

Resistant CMV Infection: Mechanisms, Management, and Insight

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Disclosures

I have no disclosures.

Objectives

By the end of this presentation, participants will be able to:

- **Describe the epidemiology, clinical impact, and risk factors** for CMV infection and reactivation in solid organ transplant recipients.
- **Differentiate diagnostic approaches** for CMV, including virologic monitoring and resistance testing.
- **Summarize first-line antiviral therapies** and their mechanisms of action.
- **Explain molecular mechanisms of antiviral resistance** and evaluate emerging treatment options for drug-resistant CMV.
- **Interpret institutional trends in resistant CMV** to inform prevention, detection, and stewardship strategies in clinical practice.

CMV General Overview

- **CMV (Human Herpesvirus 5)** is a **double-stranded DNA virus** in the Herpesviridae family.
- After primary infection, it establishes **lifelong latency**, primarily in CD34+ hematopoietic stem cells, myeloid progenitors, and monocytes
- Reactivation can occur during **immunosuppression** or critical illness.
- CMV can be acquired:
 - **Congenitally** (via placenta)
 - **Perinatally** (breast milk, vaginal secretions)
 - **Horizontally** (saliva, urine, sexual contact)
 - **Iatrogenically** (blood transfusion, organ transplantation)

Epidemiology

- **Seroprevalence** varies widely based on geography, age, and socioeconomic status:
 - Globally, the seroprevalence is estimated to be ~ 60 – 90%
 - In the U.S., ~**50–60%** of adults are seropositive.
- **CMV is the most common congenital infection** worldwide (~0.5–1% of all live births in developed countries)
- In **healthy immunocompetent individuals**, primary CMV is usually asymptomatic or causes a **mononucleosis-like syndrome**.
- **Reactivation or primary infection** in **immunocompromised patients** (e.g., transplant, HIV, chemotherapy) can lead to **life-threatening disease**:
 - Presentation can range from asymptomatic viremia to CMV infection to end-organ involvement

CMV Immunology: What Matters Clinically

Innate Response

- NK cells, macrophages, and dendritic cells provide initial control

Adaptive Response

- **CD8+ T cells** are the primary defense: clear primary infection and suppress reactivation
- CMV-specific CD8+ T cells can make up 5–10% of circulating memory T cells (up to 50% of total CD8+ T cells in older adults — "memory inflation")
- **CD4+ T cells** support CD8+ responses; CD4 depletion (e.g., HIV) is strongly associated with CMV disease

Latency & Reactivation

- CMV is latent in **monocytes and myeloid progenitor cells**
- Reactivation is triggered by **myeloid differentiation** (e.g., into macrophages) and impaired T cell surveillance

So, Why Does This Matter?

- Transplant patients rely heavily on **cell-mediated immunity** to control CMV.
- **T-cell depletion** (e.g., anti-thymocyte globulin, alemtuzumab) and **calcineurin inhibitors** weaken CMV-specific immunity.
- Immune reconstitution after transplant (especially in stem cell transplant) determines **risk for CMV reactivation**.
- Ultimately, CMV risk is driven by the patient's net state of immunosuppression—the cumulative impact of immunosuppressive therapy and host factors—not donor/recipient serostatus alone
- **Reactivation is responsible for most cases of CMV viremia** and infection (about 70–80%), while primary infection accounts for 20–30% in solid organ transplant recipients

