring intense intravenous hydration and close monitoring of renal function and electrolytes during administration. Cidofovir, another viral DNA polymerase inhibitor, is highly nephrotoxic. It results active against UL97 mutations but generally not against UL54. Its use is limited by marked nephrotoxicity and possible uveitis, making a latter- line option(6,21,29). At least Maribavir has emerged as an important option for refractory or resistant CMV infection, particularly because it avoids Ganciclovir related myelotoxicity and Foscarnet/Cidofovir nephrotoxicity but its use is limited in mild to moderate disease (30,31).

In selected complex cases, treatment may also require further reduction of immunosuppression, by stopping corticosteroid and lowering calcineurin-inhibitor, resistance-guided antiviral switching, and, where available, adjunctive strategies such as CMV-specific immunoglobulin or adoptive T-cell therapy.

TABLE 6. Treatment of CMV by clinical scenario. *Adjusted for renal function; duration is typically about 21 days and is guided by clinical and virological response until viremia is undetectable [6,28].

Clinical scenario	First step	Antiviral agent	Dose / route
Asymptomatic viremia, low load	Stop antimetabolite; monitor load	Add antiviral only if load rises	—
Mild–moderate / CMV syndrome	Reduce immunosuppression + antiviral	Valganciclovir (oral)	900 mg twice daily*
Severe / tissue-invasive disease	Reduce immunosuppression + antiviral	Ganciclovir (intravenous)	5 mg/kg twice daily*
Refractory / resistant	Reassess dose, adherence, immunosuppression; genotype UL97/UL54	Maribavir / foscarnet / cidofovir	Per mutation and renal function

TABLE 7. Antiviral agents used in CMV prophylaxis and treatment. UL54 mutations may confer cross-resistance to ganciclovir/valganciclovir, cidofovir, and/or foscarnet [6,21,27,29,30].

Agent	Mechanism / target	Main use	Key toxicity / limitation
Valganciclovir (oral)	Ganciclovir prodrug; UL97-dependent activation	Prophylaxis; mild–moderate treatment	Myelotoxicity, gastrointestinal intolerance
Ganciclovir (IV)	DNA polymerase inhibitor (UL54)	Severe / tissue-invasive disease	Myelotoxicity
Letermovir	CMV terminase complex inhibitor	Prophylaxis (especially myelotoxicity risk)	Limited treatment data; drug interactions
Foscarnet	Pyrophosphate analogue (UL54, UL97)	Resistant disease	Nephrotoxicity, electrolyte disturbance
Cidofovir	DNA polymerase inhibitor	Resistant disease (later-line)	Marked nephrotoxicity, uveitis
Maribavir	UL97 kinase inhibitor	Refractory / resistant CMV	Limited to mild–moderate disease; dysgeusia

CMV Management in Resource-Limited Settings

Numerous evidences along the years confirmed that kidney transplant resulted superior to hemodialysis in terms of patient and graft survival and quality of life. According to that, numerous transplant programmes in low and middle income countries, where chronic kidney disease is even higher, have started. Unfortunately many diagnostic, follow up and treatment tools, necessary to ensure a proper long-term follow-up of post transplant complications, are missing.

As mentioned, CMV represents a wide spread and complex opportunistic infection in kidney transplant due to its elevated organ tropism, aspecific clinical manifestations, immuno-modulatory capability and risk for antiviral resistance-gaining mutations. These characteristics make CMV management particularly challenging in a limited-resources context.

While current guidelines emphasize risk stratification, repeated quantitative PCR monitoring, timely antiviral therapy and resistance testing when needed, these components may be difficult to implement consistently in developing transplant systems (35).

Limited access to regular CMV quantitative PCR, delayed laboratory turnaround, assay variability, high costs of antivirals, and restricted availability of second-line agents may compromise both prevention and treatment strategies. In this context, CMV care should be based on a structured but feasible approach that prioritizes donor–recipient serostatus, intensity of immunosuppression, clinical risk factors, and locally available monitoring schedules. Universal prophylaxis may be favored when reliable pre-emptive surveillance cannot be ensured, whereas pre-emptive therapy requires strong laboratory organization and rapid clinical response. Standardization of national diagnostic pathways, use of the same specimen type and laboratory over time, careful adjustment of antiviral dosing, and early recognition of refractory or recurrent infection are essential to improve outcomes(6,23,24,32). Therefore, in resource-limited settings, effective CMV management depends not only on applying guideline-based recommendations, but also on building sustainable systems for post-transplant surveillance, laboratory harmonization, and equitable access to antiviral treatment (35).

