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Review article

Management of cytomegalovirus in adult solid organ transplant patients: GESITRA-IC-SEIMC, CIBERINFEC, and SET recommendations update

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Abbreviations: ATC, adoptive T-cell; ATG, anti-thymocyte globulin; BAL, bronchoalveolar lavage; CIBERINFEC, Biomedical Research Center Network in Infectious Diseases; CMI, cell-mediated immunity; CMV, cytomegalovirus; CMV IG, Anti-CMV immunoglobulins; D, donor; EC_{50}, half maximal effective concentration; ELISA, enzyme-linked immunosorbent assays; ELISpot, enzyme-linked immunosorbent spot assays; FOS, foscarnet; GCV, ganciclovir; GESITRA-IC, Group for the Study of Infection in Transplantation and the Immunocompromised Host; GRADE, Grading of Recommendations Assessment, Development and Evaluation system; HSCT:, hematopoietic stem cell transplantation; HT, heart transplant; ICS, intracellular cytokine staining; IFN-γ, interferon-gamma; IGRA, interferon-γ release assay; IV, intravenous; KT, kidney transplant; LET, letermovir; LT, lung transplant; mAb, monoclonal antibody; MBV, maribavir; mTOR, mammalian target of rapamycin; NGS, next-generation sequencing; NK, natural killer; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction; QNAT, quantitative nucleic acid amplification test; R, recipient; RCT, randomized controlled trial; SEIMC, Spanish Society of Infectious Diseases and Clinical Microbiology; SET, Spanish Society of Transplantation; SOT, solid organ transplantation; VGCV, valganciclovir; VST, virus-specific T cell.

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ABSTRACT

Cytomegalovirus (CMV) infection remains a significant challenge in solid organ transplantation (SOT). The last international consensus guidelines on the management of CMV in SOT were published in 2018, highlighting the need for revision to incorporate recent advances, notably in cell-mediated immunity monitoring, which could alter the current standard of care. A working group including members from the Group for the Study of Infection in Transplantation and the Immunocompromised Host (GESITRA-IC) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Society of Transplantation (SET), developed consensus-based recommendations for managing CMV infection in SOT recipients. Recommendations were classified based on evidence strength and quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The final recommendations were endorsed through a consensus meeting and approved by the expert panel.

1. Introduction

Cytomegalovirus (CMV) infection in solid organ transplantation (SOT) recipients continues to pose a significant threat to their health. The last international consensus guidelines on the management of CMV in SOT were published in 2018 [1]. Since then, new anti-CMV drugs and methods to evaluate cell-mediated immunity (CMI) against CMV have been incorporated into clinical practice.

2. Methods

We created a working group composed of members of the Group for the Study of Infection in Transplantation and the Immunocompromised Host (GESITRA-IC) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Center for the Biomedical Research Network in Infectious Diseases (CIBERINFEC) and the Spanish Society of Transplantation (SET), to reach a consensus on the management of CMV infection in SOT recipients. As an initial step, the coordinators (JTC, JMA) proposed a series of clinical questions that were approved by the GESITRA-IC Board. The selected questions were distributed among different working groups of the expert panel. The MEDLINE, CENTRAL, Embase, and Clinical Trials databases were searched to retrieve relevant studies published until September 30, 2023. Unpublished communications to congresses, clinical cases, and small case series were excluded. The recommendations were classified by level of evidence and graded following the Grading of Recommendations Assessment, Development and Evaluation system (GRADE), which includes an assessment of the strength of the recommendation (i.e., strong, weak) and the quality of evidence (i.e., high, moderate, low, very low) [2–5]. Expert opinion grading was applied to recommendations with very low-quality evidence or those subject to controversy. All recommendations were discussed in The CMV Consensus Meeting held by GESITRA-IC/CIBERINFECT/SET on January 25, 2024, in Cordoba, Spain. Each working group proposed its recommendations and grading. These were discussed globally at the Consensus Meeting and agreed upon by majority vote. Specifically, recommendations based on expert opinion required a 2/3 majority of the expert panel to be approved. The final recommendations received support from patient associations collaborating with SEIMC and SET, in addition to all the members of both societies.

3. Recommendations

3.1. Virological monitoring

Few advances in virological monitoring have been made since our last consensus [6]. Importantly, a specific CMV viral load threshold for initiating preemptive treatment in asymptomatic patients is still pending [1], and different scenarios, including patient individual risk stratification, should be considered.

Quantitative nucleic acid amplification tests (QNATs), mainly those based upon real-time polymerase chain reaction (PCR), are the first choice for monitoring CMV DNAemia. Both whole blood and plasma specimens are equally suitable for monitoring. However, due to variability, it is necessary to use the same specimen for its consecutive monitoring [7]. Commercially available real-time QNAT assays have not been validated for CMV DNA quantitation in specimens other than whole blood and plasma, so the use of these techniques in bronchoalveolar lavage (BAL) or intestinal biopsies may be ancillary to cell-culture-based assays and histopathology. Since no consistent CMV DNA threshold for diagnosis of end-organ disease has been defined, only the lack of detection of CMV DNA in these specimens could have a high negative predictive value [8]. The dynamics of CMV loads over time may be more important in managing CMV infection than any absolute viral load value [9]. Specifically, using CMV DNA doubling time to initiate preemptive therapy may reduce variability across centers that apply different real-time QNATs [10–13]. Finally, virological monitoring during universal prophylaxis should be based on clinical criteria rather than being conducted systematically.

3.1.1. Consensus recommendations

- Insufficient evidence precludes recommending a specific threshold of DNAemia for triggering the inception of preemptive therapy in asymptomatic patients. Alternatively, we recommend individualizing each case based on risk stratification (**strong, low**).
- Real-time PCR assays performed on BAL or gastrointestinal biopsies display a high negative predictive value for diagnosing CMV pneumonitis or CMV gastrointestinal disease (**strong, low**).