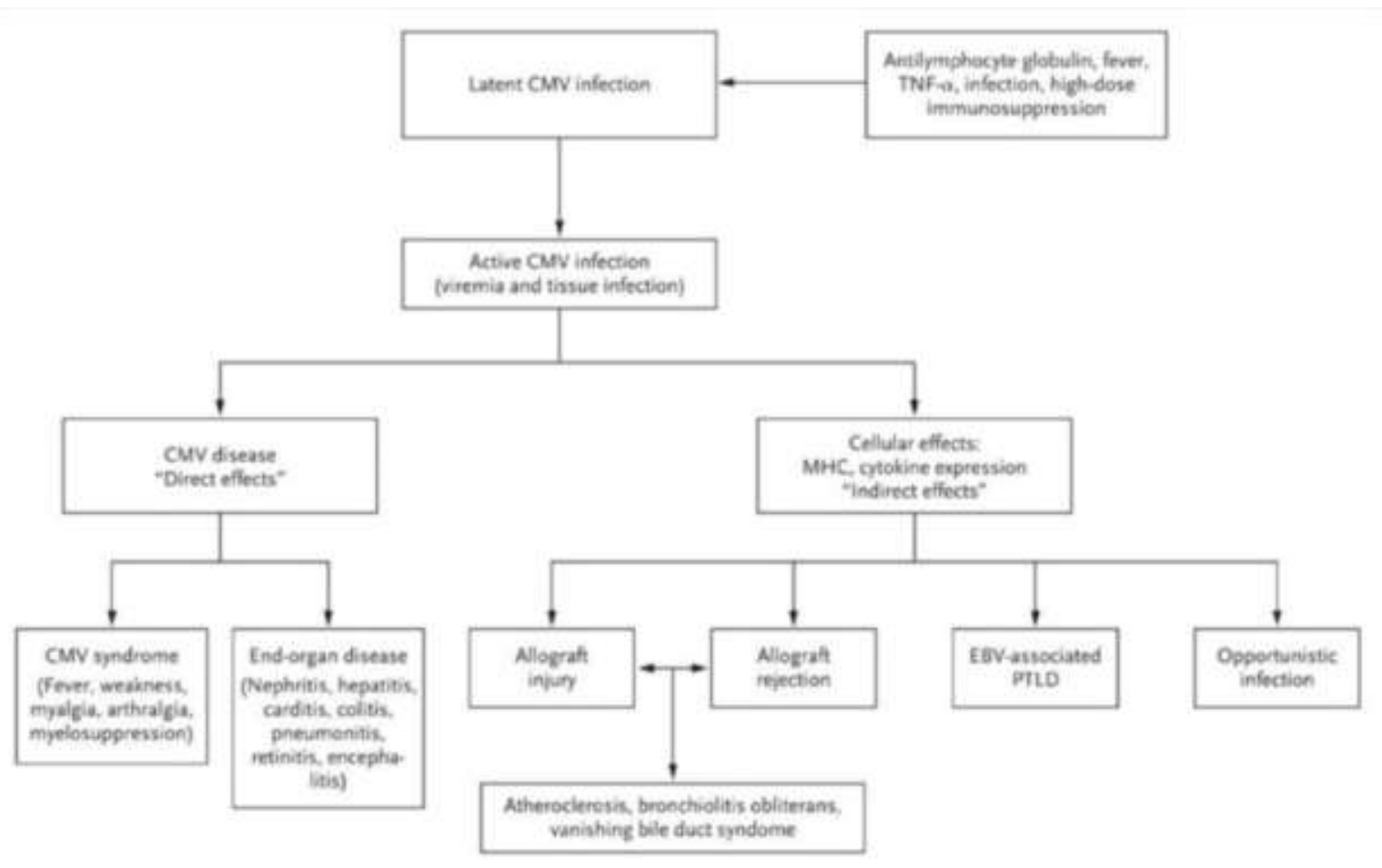
Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33(9):e13512. doi:10.1111/ctr.13512

Stewart AG, Kotton CN. What's New: Updates on Cytomegalovirus in Solid Organ Transplantation. *Transplantation*. 2024;108(4):897-897. doi:10.1097/TP.0000000000004855

CMV Screening in Solid Organ Transplant

- Donor and recipients screened for CMV serology
- Prophylaxis vs preemptive therapy based on D/R serostatus and center protocols
 - D+/R- is highest risk in SOT
 - R+ is highest risk in HSCT
- Direct and Indirect effects of CMV infection cause high morbidity/mortality in SOT population

CMV Direct and Indirect Effects



Fishman, J. A. Infection in Organ Transplantation. *Am J Transplant* **17**, 856–879 (2017)

