Cytomegalovirus in solid organ transplant recipients: Management strategies and emerging therapeutic options

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Management challenges in solid organ transplant recipients with cytomegalovirus

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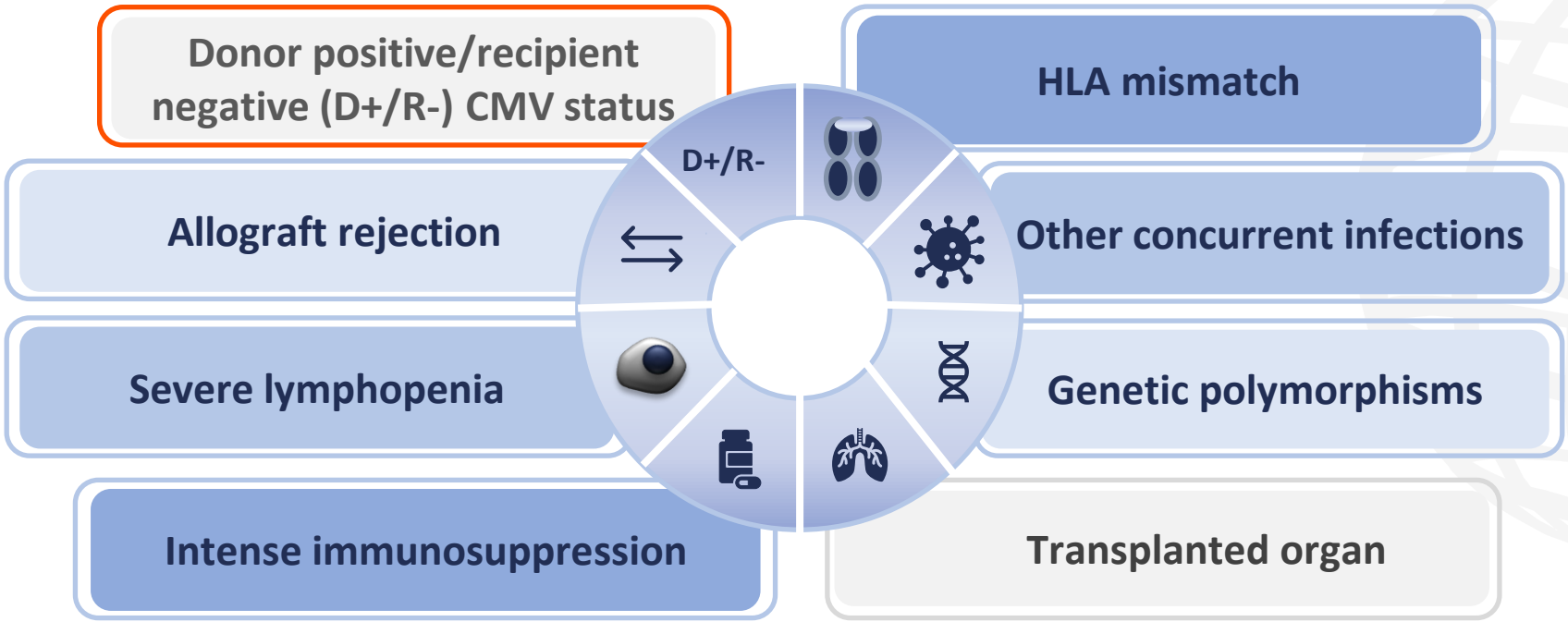
Risk factors for CMV after solid organ transplant



CMV, cytomegalovirus; HLA, human leucocyte antigen.
Kotton CN, et al. *Transplantation*. 2018;102:900–31.

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Pre-emptive and prophylaxis strategies for CMV infection

	Prophylaxis	Pre-emptive therapy
Early CMV DNAemia/infection	Rare	Common
Prevention of CMV disease	Good efficacy	Good efficacy
Late CMV (infection/disease)	Common	Rare
Resistance	Uncommon	Uncommon (with weekly testing)
Ease of implementation	Relatively easy	More difficult
Prevention of other herpes viruses	Prevents HSV/VZV	Does not prevent
Other opportunistic infections	May prevent	Unknown
Costs	Drug costs	Monitoring costs
Safety	Drug side effects	Less drug toxicity
Prevention of rejection	May prevent	Unknown
Graft survival	May improve	May improve

CMV, cytomegalovirus; HSV, herpes simplex virus; VZV, varicella zoster virus.