Table 1
Summary of recommended primary prevention strategies and their potential modifications based on CMV-CMI monitoring availability.

Organ	Serostatus	Standard of care	Strength of recommendation; Quality of evidence	Potential modifications based on cell-mediated immune monitoring	Strength of recommendation; Quality of evidence
Kidney	D+/R-	Universal prophylaxis with VGCV[a] or LET[b] for 6 months (alternative: preemptive therapy with close monitoring[c]).	**Strong; high** [14–18,19,20,21]	**Test CMV-CMI at the time of discontinuation[e]** -If positive: stop prophylaxis and continue with preemptive therapy[d]. -If negative (or indeterminate): continue prophylaxis. Alternatively, switch to preemptive therapy with close monitoring and reassess CMV-CMI monthly.	**Weak; moderate-low** [22–29]
	R+	3 months of preemptive therapy (alternative: universal prophylaxis with VGCV[a] if close monitoring cannot be guaranteed).	**Strong; high** [14–16,30,31]	**Baseline (pretransplant) or early (between 15-30 days) posttransplant monitoring of CMV-CMI:** -If negative (or indeterminate): if D+, consider it as a high-risk (D+/R-) transplant.	**Strong; moderate** [32–37]
		Consider universal prophylaxis with LET[b].	**Expert opinion; no evidence available**	**Test CMV-CMI at the time of discontinuation[e]:** -If positive: stop preemptive therapy. -If negative (or indeterminate): continue preemptive therapy with close monitoring and reassess CMV-CMI monthly.	**Expert opinion; not specifically tested in RCTs**
	R+ with ATG treatment or increased immunosuppression[f]	Universal prophylaxis with VGCV[a] for at least 3 months.	**Strong; moderate** [38–42]	**Minimum 1 month of universal prophylaxis. Test CMV-CMI from then on:** -If positive: stop prophylaxis and continue with preemptive therapy[d].	**Strong; high** [27,43]
		Consider universal prophylaxis with LET[b].	**Expert opinion; no evidence available**	-If negative (or indeterminate): continue prophylaxis and reassess CMV-CMI monthly.	
Liver	D+/R- and R+ with increased immunosuppression[f]	Preemptive therapy for 3 months, as long as close monitoring[c] is available (alternative: universal prophylaxis with VGCV[a]).	**Strong; high** [44–49]	**Test CMV-CMI at the time of discontinuation[e]:**	**Strong; moderate** [24,50,27,29]
		Consider universal prophylaxis with LET[b].	**Expert opinion; no evidence available**	-If positive: stop prophylaxis and consider continuing with preemptive therapy[d] depending on the individual patient's risk. -If negative (or indeterminate): extend universal prophylaxis or switch to preemptive therapy with close monitoring[c].	
	R+	Preemptive therapy for 3 months.	**Strong; high** [46–49]	**Baseline (pretransplant) or early (between 15-30 days)) posttransplant monitoring of CMV-CMI:** - If negative (or indeterminate): if D+, consider it as a high-risk (D+/R-) transplant.	**Weak; low** [51,52]
				Follow same strategy as in D+/R- transplant recipients at the time of discontinuation[e].	**Expert opinion; not specifically tested in RCTs**
Heart	D+/R- and R+ with increased immunosuppression[f]	Universal prophylaxis for 3 to 6 months with VGCV[a]. Consider universal prophylaxis with LET[b].	**Strong; moderate-low** [53,54,55] **Expert opinion; no evidence available**	**Test CMV-CMI at the time of discontinuation[e]:** -If positive: stop prophylaxis and consider continuing with preemptive therapy[d] depending on the individual patient's risk. -If negative (or indeterminate): continue prophylaxis and reassess CMV-CMI monthly (alternative: switch to preemptive therapy with close monitoring[c])	**Weak; low** [24,56]

(*continued on next page*)

- Systematic virological monitoring is not recommended during universal prophylaxis (**expert opinion, controversial evidence**).

Table 1 (*continued*)

Organ	Serostatus	Standard of care	Strength of recommendation; Quality of evidence	Potential modifications based on cell-mediated immune monitoring	Strength of recommendation; Quality of evidence
	R+	Universal prophylaxis for 3 months with VGCV[a] (alternative: preemptive therapy with close monitoring[c]).	**Strong; moderate** [57,58]	**Baseline (pretransplant) or early (between 15-30 days) posttransplant monitoring of CMV-CMI:** -If negative (or indeterminate): if D+, consider it as a high-risk (D+/R-) transplant.	**Expert opinion; no evidence available**
		Consider universal prophylaxis with LET[b].	**Expert opinion; no evidence available**	**Follow same strategy as in D+/R- transplant recipients at the time of discontinuation[e].**	**Weak; low** [59]
Lung	D+/R-	Universal prophylaxis for 12 months with VGCV[a] (consider continuation with preemptive therapy[d] depending on the individual patient's risk).	**Strong; moderate** [54,60–62,63,64]	**Test CMV-CMI at the time of discontinuation[e]:**	**Strong; moderate** [65,24,66]
		Consider universal prophylaxis with LET[b].	**Expert opinion; no evidence available**	-If positive: stop universal prophylaxis and consider continuing with preemptive therapy[d] depending on the individual patient's risk. -If negative (or indeterminate): continue with universal prophylaxis or switch to preemptive therapy with close monitoring[c] and reassess CMV-CMI monthly.	
	R+	Universal prophylaxis for at least 6 months with VGCV[a], followed by preemptive therapy[d] for another 6 months.	**Strong; moderate** [54,60,62,63,64,67,68]	**Baseline (pretransplant) or early (between 15-30 days) posttransplant monitoring of CMV-CMI:** -If negative (or indeterminate): if D+, consider it as a high-risk (D+/R-) transplant.	**Weak; low** [36]
		Consider universal prophylaxis with LET[b].	**Expert opinion; no evidence available**	**Follow same strategy as in D+/R- transplant recipients at the time of discontinuation[e].**	**Strong; moderate** [65,69,66,70]
	R+ with increased immunosuppression[f]	Universal prophylaxis for at least 6 months with VGCV[a], followed by preemptive therapy[d] for another 6 months.	**Weak; low** [71]	**Follow same strategy as in D+/R- transplant recipients at the time of discontinuation[e].**	**Expert opinion; not specifically tested in RCTs**
		Consider universal prophylaxis with LET[b].	**Expert opinion; no evidence available**		
Intestinal, multivisceral, composite tissue	High risk no matter D/R serostatus	Universal prophylaxis with VGCV[a] for at least 6 months, followed by an indeterminate period of preemptive therapy[d].	**Weak; low** [47,72–74]	**Test CMV-CMI at the time of discontinuation[e]:**	**Expert opinion; no evidence available**
		Consider universal prophylaxis with LET[b].	**Expert opinion; no evidence available**	-If positive: stop prophylaxis (alternative: continue with preemptive therapy[d]). -If negative (or indeterminate): continue prophylaxis or switch to preemptive therapy with close monitoring[c] and reassess CMV-CMI monthly.	
Pancreas	High risk regardless of D/R serostatus	Universal prophylaxis with VGCV[a] for 3 to 6 months.	**Weak; low** [75–77]	**Follow same strategy as in high-risk kidney transplant.**	**Expert opinion; no evidence available**
		Consider universal prophylaxis with LET[b].	**Expert opinion; no evidence available**		
Liver, Heart, Lung, Kidney	R+ on preemptive therapy with asymptomatic viremia	Individualize each case, considering clinical aspects.	**Expert opinion; controversial evidence**	**Test CMV-CMI:** -If positive: withhold antiviral treatment.	**Weak; low** [78,79]