CMV Risk Factors in SOT

Risk Factors for CMV Infection

- **Serostatus mismatch:** Donor positive / Recipient negative (D+/R-) highest risk
- **Type of transplant:** Lung and intestinal transplants have higher incidence
- Intensity of immunosuppression: Use of antithymocyte globulin (ATG), high-dose steroids
- Delayed or inadequate antiviral prophylaxis
- High baseline CMV viral load or exposure

Risk Factors for CMV Reactivation

- **Recipient CMV seropositivity (R+)**
- **Use of potent immunosuppressive agents** (e.g., lymphocyte-depleting therapies)
- **Episodes of allograft rejection requiring intensified immunosuppression**
- Chronic graft dysfunction or delayed graft function
- Suboptimal antiviral drug exposure or adherence

CMV Risk Factors in HSCT

- **Highest risk: CMV-seropositive recipients (R+)**, due to risk of **viral reactivation**
 - **Donor serostatus** less critical, though **D-/R+** lacks adoptive CMV immunity and increases risk
 - **A seropositive donor may confer CMV-specific immunity**, which can help control viral replication
- **Transplant-related factors:**
 - **Allogeneic > autologous**
 - Increased risk with unrelated, mismatched, or haploidentical donors
- **Immunosuppression-related risk:**
 - **T-cell depletion** (e.g., ATG, alemtuzumab)
 - **Graft-versus-host disease (GVHD)** and corticosteroid therapy
- **Additional risk factors:**
 - Delayed immune reconstitution
 - Myeloablative conditioning
 - Lack of CMV-specific T-cell recovery

What is Universal Prophylaxis

Antiviral therapy (usually **valganciclovir**) is started **immediately after transplant** and continued for a **defined period** (commonly **3–6 months**, longer in high-risk patients).

Advantages

- **Prevents both CMV disease and asymptomatic viremia**
- Provides coverage during high-risk immunosuppressive period
- Reduces incidence of indirect effects (e.g., allograft injury, rejection, other infections)

Disadvantages

- **Drug toxicity** (e.g., leukopenia, neutropenia)
- High cost of prolonged antiviral use
- Late-onset CMV disease can occur after prophylaxis ends
- Potential for antiviral resistance with prolonged exposure

Best for:

- High-risk groups: **D+/R–** recipients, **lung and intestinal** transplants

What is Pre-Emptive Therapy

Regular **CMV PCR or antigenemia monitoring** (e.g., weekly)

Antiviral therapy is **only initiated** if **viremia exceeds a threshold**, before clinical disease develops

Advantages

- Limits **unnecessary drug exposure**
- Reduces **toxicities** and **resistance pressure**
- May lower cost in some settings

•Disadvantages

- Requires **infrastructure** for **frequent, reliable monitoring**
- **Missed or delayed testing** can lead to progression to CMV disease
- Doesn't fully prevent indirect effects
- May be challenging in outpatient settings

•Tends to be Better for:

- **Intermediate-risk patients** (e.g., D+/R+, D-/R+)
- Centers with robust outpatient **CMV monitoring programs**

Example Universal Prophylaxis Regimens (Regimens and Dosing Will Vary By Institution)

CMV Prophylaxis Regimens by Risk Category

Risk Level	CMV Serostatus	Typical Organs	Recommended Strategy	Antiviral	Duration
High Risk	D+/R-	Lung, Intestine, Heart	Universal prophylaxis	Valganciclovir 900 mg once daily (renal adjust)	≥6 months (12 months for lung/intestine)
Intermediate Risk	D+/R+ or R+	Kidney, Liver, Heart	Prophylaxis or Preemptive	Valganciclovir 900 mg once daily	3 months (prophylaxis), or per CMV PCR (preemptive)
Low Risk	D-/R-	All organs	Often no prophylaxis	Observation or short-course valacyclovir/acyclovir	None or up to 1 month