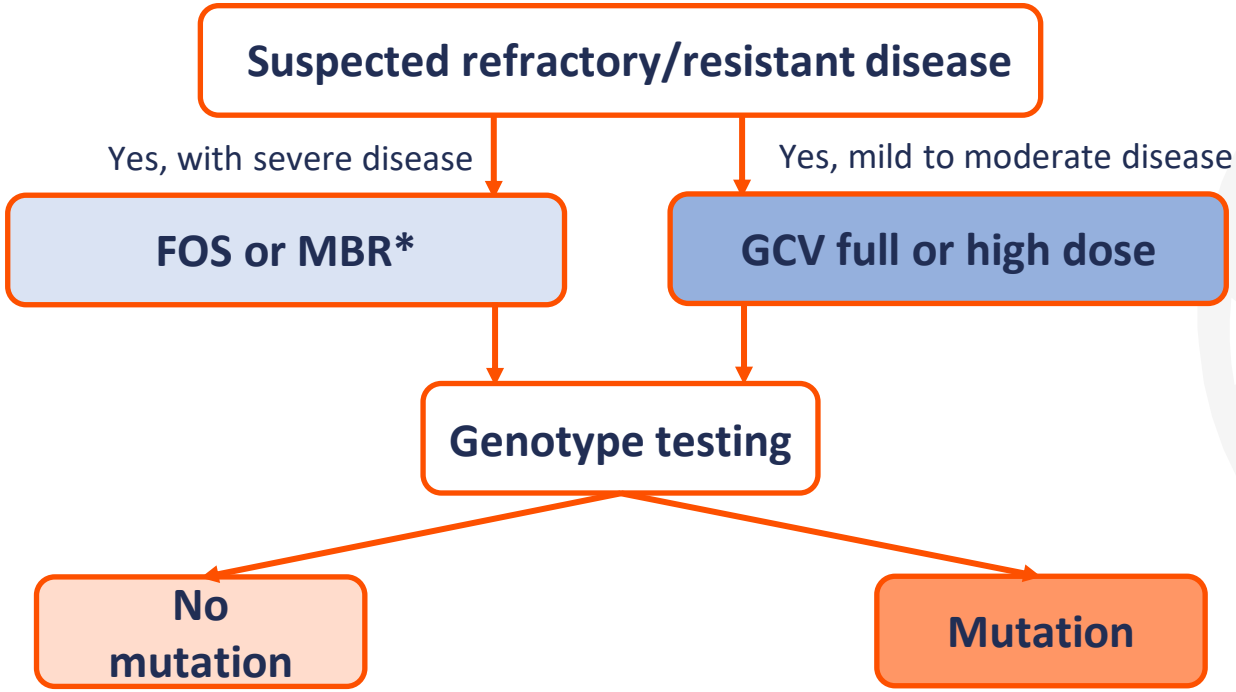
Kotton CN, et al. *Transplantation*. 2018;102:900–31.

Safety profile of current treatment options for solid-organ transplant recipients with CMV infection?

Agent	Most common adverse events	Monitoring
Ganciclovir/valganciclovir	Myelosuppression	Standard*
Foscarnet	Nephrotoxicity and electrolyte wasting	Standard*
Cidofovir	Nephrotoxicity, Fanconi syndrome and ocular toxicity	Standard*
Maribavir	Diarrhoea, dysgeusia, tremor and DDI	Monitor tacrolimus substrate levels
Immunoglobulins	Nephrotoxicity, thrombosis, haemolysis and TRALI	CBC differential, vital signs, respiratory function and oxygen requirements

*Standard monitoring includes CBC differential, serum creatinine and serum electrolytes.
CBC, complete blood count; CMV, cytomegalovirus; DDI, drug–drug interactions; TRALI, transfusion-related acute lung injury.
El Helou G, Razonable RR. *Expert Opin Drug Saf.* 2019;18:1017–30.

Management of suspected CMV resistance (1/2)



*Do not use MBR if ophthalmologic or CNS disease.
CMV, cytomegalovirus; CNS, central nervous system; FOS, foscarnet; GCV, ganciclovir; MBR, maribavir.
Kotton CN, et al. *Transplantation*. 2018;102:900–31.