ATG: anti-thymocyte globulin; CMV: cytomegalovirus; CMV-CMI: CMV-specific cell-mediated immunity; D: donor; GCV: ganciclovir; Ig: immunoglobulin; LET: letermovir; R: recipient; RCT: randomized controlled trial; VGCV: valganciclovir.

[a] In cases of oral intolerance, consider intravenous GCV.

[b] In case of neutropenia or difficulties managing VGCV/GCV.

[c] Strict preemptive protocol with weekly viral load monitoring, prompt reporting, and immediate therapy initiation.

[d] If preemptive therapy is initiated after completing universal prophylaxis, the frequency of CMV monitoring could be extended to every two weeks.

[e] Discontinuation of treatment can occur for various reasons, such as the completion of the recommended universal prophylaxis period, drug toxicity, or clinical criteria.

[f] Therapies that induce profound immunosuppression, such as acute rejection treatment or ABO-incompatible protocols.

3.2. Prevention (Table 1)

3.2.1. Standard of care: universal prophylaxis and preemptive therapy

The duration of prophylaxis depends on the type of organ transplanted, the donor (D)/recipient (R) CMV serostatus, and the type of immunosuppression used. Table 1 summarizes recommendations regarding the standard prevention of CMV disease in SOT recipients.

3.2.1.1. Consensus statement. Universal prophylaxis and preemptive therapy are equally effective in preventing CMV disease if a strict preemptive protocol is followed. The decision to choose preemptive therapy is conditioned by the hospital's logistic capacity. The panel of experts advocates for clinicians to follow a strict preemptive protocol with weekly viral load monitoring, prompt reporting, and immediate therapy initiation. If preemptive therapy is initiated after completing universal prophylaxis, the frequency of CMV monitoring could be extended to every two weeks.

The quality of evidence supporting preemptive therapy compared to universal prophylaxis varies across different organ transplant contexts. Of particular concern are the potential indirect effects of viral replication on graft viability, especially in heart and lung transplantation. In the latter, immunoguided prophylaxis has recently provided new insights into the safety of the preemptive strategy (see below).

3.2.1.2. Kidney recipients. In the first randomized controlled trial (RCT) on seropositive (R+) kidney transplant (KT) recipients, it was found that preemptive therapy led to a higher incidence of CMV infection and disease compared to universal prophylaxis. However, they used a low-intense CMV surveillance protocol, and no differences were observed in terms of rejection, graft loss, and death [30,31]. Another meta-analysis in CMV R+ KT recipients showed that universal prophylaxis was better than preemptive therapy in the prevention of CMV disease [14]. However, the universal prophylaxis group required a high number of patients to be treated to achieve this outcome.

A recent RCT performed in CMV mismatch (D+/R-) and R+ recipients found that both regimens were effective in preventing CMV disease without increasing the risk of acute rejection. Nevertheless, preemptive therapy resulted in significantly higher rates of CMV DNAemia and lower neutropenia [15]. This is consistent with the results of a previous systematic review of RCTs, which showed that universal prophylaxis significantly reduced the rates of early CMV infection but led to higher rates of late infection and hematological adverse events [16]. A recently published meta-analysis of preemptive therapy stratified studies according to high or low threshold surveillance protocol in CMV D+/R- KT recipients. They found that a low threshold preemptive therapy (initiation of antiviral at any level of CMV DNAemia) was associated with a significantly lower CMV disease incidence than 6 months of universal prophylaxis or a high threshold preemptive therapy strategy [17]. Moreover, a retrospective study conducted on D+/R- KT recipients found no differences in long-term outcomes such as patient death, graft loss, or death-censored graft loss among both strategies [18].

3.2.1.3. Liver recipients. A single RCT conducted in high-risk (D+/R-) liver transplant recipients reported a lower incidence of CMV disease after one year of follow-up in patients managed with a preemptive approach compared to universal prophylaxis. There were no significant differences in terms of allograft rejection, opportunistic infections, graft loss, neutropenia, and all-cause mortality between both strategies [44]. In a post-hoc analysis of these results, preemptive therapy even showed protection against mortality [45]. Other meta-analyses [46–48] and a systematic review [49] concluded similar efficacy in the prevention of CMV disease of both strategies, regardless of serostatus, with no apparent impact on rejection, opportunistic infections, and mortality. An increased incidence of CMV infection was observed only in D+/R- patients treated with preemptive therapy. This analysis excluded the only RCT in which this variable was not studied [48]. Finally, a preemptive strategy is also linked to lower overall costs compared to universal prophylaxis in high-risk patients [80,81].