Epidemiology and Clinical Features in SOT

- **Reactivation is responsible for most cases of CMV viremia and infection (about 70–80%), while primary infection accounts for 20–30% in solid organ transplant recipients.**
- Without prophylaxis, infection is most common 1 to 6 months after transplant and is dependent on organ type and immunosuppressive regimen
- The greatest risk of infection is in immunologically naïve, seronegative recipients (R–) of seropositive organs (D+) with up to a 91.9% incidence of viremia and 50–65% rate of symptomatic infection by 90 days posttransplant without prophylaxis
- Viremia and symptomatic infections are rare during effective antiviral prophylaxis but may occur after the cessation of prophylaxis with 25–40% developing symptomatic disease
 - Median time to infection after stopping prophylaxis: **60 – 90 days**

• Fishman, J. A. Infection in Organ Transplantation. *Am J Transplant* **17**, 856–879 (2017)

• Stewart AG, Kotton CN. What's New: Updates on Cytomegalovirus in Solid Organ Transplantation. *Transplantation*. 2024;108(4):884–897. doi:10.1097/TP.0000000000004855

Clinical Features, ie Viremia vs. Syndrome vs. Disease

- CMV viremia refers to the detection of cytomegalovirus in the blood, typically by nucleic acid amplification testing (NAAT), and many infections are often asymptomatic.
- CMV syndrome refers to presence of CMV viremia plus systemic symptoms such as fever, malaise, leukopenia, thrombocytopenia, or elevated transaminases
- CMV disease encompasses both CMV syndrome and tissue-invasive disease, the latter being characterized by evidence of CMV in tissue (e.g., biopsy-proven) with attributable clinical symptoms.
- Invasive disease often involves the allograft

Fishman, J. A. Infection in Organ Transplantation. *Am J Transplant* **17**, 856–879 (2017)

Diagnosis and Treatment (Overview)

- Can be diagnosed by PCR in serum, CSF, BAL or vitreous fluid OR pathology showing cytopathic demonstration of “owl's eye” intracellular inclusions or positive immunohistochemical stains from tissue biopsy
 - PCR alone cannot distinguish asymptomatic viremia from end-organ involvement; **biopsy with CMV immunohistochemistry is gold standard**
 - **Negative plasma PCR does not exclude tissue-invasive CMV**
 - Especially true in gastrointestinal or localized disease; tissue biopsy may be needed even with undetectable viremia
- Initial treatment:
 - Mild/moderate = Valganciclovir (PO)
 - Severe disease = Ganciclovir (IV)

CMV Treatment Pearls

- Continue therapy until CMV PCR is undetectable weekly x2 then stop or consider secondary prophylaxis (depends on severity, time course, increased IS, and current ALC)
 - Monitor q 1 week for 1 month, q2 weeks for month 2, then monthly
 - Monitoring frequency may vary
- For severe infection, can switch from IV Ganciclovir → PO Valganciclovir once clinical improvement/decrease in viral log >1 log or VL <10,000
- Concern for resistance, ie rising viral load?
 - Send CMV resistance panel
 - Escalate treatment to Foscarnet, Maribavir, or Cidofovir

CMV Resistance

Rare but important complication in transplant recipients

Resistant CMV: Detection of a viral mutation associated with reduced antiviral susceptibility

Estimated incidence of ganciclovir resistance:

- ~1% overall in SOT recipients receiving antivirals

- Risk Factors include:
 - High baseline viral load
 - Prolonged viremia
 - Intense Immunosuppression
 - Early Discontinuation of Prophylaxis

- But the single most important risk factor for developing resistance?
 - **Prolonged or subtherapeutic antiviral exposure**

Fisher CE, Knudsen JL, Lease ED, et al. Risk Factors and Outcomes of Ganciclovir-Resistant Cytomegalovirus Infection in Solid Organ Transplant Recipients. *Clin Infect Dis*. 2017;65(1):57-63. doi:10.1093/cid/cix259

Common CMV Resistance Mutations

UL97 Mutations

- **Target:** Viral kinase responsible for the phosphorylation and activation of ganciclovir and valganciclovir
- **Representative Mutations:** M460V/I, A594V, L595S/W, C603W
- **Clinical Implications:**
 - › **Most common resistance mutations in SOT recipients**
 - › Often emerges first, especially with prolonged valganciclovir
 - › Confers resistance to **ganciclovir and valganciclovir**, but not to foscarnet or cidofovir
- **Response to High-Dose Ganciclovir:**
 - › High-dose intravenous ganciclovir (e.g., 7.5–10 mg/kg IV q12h) may partially overcome low-level resistance (e.g., M460V/I)
 - › Less effective for higher-resistance mutations (e.g., C603W)