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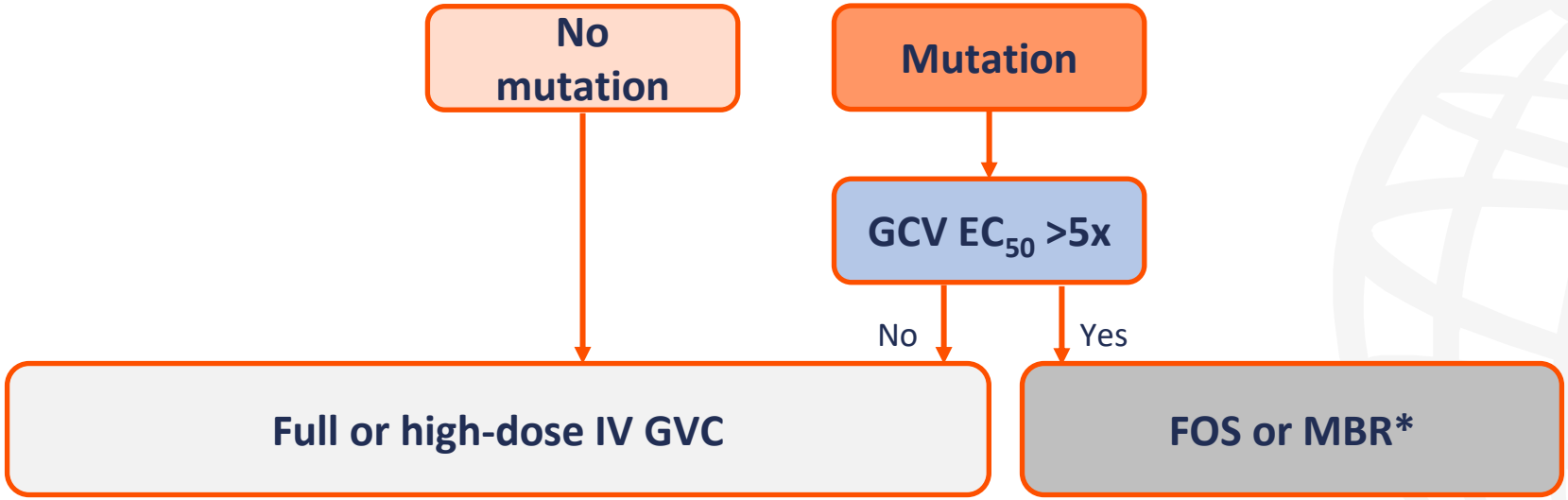
Management of suspected CMV resistance (2/2)



If no improvement in viral load after 3 weeks, repeat resistance genotyping and consider non-standard or experimental treatment

*Do not use MBR if ophthalmologic or CNS disease.

CMV, cytomegalovirus; CNS, central nervous system; EC_{50}, half maximal effective concentration; FOS, foscarnet; GCV, ganciclovir; IV, intravenous; MBR, maribavir; R, resistance.

Kotton CN, et al. *Transplantation*. 2018;102:900–31.

Treatment options for refractory/resistant cytomegalovirus in solid organ transplant recipients

Dr Raymund Razonable

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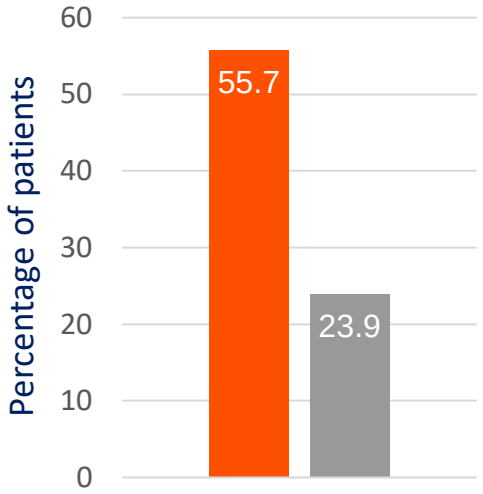
Phase III trial of maribavir vs investigator-assigned therapy

Primary endpoint

CMV clearance at end of week 8



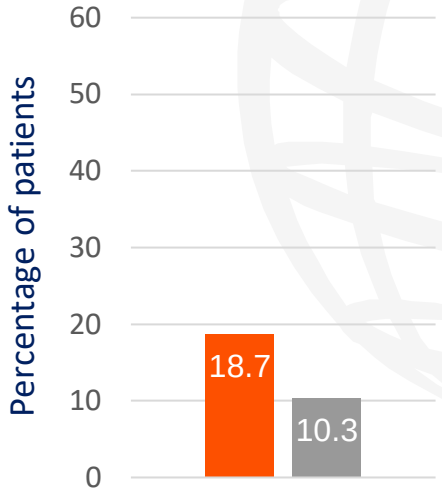
TEAEs

- Less acute kidney injury vs foscarnet (8.5% vs 21.3%)
- Less neutropenia vs valganciclovir/ganciclovir (9.4% vs 33.9%)
- Fewer patients discontinued treatment due to TEAEs (13.2%) than IAT (31.9%)