3.2.1.4. Heart recipients. There is a lack of RCTs comparing both strategies in heart transplant (HT) recipients. In these patients, the effect of CMV replication in the development of graft vascular disease is well-documented [53,54], and universal prophylaxis is generally preferred. In fact, a preemptive strategy in R+ patients has been associated with an increased risk of CMV infection and CMV-related hospitalization in retrospective studies and may be associated with worse post-transplant graft outcomes [57,58].

3.2.1.5. Lung recipients. No RCT has compared preemptive versus universal prophylaxis in lung transplant (LT). However, one study has evaluated the outcomes using a hybrid strategy (see immunoguided prevention below) [65], and another is pending publication [82]. The risk of CMV infection and disease is notably elevated in LT recipients, and the indirect effect of CMV replication on graft survival is well-documented [54]. For this reason, universal prophylaxis is preferred [60–62].

3.2.1.6. Small bowel, pancreas, multivisceral, and composite tissue transplant recipients. Although few data have been published, intestinal and multivisceral transplant recipients are considered at high risk of CMV infection, and universal prophylaxis is generally prioritized over preemptive therapy [47,72,73], regardless of serostatus. A similar strategy is suggested for composite tissue transplants [74].

3.2.2. Antivirals for prophylaxis

Once-daily 900 mg of valganciclovir (VGCV), with normal renal function, remains the preferred regimen in any prophylaxis indication [1,6]. However, its utilization may be constrained by significant side effects, particularly neutropenia. In cases of oral intolerance, 5 mg/kg/day of intravenous (IV) ganciclovir (GCV) is an option, although it presents logistical drawbacks. Letermovir (LET) represents an oral alternative due to its similar efficacy and lower toxicity. It has been approved by both the EMA and FDA for primary prophylaxis in D+/R- KT recipients, following a recent RCT where LET was shown to be noninferior to VGCV in preventing CMV disease, with a lower incidence of neutropenia [19]. The dose of LET for prophylaxis is 480 mg per day (240 mg in case of coadministration with cyclosporine), and drugs to prevent herpes simplex and varicella virus infection should be added to this regimen [19]. Even though the use of low-dose VGCV (450 mg/day) was previously reported as an active off-label practice in a third of transplant centers [83], there is still a concern about viral replication progress and the emergence of GCV resistance, especially in high-risk transplant recipients [84–86].

The use of mammalian target of rapamycin (mTOR) inhibitors, alone or in combination with calcineurin inhibitors, as de novo or early conversion immunosuppression maintenance therapy has been shown to significantly reduce the incidence of CMV infection after kidney transplantation [87–90], especially in patients with low/moderate immunological risk and R+, but also in high-risk D+/R patients [88]. Similarly, converting mycophenolic acid to mTOR inhibitors in R+ KT patients after the first episode of treated infection is an effective and safe strategy for preventing recurrent episodes [91]. In heart and lung recipients, RCTs have also demonstrated a reduction in CMV infection rate [92–95]. It has been suggested that mTOR inhibitors have an immunomodulatory effect in R+ recipients, promoting the activation of antiviral memory and effector immune responses [90,96]. However, there is limited data regarding their potential long-term nephrotoxicity.

3.2.2.1. Consensus recommendations

- In patients with leukopenia or difficulties managing GCV/VGCV, LET is the alternative for D+/R- KT recipients (**strong, high**). This could be extended to the rest of the organs (**expert opinion, no evidence available**).
- LET should be the first choice in case of toxicity over low-dose VGCV (**expert opinion, no evidence available**).
- Switching to mTOR inhibitors is recommended in R+ KT recipients with CMV viremia while on preemptive therapy (**strong, high**).
- The use of mTOR inhibitors as de novo or early conversion immunosuppression maintenance therapy is suggested in patients with low/moderate immunological risk (**weak, moderate**).

3.2.3. Use of immunoglobulins in primary CMV disease prevention

Anti-CMV immunoglobulins (CMV IG) have been used as a prophylactic measure for many years, primarily in combination with antivirals. They are mainly used in D+/R- high-risk patients and in cases of severe hypogammaglobulinemia [97], especially in cardiothoracic transplantation [98,99]. An observational study of heart and lung transplant recipients showed that patients who received combined prophylaxis had less CMV disease, fewer rejections, and better survival than those treated with IV GCV alone. Immunoglobulins have also been associated with a better immune profile in HT recipients [100]. In terms of duration, another observational study showed that there were no differences in the rate of acute rejection between LT recipients treated with 12 months and those treated with 24 months [101]. Data on the use of CMV IG during hypogammaglobulinemia is limited [102–104]. However, studies on HT recipients have demonstrated the prevention of CMV disease [105–108].

3.2.3.1. Consensus recommendations

- We recommend a personalized administration of CMV IG, along with antivirals, during the first months post-transplantation for high-risk lung and heart transplant recipients (D+/R-), especially in patients with moderate to severe hypogammaglobulinemia (**weak, moderate-low**).

3.2.4. Immunoguided prevention

3.2.4.1. Immunologic monitoring. Some immune biomarkers, such as absolute lymphocyte count [109–111], natural killer (NK) cell counts [112], CD4+/CD8+ T cell subsets [113,114], total serum immunoglobulin [97] and/or complement levels have been suggested to evaluate the risk of infection during the post-transplant period [115–117]. However, current risk-stratification algorithms are still based on pre-transplant D/R CMV serostatus and post-transplant viral load testing. Hypogammaglobulinemia in the post-transplant period ranges from 12% to 70% in different series [118–122] and is related to a significant increase in the risk of suffering various infections [105,123–125], including CMV [122,126,127].