Common CMV Resistance Mutations

UL 54 Mutations

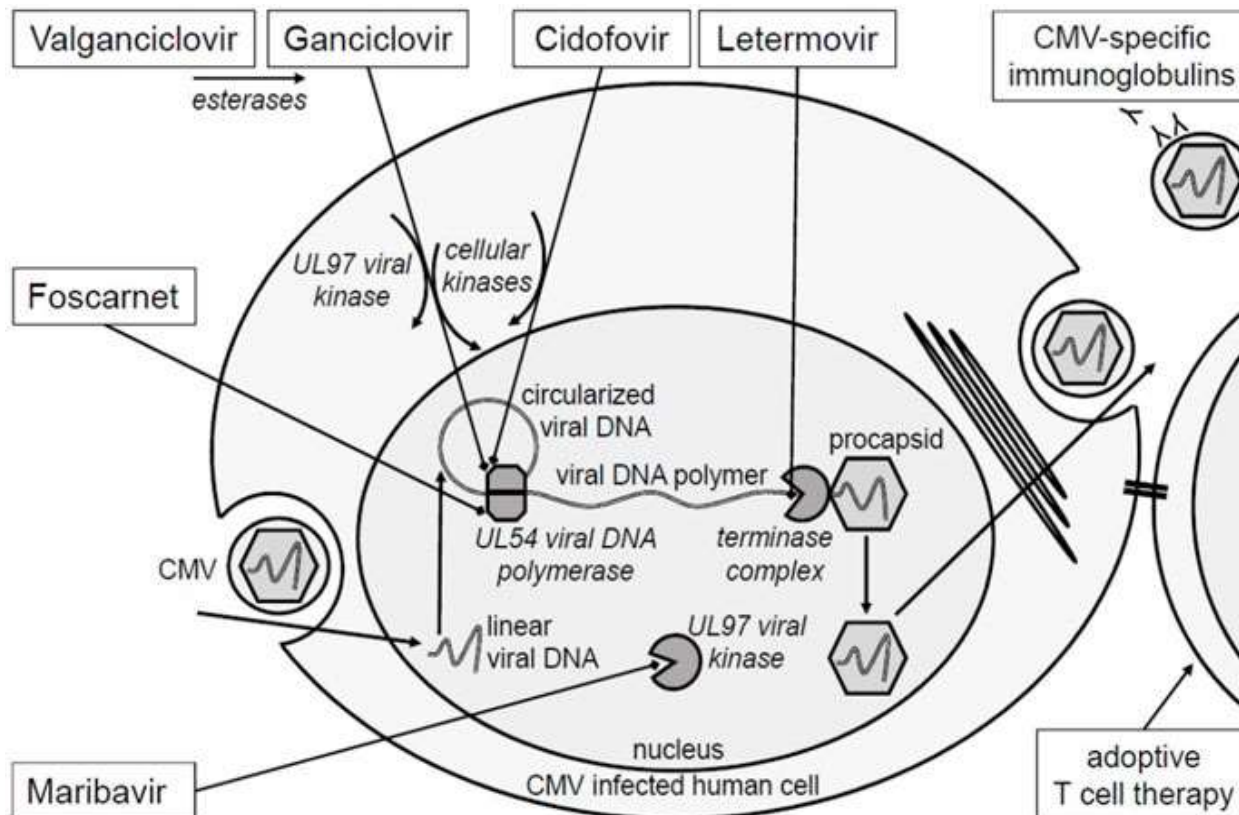
- **Target:** Viral DNA polymerase (direct target of ganciclovir, cidofovir, and foscarnet)
 - Representative Mutations include: D301N, F412C, A987G
- **Effect:** Alters drug-binding site of DNA polymerase → reduces susceptibility to multiple antivirals
- **Clinical Relevance:**
 - Often occurs after or alongside UL97 mutations
 - Can cause **cross-resistance** to ganciclovir, cidofovir, and sometimes foscarnet
 - Indicates multidrug-resistant CMV
- **High-Dose Ganciclovir?**
 - **Generally ineffective**; does **not** overcome UL54-associated resistance