Maribavir (n=235)
IAT (n=117)

Secondary endpoint

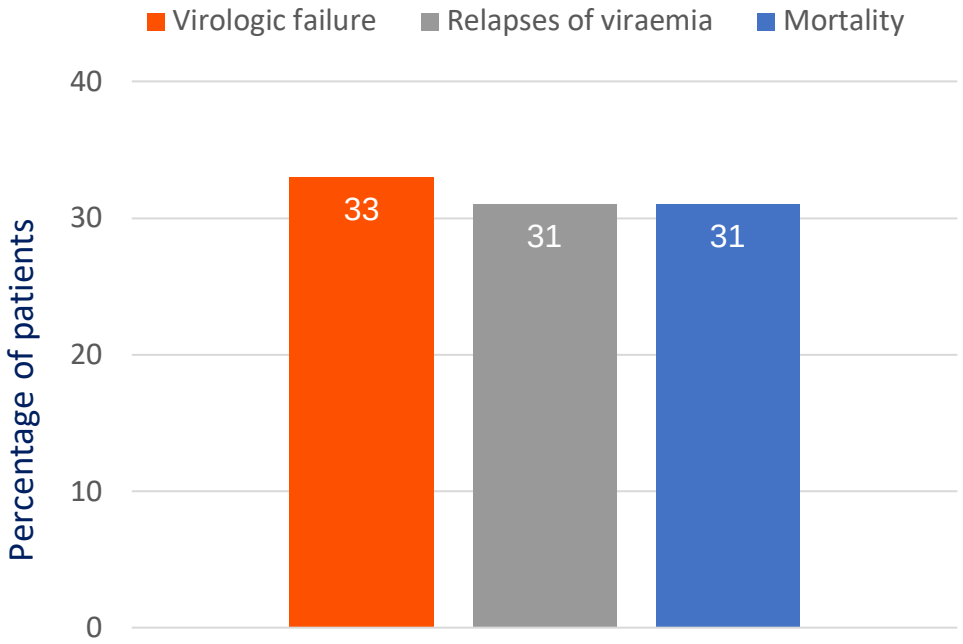
CMV clearance and symptom control at end of week 8, maintained through week 16

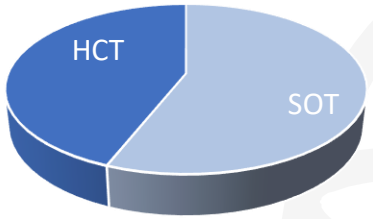


CMV, cytomegalovirus; IAT, investigator-assigned therapy; TEAE, treatment-emergent adverse event.

Avery RK, et al. *Clin Infect Dis*. 2021;Dec 2:ciab988.

Retrospective review of foscarnet treatment for ganciclovir-resistant/refractory CMV infection





N=39 (HCT n=17; SOT n=22); 15 had ganciclovir resistance mutations and 11 had tissue-invasive CMV

- Mortality was higher in HCT than SOT (p=0.001)
- Ganciclovir resistance was more common in SOT (p=0.003)
- Renal dysfunction occurred in 51% of patients by the end of treatment and in 28% after 6 months

CMV, cytomegalovirus; HCT, haematopoietic cell transplant; SOT, solid organ transplant.

Avery RK, et al. *Transplantation*. 2016;100:e74–80.

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Letermovir in SOT recipients with R/R CMV disease

- Approved only for **prophylaxis** of CMV infection and disease in adult CMV-seropositive allogenic HSCT recipients[1]
- CMV DNA terminase complex inhibitor rather than acting at the DNA polymerase level; therefore, activity is expected against CMV isolates resistant to other agents[2]
- Not currently indicated for treatment of CMV; however, it is used off-label in SOT recipients[2]
- Limited data, primarily case studies, support the use in SOT recipients[2]

CMV, cytomegalovirus; HSCT, haematopoietic stem cell transplant; R/R, refractory/resistant; SOT, solid organ transplant.