For initial risk assessment before transplantation, it is recommended the determination of D/R CMV-specific IgG antibodies using serological tests with high sensitivity and specificity. Recent studies have shown controversial data about the quantification of IgG antibodies' usefulness in the pre-transplant setting [128,129]. Determination of CMV IgM is not routinely recommended unless primary CMV infection is suspected.

In the last decade, it has become clearer that CMV-CMI is critical in controlling CMV reactivation [130]. Several methods are currently available. Most of them rely on the detection of interferon (IFN)-γ production or release (interferon-γ release assay [IGRA]) following stimulation of whole blood or peripheral blood mononuclear cells (PBMCs) with CMV-specific proteins (pp65 and IE-1) or CMV-infected dendritic cells [131]. The most common methods include enzyme-linked immunosorbent assays (ELISA), enzyme-linked immunosorbent spot assays (ELISpot), and intracellular cytokine staining (ICS) assays with flow cytometry. In general, all assays measure T-cell mediated effector immune responses of IFN-γ production in response to pp65 and IE-1 [131]. The nature of each assay provides specific advantages and drawbacks related to the technical procedure itself or the biological insight. Moreover, there is no consensus on the appropriate cut-off for defining protection from active CMV infection or disease [22,23,32,33,78,132–134]. The best CMV-CMI assay in SOT is open to debate. Table 2 provides a concise summary of commercially available methods.

Table 2
Overview of commercially available functional methods for measuring CMV-specific T-cell mediated immune response.

Assays	Brand names	Sample required	Turnaround time	Target cells	CMV stimulating antigen	Advantages	Disadvantages
ELISpot (IGRA)	T-SPOT.CMV® T-Track CMV®	PBMCs (10 mL)	24–48 h	CD4+/ CD8+/ NK/ NKT	Immunogenic peptides or proteins covering Pp65 and IE-1 proteins (separately)	Measures both CD4+ and CD8+ response Not limited by HLA CE marking	Requires ELISpot reader Requires PBMC isolation procedure Lack of cut-off standardization Unable to differentiate between CD4+ or CD8+ response
ELISA (IGRA)	QuantiFERON-CMV®	Whole blood (3–5 mL)	24 h	CD8+	Immunogenic peptides mapped within pp65, IE-1, IE-2, pp50 and gB	Standardized Simple to perform in laboratories Full automation CE marking	HLA Class I restricted Sensitive to lymphopenia Only measures CD8+ T cells (not CD4+ T cells)
ICS by flow cytometry	Viracor® CMV T-cell Immunity Panel (TCIP)	PBMCs or whole blood (1-2 mL)	8–10 h	CD4+/ CD8+	Usually pp65, IE-1, gB immunogenic peptides (overlapping peptides libraries) or pp65/IE-1/gB proteins	Differentiates between CD4+ and CD8+ response Allows phenotypic characterization Potential to measure a variety of cytokines and cell surface markers	Requires flow cytometer High cost Lack of technical standardization Labour-intensive No CE marking

CE, European conformity; ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immunoabsorbent spot assay; gB, glycoprotein B; HLA, human leukocyte antigen; ICS, intracellular cytokine staining; IE, immediate-early; IGRA, Interferon-gamma release assay; NK/NKT, Natural Killer/Natural Killer T Cells; PBMCs, peripheral blood mononuclear cells; pp65, phosphoprotein 65.

Table 3
Observational studies and RCTs that have evaluated the clinical application of CMV-CMI monitoring in different clinical scenarios.

Clinical scenario	Predicted event	Proposed intervention	Observational studies	RCTs	Monitoring method
High-risk patients (D+/R-, T-cell-depleting antibodies, lung transplantation) during antiviral prophylaxis or at the time of discontinuation	Late-onset disease[a]	Prolong antiviral prophylaxis or close monitoring for viremia in patients with no protective CMV-CMI	Yes [22,134,23–25,33,50,66,28,135,29,70,136]	Yes [65,27,43]	QTF-CMV, ELISpot
Early posttransplant (between 15-30 days) monitoring in intermediate-risk (R+) patients	Post-transplant viremia and/or disease	Initiate antiviral prophylaxis in patients with no protective CMV-CMI	Yes [33,34,36,37,51,52]	Yes [32]	QTF-CMV, ELISpot, ICS
Intermediate-risk patients (R+) on preemptive therapy with no concurrent viremia	Subsequent viremia and/or disease	Reduce the frequency and/or discontinue monitoring of viremia if adequate response	Yes [33,34,28,135,137–140,141]	No	QTF-CMV, ELISpot, ICS, MHC-tetramer staining
Intermediate-risk patients (R+) on preemptive therapy with asymptomatic viremia	Spontaneous clearance	Withhold antiviral therapy if adequate response	Yes [78,79]	No	QTF-CMV
Active CMV infection or disease after discontinuation of antiviral treatment	Post-treatment relapse	Initiate secondary antiviral prophylaxis if inadequate response	Yes [142]	Yes [143]	QTF-CMV, ICS

CMV: cytomegalovirus; CMV-CMI: cytomegalovirus-specific cell-mediated immunity; D: donor; ELISpot: enzyme-linked immunosorbent spot assay; ICS: Intracellular cytokine staining; QTF-CMV: QuantiFERON-CMV assay; MHC: major histocompatibility complex; R: recipient; RCT: randomized controlled trial.
[a] Refers to the occurrence of CMV disease after discontinuing antiviral prophylaxis with ganciclovir or valganciclovir (usually administered for 100–200 days).

3.2.4.1.1. Consensus recommendations

- During the early post-transplant period, we suggest determining other immune parameters such as absolute lymphocyte count, CD4+/CD8+ T cell subset, and total serum immunoglobulin for a global assessment of the immunological risk of CMV infection **(weak, low).**
- We recommend monitoring IgG levels during the first six months posttransplantation and whenever particularly severe or recurrent infections appear (**strong, moderate**).
- Monitoring CMV-CMI is recommended to optimize the preventive strategy (**strong, moderate**).
- An optimal CMV-CMI test should be cost-effective, reproducible, and applicable to assistance laboratories. No recommendation can be made regarding the best method to be used (**expert opinion, controversial evidence**).