Common CMV Resistance Mutations

UL 56 Mutations

- **Target:** Terminase complex — target of **letermovir**
- **Common Mutations:** V236M, L241P, C325Y
- **Effect:** Disrupts binding of letermovir to viral terminase → letermovir resistance
- **Clinical Relevance:**
 - Rare in solid organ transplant; more commonly seen in **HSCT patients**
 - Emerging with **off-label or prophylactic letermovir use** in SOT
- **High-Dose Ganciclovir?**
 - **Not relevant** (UL56 mutations do not affect ganciclovir activity)

Mechanism of Resistance



Walti CS, Khanna N, Avery RK, Helanterä I. New Treatment Options for Refractory/Resistant CMV Infection. *Transpl Int*. 2023;36:11785. Published 2023 Oct 12. doi:10.3389/ti.2023.11785

Maribavir: A Novel Agent for the Treatment of Resistant CMV

- Prior to maribavir, limited treatment options for resistant CMV and all associated with significant side effects
- **Mechanism of action:**
 - Inhibits the UL97 kinase → blocks CMV DNA packaging and nuclear egress (distinct from ganciclovir)
 - Unlike ganciclovir, **does not require phosphorylation by UL97** to inhibit viral replication
- **Indication:**
 - FDA-approved for **refractory or resistant CMV infection** in SOT and HSCT (2021)

What was the trial that supports Maribavir in SOT?

Clinical Infectious Diseases

MAJOR ARTICLE

 **IDSA**
Infectious Diseases Society of America

 **hivma**
HIV Medicine Association

 **OXFORD**

Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomized Clinical Trial

Robin K. Avery,¹ Sophie Alain,² Barbara D. Alexander,³ Emily A. Blumberg,⁴ Roy F. Chemaly,⁵ Catherine Cordonnier,⁶ Rafael F. Duarte,⁷ Diana F. Florescu,⁸ Nassim Kamar,⁹ Deepali Kumar,¹⁰ Johan Maertens,¹¹ Francisco M. Marty,^{12,3} Genovefa A. Papanicolaou,^{13,14} Fernanda P. Silveira,¹⁵ Oliver Witzke,¹⁶ Jingyang Wu,¹⁷ Aimee K. Sundberg,¹⁸ and Martha Fournier¹⁸, for the SOLSTICE Trial Investigators³

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Study Design

Study Design:

- Phase 3, **multicenter, open-label, randomized controlled trial**
- Included **HSCT and solid organ transplant recipients with refractory or resistant CMV infection**
- Patients randomized 2:1 to **maribavir vs. investigator-assigned therapy (IAT)**
 - IAT: valganciclovir/ganciclovir, foscarnet, or cidofovir

Participants

- **352 patients** randomized (maribavir n=235; IAT n=117)
- Refractory = persistent viremia after ≥ 14 days of antiviral therapy
- Resistance confirmed in $\sim 33\%$ of patients by genotypic testing

Primary Endpoint

- **Confirmed CMV viremia clearance at Week 8** (by central lab PCR)

Study Results

- **Superior efficacy in clearing CMV viremia at 8 weeks:**
 - 55.7% clearance with maribavir vs. 23.9% with standard therapy ($P < 0.001$)
- **Effective in patients with refractory or genotypically resistant CMV**
- Approximately one-third of patients had confirmed resistance mutations
- **Improved safety and tolerability profile:**
 - Fewer discontinuations due to adverse events (13.2% vs. 31.9%)
 - Lower nephrotoxicity compared to foscarnet
 - Less myelosuppression compared to (val)ganciclovir
- Benefit demonstrated across different transplant types, including solid organ transplants
- **Led to FDA approval for treatment of refractory or resistant CMV infection in post-transplant patients** due to clear advantages in efficacy and safety over existing therapies