Beyond CMV, other viral complications of kidney transplantation — such as parvovirus B19, a frequently under-recognized cause of severe, erythropoietin-resistant anemia — may be particularly difficult to detect and to treat with the most current diagnostic and therapeutic tools in resource-limited settings, where a high index of clinical suspicion and a tailored, multidisciplinary approach remain essential (34).

TABLE 8. Adapting guideline recommendations to resource-limited settings [6,23,24,32].

Guideline standard	Feasible adaptation in resource-limited settings
Frequent real-time quantitative PCR monitoring	Favor universal prophylaxis when reliable surveillance cannot be ensured
Standardized assay platforms, IU/mL reporting	Use the same specimen type and laboratory over time
Rapid turnaround enabling pre-emptive therapy	Risk-prioritized, simplified monitoring schedules
Genotypic resistance testing	Clinical reassessment of dose, adherence and immuno-suppression first
Access to newer antivirals (letermovir, maribavir)	Careful antiviral dosing; standardized national diagnostic pathways

A Practical Risk-Based Algorithm for Kidney Transplant Programs

A practical risk-based algorithm for CMV disease in kidney transplant programs should integrate immunological risk, net immunosuppression status, comorbidities, diagnostic feasibility and therapeutic availability. The first step is to define the pre-transplant immunological status in order to identify low to high risk patients based on CMV serology of both donor and recipient. Second is crucial to define the presence of additional risk factors such as use of lymphocyte-depleting agents, Mofetil Mycophenolate based maintenance therapy, profound or persistent lymphopenia, previous or concomitant transplant, HIV infection.

If low risk patient (e.g. D-/R- without additional risk factors) pre-emptive therapy can be adopted, in the other cases a 3 to 6 months universal prophylaxis is generally considered acceptable even in a limited-resources setting where access to sequential molecular monitoring may be difficult.

If available, real time quantitative PCR should be performed using the same specimen type, assay platform, and laboratory whenever possible, avoiding isolated decisions based on non-standardized cut-offs. In patients with persistent, recurrent, or rising CMV DNAemia despite appropriate treatment, the algorithm should include reassessment of antiviral dosing, adherence, gastrointestinal absorption, immunosuppressive intensity, and possible resistance testing. In resource-limited settings, such an algorithm should remain simple, reproducible, and adaptable, prioritizing high-risk patients for closer surveillance while promoting standardized national pathways for prevention, diagnosis, treatment, and long-term post-transplant monitoring.

FIGURE 1. Practical risk-based algorithm for CMV management in kidney transplant programs, integrating donor–recipient serostatus, net state of immunosuppression, diagnostic feasibility and treatment of refractory or resistant disease.



D, donor; R, recipient; MMF, mycophenolate mofetil; PCR, polymerase chain reaction; GI, gastrointestinal

Conclusions

CMV remains a major challenge after kidney transplantation because of its direct viral effects, indirect impact on graft outcomes, and strong relationship with the net state of immunosuppression. Although recent guidelines provide a more standardized and risk-adapted framework, their application may be difficult in resource-limited settings, where access to quantitative PCR, rapid reporting, antiviral drugs and resistance testing is not always guaranteed. For this reason, CMV management should be adapted to local resources. Pre-transplant donor-recipient serostatus, induction therapy, maintenance immunosuppression and host-related factors should guide prevention and monitoring strategies. Universal prophylaxis may be preferred in high-risk patients or when strict PCR surveillance is not feasible, while pre-emptive therapy requires reliable and repeated viral-load monitoring. In resource-limited transplant programs, a simple and reproducible risk-based algorithm may help prioritize high-risk patients, standardize follow-up, ensure timely treatment and reduce unnecessary antiviral exposure. Therefore, effective CMV care should combine guideline-based recommendations with feasible local pathways for diagnosis, monitoring and treatment.

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