3.2.4.2. Preventive strategies relying on CMV-CMI monitoring. Over the past years, many observational studies and RCTs have investigated the clinical application of CMV-CMI monitoring. This research comprises heterogeneous immune assays, study designs, transplant types, and clinical scenarios (high-risk [D+/R- or T-cell-depletion] or intermediate-risk [R+] patients), which are all summarized in Table 3. Based on these data, we make our recommendations in Table 1 that unify recommended primary preventive strategies by organ and the suggested modifications eventually based on CMV-CMI monitoring availability.

There are four main clinical scenarios in which CMV-CMI monitoring has been applied in CMV prevention. The strategy with the most evidence supports tailoring the duration of antiviral prophylaxis for high-risk patients (D+/R- and R+ treated with T-cell-depleting agents) based on the presence of a protective immune response rather than using a fixed-duration regimen. Observational studies have shown that those with a reactive assay at the end of the planned course of prophylaxis had a lower incidence of late CMV disease than those with a negative (or indeterminate) result [24–26,50,59,69], and even a lower incidence of high-level CMV replication was observed in LT recipients [66]. Three open-labeled RCTs have recently confirmed the safety and effectiveness of this strategy [65,27,43], and another one is pending publication [82]. In a single-center trial, 118 LT recipients were randomly assigned to receive either a fixed 5-month course or a variable length of VGCV prophylaxis based on QuantiFERON® (QTF)-CMV assay results [65]. The incidence of CMV replication in BAL was significantly lower in the immunoguided arm and there were no differences in secondary outcomes, including acute cellular rejection, chronic lung allograft dysfunction, and death within 18 months of therapy, except for a lower recurrence rate of CMV viremia in the experimental arm [65]. The multicenter non-inferiority TIMOVAL trial [43] randomized 150 R+ KT recipients treated with anti-thymocyte globulin (ATG) to receive a fixed three-month course of VGCV prophylaxis or a variable duration based on the results of the QTF-CMV assay. Patients in the experimental group with a reactive QTF-CMV assay discontinued prophylaxis beyond the first post-transplant month to be subsequently managed by preemptive therapy up to month 3. The 12-month incidence of CMV disease was comparable between the experimental and control arms, as was the occurrence of CMV replication. The duration of prophylaxis was significantly reduced in the immunoguided group, and no differences were observed in terms of adverse events, including acute rejection, except neutropenia rate, which benefited the immunoguided arm [43]. Finally, in an open-label RCT carried out in six Swiss centers [27], they randomized 185 high-risk KT and liver transplant patients (R+ recipients receiving ATG or D+/R-) to receive a fixed-duration VGCV prophylaxis (3 or 6 months, depending on the risk group) or monthly CMV-CMI monitoring with an ELISpot assay (T-Track® CMV), discontinuing prophylaxis in the presence of a positive assay result. The clinically significant CMV infection incidence was similar between both groups, although non-inferiority could not be demonstrated. However, the duration of prophylaxis was shortened in the immunoguided group, and there were no differences in the incidence of acute rejection and allograft/patient survival at 1-year follow-up [27].

A second application of CMV-CMI monitoring allows stratifying the intermediate-risk R+ patients without T-cell-depleting induction therapy according to the presence of protective immunity at baseline or early after transplantation. About one-third of R+ patients have been found to lack a detectable CMV-CMI response before transplantation [34–37,56]. Mounting evidence suggests that this subgroup should be considered functionally comparable to R- patients, which would place them in the high-risk category if they receive an organ from a D+ [33,34,36,37,56,144]. Moreover, an early assessment (between 15-30 days posttransplantation) may provide an increased predictive capacity than the pre-transplant evaluation since some patients with robust pre-formed responses may lose their functional CMV-CMI following induction

Table 4
Principal clinical trials of CMV vaccines in solid organ transplantation. Adapted from [145].

Vaccine name	Vaccine type	NCT number	Phase	Route	Study cohort	Primary endpoint	Efficacy
Live-attenuated vaccine and disabled-infectious single cycle vaccine							
Towne vaccine	Attenuated Towne strain	NCT00370006 NCT00373412	I	sc	KT KT CMV HR-R (−) / D (+)	CMV infections	- No benefit in CMV (+). In HR, infection rates similar, less severe CMV disease - Infection rates similar, less severe CMV disease
Adjuvanted recombinant protein vaccine							
gB/MF59	MF59-adjuvanted recombinant soluble Towne strain gB	NCT00299260	II	im	Adults awaiting a KT or LT	Safety and immunogenicity	↑ gB-Ab in CMV (+ and -) vs placebo. In HR, ↓ duration of viraemia and number of days of ganciclovir treatment
DNA vaccine							
ASP0113 (VCL-6365, VCL-6368)	Poloxamer formulated, bivalent DNA vaccine expressing HCMV pp65 and gB	NCT01974206	II	im	Adults KT CMV HR R (−)/D (+)	CMV viremia from 100 d - 1y after the first study vaccine injection	Not efficacy in the prevention of CMV viremia in this cohort KT
Viral vectored vaccine							
HB-101	Bivalent vaccine containing 2 replication deficient lymphocytic choriomeningitis viruses expressing CMV pp65 and gB	NCT03629080	II	im	R (−) adults awaiting a KT from D (+)	Safety, immunogenicity and efficacy	• Results pending

CMV: cytomegalovirus; HR: high-risk patients, CMV D: donor CMV; CMV R: recipients CMV; KT: kidney transplant; LT: liver transplant; sc: subcutaneous; im: intramuscular; CMV: cytomegalovirus; gB: glycoprotein B; SOT: solid organ transplantation.

therapy [32,34]. Another application where CMV-CMI could be useful is to initiate secondary antiviral prophylaxis after discontinuation [143,142]. Finally, various observational studies have assessed the role of CMV-CMI monitoring in preemptively managed intermediate-risk (R+) patients to predict protection against CMV infection [78,33,34,28,79,135,137–141], discriminating those who will be able to spontaneously clear the infection.