Overview Maribavir Advantages and Limitations

- **Advantages:**

- Active against resistant and refractory CMV
- Oral formulation allows outpatient management
- **Well tolerated**
 - Minimal **myelotoxicity** (vs. ganciclovir/valganciclovir)
 - Minimal **nephrotoxicity** (vs. foscarnet)
- Fewer treatment discontinuations due to adverse effects

- **Limitations:**

- **Not approved for prophylaxis** (but sometimes used off-label)
- Most common adverse effect: **dysgeusia**
- **Less data to support use for tissue-invasive disease**
- Risk of UL97-mediated resistance
- **Inhibits P-gp/CYP3A4** → raises tacrolimus AUC by **~51%**; monitor immunosuppressant levels closely on initiation and discontinuation

Maribavir Pearls

- Maribavir **efficacy declines with increasing baseline CMV viral load** (62% clearance if <9,100 IU/mL, 47% if 9,100–90,999 IU/mL, and 29% if ≥91,000 IU/mL from a sub-group analysis).
- Consider alternative or intensified initial strategies in patients with **severe disease or very high-level viremia** (e.g., short-course foscarnet to reduce viral burden prior to maribavir initiation or combination therapy in select cases).
- Most clinical data are derived from patients with **CMV DNAemia** rather than tissue-invasive disease.
- Assess for drug-drug interactions and monitor **immunosuppressant levels** when initiating or discontinuing therapy.
- Resistance can emerge during therapy; **persistent or rising viremia** should prompt reassessment and repeat resistance testing when appropriate.

<https://www.livtencity.com/efficacy#efficacyTabs-item-85a2d5735e-tab>

Hill John A. et al. *ASTCT/EBMT/ECIL Consensus Recommendations for the Management of Resistant and Refractory Cytomegalovirus Infection in Hematopoietic Cell Transplantation and Cellular Therapy Recipients*. 2025. Recommendation primarily on expert opinion and limited clinical data (B-II/C-III).

Recent Updates in CMV

4th International CMV Consensus Guidelines (2025)

- Establishes updated standards for letermovir prophylaxis and maribavir use in refractory/resistant disease
- Incorporates cell-mediated immune monitoring and standardizes international CMV-QNAT reporting thresholds

Letermovir vs. Valganciclovir in D+/R- Kidney Recipients

- Non-inferior efficacy at 52 weeks (10.4% vs. 11.8% CMV disease)
- Significantly lower rates of leukopenia (11.3% vs. 37.0%) and neutropenia (2.7% vs. 16.5%)
- No letermovir resistance detected during the study

Immune-Guided CMV Management

- CMV-specific T-cell assays show promise for individualizing prophylaxis duration
- Key tool for identifying patients at high risk for late-onset or recurrent disease; prospective validation ongoing

Kotton CN, Kumar D, Caliendo AM, et al. The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation. *Transplantation*. 2025;109(7):1066–1110. doi:10.1097/TP.0000000000005374. Limaye AP, Budde K, Humar A, et al. Letermovir vs valganciclovir for prophylaxis of cytomegalovirus in high-risk kidney transplant recipients: a randomized clinical trial. *JAMA*. 2023;330(1):33–42. doi:10.1001/jama.2023.9108. Dadwal S, Taplitz R, et al. American Society for Transplantation and Cellular Therapy, European Bone Marrow Transplantation, and European Conference on Abstracts in Leukaemia consensus recommendations for the management of resistant and refractory cytomegalovirus infection. *Transplant Cell Ther*. 2025.