1. FDA. Letermovir PI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017.pdf (accessed 19 August 2022);
2. Linder KA, et al. *Transpl Infect Dis*. 2021;23:e13687.

Potential role of immunoglobulin for treating SOT recipients with CMV infection

Adjunct to ganciclovir prophylaxis for select high-risk heart and/or lung transplant recipients, and as an adjunct to antiviral drug treatment of severe CMV disease

Generally well tolerated but associated with:

- Nephrotoxicity
- Thrombotic events
- Neurotoxicity
- Haemolysis
- TRALI

CMV, cytomegalovirus; SOT, solid organ transplant; TRALI, transfusion-related acute lung injury.

El Helou G, Razonable RR. *Expert Opin Drug Saf.* 2019;18:1017–30.

Best practice in the management of refractory/resistant CMV

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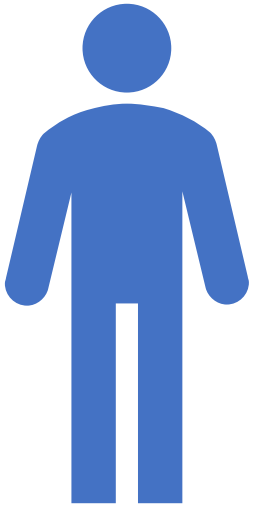
Patient case overview



- 45-year-old recipient of a kidney transplant
- Despite treatment with ganciclovir, two consecutive qPCR tests separated by 2 days showed CMV DNA value of 1,110 IU/mL

CMV, cytomegalovirus; qPCR, quantitative polymerase chain reaction.

Mutations in refractory/resistant CMV

UL97

- Encodes for the thymidine kinase essential for phosphorylation of ganciclovir into its active form[1]
- In patients initially treated with ganciclovir, *UL97* kinase gene mutations appear first in about 90% of cases[2]

UL54[2]

- Mutations usually evolve later, conferring increased ganciclovir resistance and likely cross-resistance to cidofovir and/or foscarnet
- Not commonly the first mutation to be detected

CMV, cytomegalovirus.

1. Razonable RR, et al. *J Clin Microbiol*. 2002;40:746–52; 2. Kotton CN, et al. *Transplantation.* 2018;102:900–31.

Treatment options for refractory/resistant CMV

Agent	Most common adverse events	Monitoring
Ganciclovir/valganciclovir	Myelosuppression	Standard*
Foscarnet	Nephrotoxicity and electrolyte wasting	Standard*
Maribavir	Diarrhoea, dysgeusia, tremor and DDI	Monitor tacrolimus substrate levels
Letermovir	Vomiting and diarrhoea	GI endoscopy if severe GI adverse events to monitor for GVHD

*Standard monitoring includes CBC differential, serum creatinine and serum electrolytes.
CBC, complete blood count; CMV, cytomegalovirus; DDI, drug–drug interactions; GI, gastrointestinal; GVHD, graft versus host disease.
El Helou G, Razonable RR. *Expert Opin Drug Saf.* 2019;18:1017–30.

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Treatment options following mutated disease

Ganciclovir

- Some *UL97* mutations confer lower levels of ganciclovir resistance by themselves
- High dose, up to 10 mg/kg twice daily
- Dose should be adjusted for renal function

Maribavir

- UL97 kinase inhibitor
- Oral maribavir may be administered at 400 mg twice daily
- Most common side effects are dysgeusia, nausea and diarrhoea

CMV, cytomegalovirus.

Kotton CN, et al. *Transplantation.* 2018;102:900–31.

Treatment options following mutated disease

Foscarnet[1]

- Recommended if mutation confers higher level ganciclovir resistance
- Metabolic and renal toxicities may impair eventual treatment outcomes

Letermovir[2]

- Occasionally used off-label for treatment of ganciclovir-resistant CMV infection
- Potential low genetic barrier to resistance; therefore, use may be restricted to treatment of low viral load

CMV, cytomegalovirus.

Kotton CN, et al. *Transplantation*. 2018;102:900–31; 2. Silva JT, et al. *Microbiol Clin (Engl Ed)*. 2021;39:87–97.

Considerations when personalizing treatment

- Severity of disease
- Therapeutic drug monitoring
- D+/R- Donor/recipient status
- Continuing genotypic testing
- Severe immunosuppression
- Adjunctive therapy

Kotton CN, et al. *Transplantation*. 2018;102:900–31.