3.2.4.2.1. Consensus recommendations

- Posttransplant monitoring of CMV-CMI should be used in R+ high-risk patients to guide antiviral prophylaxis (**strong, high**). This strategy may also be applied to D+/R- patients (**weak, low**).
- Early (between 15-30 days) posttransplant monitoring should be used in R+ intermediate-risk patients to stratify the subsequent CMV infection risk (**strong, moderate**).
- Posttransplant CMV-CMI may be monitored in R+ intermediate-risk patients managed by preemptive therapy to predict CMV spontaneous clearance (**weak, moderate**).
- Posttransplant CMV-CMI could be used to predict the risk of recurrence after discontinuation of treatment (**weak, moderate**).

3.2.5. Vaccines

Published phase-II/III RCTs have been performed mainly on healthy and hematopoietic stem cell transplant (HSCT) recipients [145], with few studies testing them on SOT [146]. Vaccines were generally well tolerated, with an adequate immune response. Unfortunately, they did not clearly demonstrate clinical efficacy. Table 4 references the main advanced clinical studies of vaccines in SOT based on the targets or the technology used in vaccine design.

In transplant patients, the current benefits of vaccines apply to a minority of individuals, and the potential effects on graft dysfunction are being explored as secondary endpoints in some ongoing clinical trials. Future aims will involve the selection of multivalent vaccines, primarily focusing on mRNA and viral-vectored vaccines [147], as well as preventive pre-transplant vaccination.

3.2.5.1. Consensus recommendations

- A recommendation regarding the use of CMV vaccines in SOT recipients cannot be made as no vaccine has been approved for use in a clinical setting (**expert opinion, no evidence available**).

3.3. Treatment

3.3.1. Initial treatment and duration

The efficacy of VGCV for treating CMV disease has been demonstrated in numerous studies [148–153]. IV GCV must be given as initial treatment in patients with severe or life-threatening CMV disease, those with high viral load, and when gastrointestinal malabsorption is suspected [1,6]. Inadequate dosing can lead to ineffective treatment, resistance, and toxicity [154,155]. Consequently, frequent monitoring of renal function is recommended to guide dosage adjustments. Maribavir (MBV) and LET have not been extensively evaluated as initial treatment in SOT patients and are not approved for this indication [156]. Brincidofovir (BCV, CMX-001), given its safety concerns, and filociclovir (MBX-400 or cyclopropavir), still in the preclinical stage, are also not recommended [157–162]. Therapy with CMV-targeted monoclonal antibodies (mAbs) could be a new therapeutic alternative with potential advantages such as higher target specificity, antiviral activity, and lower toxicity [163]. However, there is still a lack of clinical data, with only one ongoing phase II RCT (NCT04225923) in KT recipients for CMV prevention.

The optimum duration should be individualized and continued until symptoms resolve; viral eradication is assessed by a viral load in one or two consecutive weekly samples and, generally, after a minimum treatment course of two weeks [153,164–166]. Secondary prophylaxis is not routinely recommended for all patients [167,168]. Many risk factors for developing recurrent CMV disease have been described, mostly related to primary disease severity and patient immunosuppression [164–166,169–171]. The therapeutic approach to patients suffering from recurrent CMV disease after a disease-free period should be the same as that used during the first episode [153].

3.3.1.1. Consensus recommendations

- CMV disease should be treated with VGCV (900 mg/12 h) or IV GCV (5 mg/kg/12 h), adjusted according to the glomerular filtration rate (**strong, high**).
- IV GCV should be the initial treatment for patients presenting with life-threatening and severe CMV disease or with gastrointestinal malabsorption (**strong, low**).
- Antiviral treatment should continue until clinical symptoms resolve and viral clearance is achieved (**strong, moderate**).
- Secondary prophylaxis is not routinely recommended (**strong, moderate**).

3.4. Refractory/resistant CMV

3.4.1. Concept of refractory/resistant CMV infection

The definitions of refractory/resistant CMV infection were updated during the revision process. We intend to incorporate these modifications into the final version of the document. Refractory CMV infection is defined as CMV viremia that increases (ie, >1 $\log_{10}$ increase in CMV DNA levels in the same blood compartment from the peak viral load as measured in the same laboratory and/or with the same commercial assay) OR persists ($\leq$1 $\log_{10}$ increase or decrease in CMV DNA levels) after at least 2 weeks of appropriate antiviral therapy [172]. Therefore, it is considered a clinical definition based on suboptimal response to treatment criteria. On the other hand, resistant CMV infection is defined as refractory CMV infection, as defined above, in addition to viral genetic alteration that decreases susceptibility to one or more antiviral drugs [172].

3.4.2. Indications for antiviral resistance study

The prevalence of CMV resistance in SOT is low, but its impact on patient outcomes remains high [173,174]. Risk factors include prolonged antiviral drug exposure, younger age, exposure to low levels of GCV or inappropriate antiviral drugs, recipients' negative serostatus, type of transplanted organ, presenting the infection on VGCV prophylaxis, and coadministration of immunosuppressive therapies [175–177].