CMV Resistant Cases in SOT at MUSC: January 2019 – December 2023

A Retrospective Review

Resistant CMV Infections in SOT at MUSC

- String of resistant CMV cases on service led to our team to study potentially preventable etiologies of CMV resistance & improve institutional practices
- Confirmed CMV resistance cases Jan 2019 – Dec 2023 with 1 year follow up
 - 18 patients with resistant CMV
 - 50% (9) were in renal transplant
 - 94% were CMV D+/R-
 - 83% were on prophylaxis at time of initial diagnosis of CMV

Variable	n=18
Transplant recipient baseline characteristics	
Median age, years [IQR]	57 [43, 60]
Male, n (%)	10 (56)
White non-Hispanic, n (%)	6 (33)
Type of Transplantation, n (%)	
Kidney	9 (50)
Liver	0
Lung	3 (17)
Heart	3 (17)
Heart-kidney	1 (6)
Kidney-pancreas	2 (11)
CMV serostatus, n (%)	
D+/R-	17 (94)
D-/R-	1 (6)
Prophylaxis type	
Valganciclovir	17 (94)
Valacyclovir	1 (6)
Was prophylaxis stopped early for any reason (compared to protocol duration)?	0
Rejection in past 6 months	0

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Resistant CMV Infections in SOT at MUSC

- Of those on prophylaxis (n=15), 9 (60%) were due to suspected or confirmed under-dosing of prophylaxis
 - 7/9 (78%) renal transplant
- Majority were asymptomatic
- Additional opportunities for improvement
 - ID was only consulted in 39% of first-time CMV infection

Diagnosis of Infection, n (%)	
Resistance test positive on first test performed	16 (89)
CMV involvement	
CMV DNAemia	10 (56)
CMV syndrome	4 (22)
CMV end-organ disease	4 (22)
Colitis	1 (6)
Pneumonitis	2 (11)
Retinitis	1 (6)
Esophagitis	1 (6)
Stage of Infectious Disease consultation	
Initial CMV infection	7 (39)
First CMV recurrence	7 (39)
Second CMV recurrence or later	2 (11)
Never	2 (11)
Treatment and Outcomes, n (%)	
Immunosuppression reduced	16 (89)
Drug choice once resistance suspected/confirmed	
Foscarnet	9 (50)
Maribavir	9 (50)
Virologic Clearance	
Clearance of DNAemia	12 (67)
Persistent DNAemia	6 (33)
Outcomes	
Graft failure	3 (17)
All-cause mortality	3 (17)
Mortality secondary to CMV	1 (6)

Take Home Points: CMV Prophylaxis and Early Management in SOT

- **Inappropriate prophylaxis dosing is a common and preventable cause of CMV breakthrough**
 - Remember, **subtherapeutic or prolonged anti-viral exposure remains the single most, consistently identified risk factor for developing resistance**
 - 60% of CMV infections in patients on prophylaxis were associated with confirmed or suspected under-dosing
- **Renal transplant recipients are disproportionately affected**
 - 78% of under-dosed cases occurred in renal transplant recipients
 - Valganciclovir is the most used agent for prophylaxis and requires renal dose adjustments
 - These patients often experience **delayed graft function and fluctuating renal clearance**, requiring ongoing dose adjustment and close monitoring

Take Home Points: CMV Prophylaxis and Early Management in SOT

- **ID consultation is underutilized in initial CMV management**

- Infectious Diseases was involved in only 39% of first-time CMV infection episodes
- Early consultation may facilitate timely resistance testing and optimization of antiviral therapy
- Lack of ID involvement may delay recognition of underdosing or emerging antiviral resistance
- Early engagement can improve coordination of longitudinal care, especially in high-risk or complex cases

- **Lack of standardized protocols contributes to missed opportunities**

- Variability in prescribing practices, monitoring frequency, and consultation patterns highlights the need for structured process improvement
- Absence of clear, system-wide CMV management pathways may contribute to delayed intervention and preventable disease progression

Improving CMV Prevention and Management

- **Prioritize accurate, renal-adjusted dosing of valganciclovir**
 - Reassess dosing regularly, especially in patients with delayed graft function or fluctuating renal function
- **Standardize CMV prevention protocols across the care continuum**
 - Include clear guidance on prophylaxis, monitoring frequency, and thresholds for intervention
- **Involve Infectious Diseases early in CMV management**
 - Ensure timely evaluation for resistance and support optimal antiviral strategy
- **Integrate CMV stewardship into transplant care pathways**
 - Align practices across teams to prevent avoidable infections, resistance, and treatment delays

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