CMV resistance has been described to all available antivirals, including MBV and LET [178]. After GCV/VGCV exposure, the most common mutations occur in the UL97 kinase gene, followed by the UL54 DNA polymerase gene [175]. The most common UL97 mutations conferring clinical GCV/VGCV resistance are clustered at codons 460, 520, and 590 to 607, typically conferring 5- to 15-fold increases in GCV 50% inhibitory concentrations (EC_{50}), except C592G, which generates 3-fold increases. UL54 mutations typically add to pre-existing UL97 mutations to increase the level of GCV resistance and confer cross-resistance to other anti-CMV drugs [179]. Additionally, after treatment with MBV, it is necessary to evaluate resistance mutations at UL97 and UL27 genes and at UL56, UL89, and UL51 genes if the patient was treated with LET [180,181]. Most diagnostic laboratories test for limited codon ranges, such as 450 to 650 for UL97, 300 to 1000 for UL54, and 229 to 369 for UL56, which cover the most common mutations. However, these approaches could potentially omit some unusual loci where resistance mutations have been reported [182]. Sanger sequencing is the most commonly used method, although its sensitivity is limited to mutations found above 20% frequency in a viral population [183]. Next-generation sequencing (NGS) provides greater sensitivity and a higher resolution for detecting emerging antiviral resistances, although the accurate interpretation of minor variant subpopulations remains a challenge [182,184]. Genotypic testing could be performed on any type of sample [185,186], including plasma and whole blood. Finally, the emergence of new resistance mutants requires their phenotypic confirmation by recombinant phenotyping, which is only performed in reference laboratories [187,188].

3.4.2.1. Consensus recommendations

- Suspect drug resistance in patients with persistent/increasing CMV DNAemia or symptomatic disease despite full-dose therapy at least for 2 weeks, particularly if they have received cumulative antiviral exposure (**strong, high**).
- Sequencing of each genetic locus should be determined based on prior drug exposure (**strong, high**).

3.4.3. Management of refractory/resistant CMV infection

Genotypic analysis should guide treatment whenever possible. In general, immunosuppression should be minimized, including possible mTOR inhibitor conversion. In the case of low viral load and mild clinical symptoms, increasing GCV dose to 10 mg/kg/12 h may be beneficial [189]. This approach seems reasonable in CMV infections with low-level resistance mutations (e.g., C529G of the UL97 gene) and in situations of refractory infection due to malabsorption. However, it poses the risk of relapse due to inefficacy, the appearance of new mutations, and the potential for side effects, particularly neutropenia. Another option is FOS, particularly in cases of high viral load or life-threatening conditions, provided that the recipient does not show renal toxicity. [1]. Nonetheless, the use of FOS has been associated with high mortality and morbidity [190,191]. MBV, with its good oral bioavailability and favorable safety profile, has provided an alternative option for patients with refractory or resistant CMV irrespective of the transplanted organ [192,193]. However, as a possible selection bias in the most recent RCT [193], patients with low viral load and who had little severe damage to other organs were included. Another study on MBV-treated patients reported a 20% resistance rate due to mutations on UL97 (T409M, H411Y, or C480F) [194].

Severe hypogammaglobulinemia has been associated with the development of severe CMV disease episodes that are sometimes refractory to antiviral therapy. Retrospective studies suggested that combined immunoglobulin administration, including patients with refractory CMV, was associated with an improved clinical course [195–199]. However, further studies are required to investigate optimal protocols and their combination with emerging antiviral treatments.

3.4.3.1. Consensus recommendations

- Treatment of resistant CMV should be based on UL97 and UL54 gene analysis (**strong, high**).
- MBV should be used as the first therapeutic option in treating refractory/resistant disease, especially in cases with mild viral load (**strong, high**).
- In patients with GCV resistance, severe CMV disease, and high viral load, we suggest using FOS as initial therapy to decrease viral load and switching to MBV once a moderate-low viral load is achieved (**expert opinion, no evidence available**).

3.5. Adoptive therapy

Adoptive T-cell (ATC) therapy has been successfully employed in HSCT to prevent and treat viral disease [200–202]. In contrast to CMV-specific T cells generated from healthy CMV-seropositive individuals for administration in HSCT [203,204], ATC therapy in SOT relies on the ability to generate CMV-specific T cells from immunosuppressed individuals [205]. However, the development of third-party virus-specific T cell (VST) banks from immunocompetent donors is likely to overcome this issue [206,207].

Most data in SOT are isolated cases describing success in individuals with refractory or resistant CMV infection or limiting forms such as CMV retinitis [208–210]. The most important experience comes from a phase I clinical trial with autologous CMV-specific VST in 13 LT, HT, and KT recipients [211]. It showed an 84% success rate and no serious side

effects, including rejection. Immunosuppressive therapy decreases VST activity. To address this, anti-calcineurin-resistant VSTs have begun to be developed, although they have not yet entered clinical trials [212]. The duration of persistent VST remains relatively unknown and is affected by the characteristics of the infused product (autologous vs. HLA mismatch) and numerous receptor-related factors, such as graft rejection or immunosuppressive medication. Randomized, placebo-controlled trials are needed to assess their actual efficacy and safety.

3.5.1. Consensus recommendations

- Adoptive therapy could be useful as rescue therapy in severe CMV disease refractory to conventional treatment (**weak, very low**). Its implementation as a preventive therapy to replace current drug treatment has not been consistently evaluated in clinical trials (**expert opinion**, **no evidence available**).

4. Conclusions

Despite the progress made in managing CMV infection, there are still several aspects that need clarification. Incorporating CMV-CMI monitoring into clinical algorithms has been shown to improve the prediction of CMV infection and reduce costs associated with preemptive therapy and the use of antivirals through universal prophylaxis. Additionally, it can help address the challenge of determining a viral load threshold for initiating preemptive treatment in asymptomatic patients. However, further studies are needed to establish a consensus on the appropriate cut-off for defining protection from active CMV infection or disease using different assays. It is also important to conduct additional research on the cost-effectiveness of these monitoring techniques.

While the approval of LET for prophylaxis in D+/R- KT recipients and MBV for refractory/resistant disease represent significant progress in disease control, further advancements, such as developing vaccines, mAbs and adoptive therapy, are necessary to reduce the incidence of this disease. Specifically, more data are needed on the use of letermovir in prophylaxis outside of renal transplantation and the use of maribavir in other clinical scenarios, such as in patients with high viral loads.

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