Prophylaxis and Management of Cytomegalovirus (CMV) in the Renal Transplant Patient	University Hospitals of Leicester NHS NHS Trust **Trust ref: C123/2016** **RRCV CMG** **Nephrology Service**

1. Introduction

In the pre-antiviral era, CMV was a major cause of mortality and graft loss secondary to increased immunosuppression after transplantation.

Following a primary infection an individual will mount an IgM antibody response and later an IgG response against CMV. It is the presence of CMV IgG antibody by serology which determines the prior exposure of donors and recipients to CMV infection. Ideally, recipient and donor should be matched according to their CMV status. In practice, however, the matching of CMV status between recipient and donor can rarely be achieved due to the dearth of available organs.

Quantitation of CMV DNA in an EDTA blood sample has now become the routine diagnostic test in the immunosuppressed host both for the diagnosis of a disseminated infection and the monitoring of the response to treatment. Biopsy of the affected organ may be subjected to histopathological investigation (intranuclear inclusion bodies and/or PCR) for the confirmation of CMV infection.

Preventative strategies include prophylaxis or a pre-emptive/screening approach

2. Scope

This guideline is intended for clinical staff involved in the management of Renal Transplant patients

3. Recommendations, Standards and Procedural Statements

3.1 Prophylaxis against CMV disease

Primary infection with CMV usually occurs 4-6 weeks post-transplantation of a sero-positive organ to a sero-negative recipient or due to reactivation of latent infection. Direct morbidity (CMV disease) ranging from viral syndrome (fever, night sweats, fatigue, myalgia) to demonstrated organ involvement (renal impairment, GI symptoms, respiratory symptoms, leucopoenia, thrombocytopenia, anaemia etc) may occur with the following associated complications:

- Acute and chronic graft rejection
- Decreased graft survival
- Opportunistic infections
- Death
- Increased cost to transplant programme
- Accelerated atherosclerosis

3.2 Antiviral management - prophylaxis.

3.2.1 Selective prophylaxis targets high-risk patients (R-/D+) and excludes D-/R- recipients and uncomplicated D-/R+ recipients.

3.2.2 Selective prophylaxis may be extended to R+/D- or R+/D+ recipients at higher risk of CMV replication and disease due to intensification of immunosuppression with high dose steroids, ATG/AlemtuzumabRituximab therapy with or without the presence of CMV DNA in plasma.

3.2.3 Prophylaxis also protects against harmful low-level CMV viral replication and is easy to administer

DONOR	RECIPIENT	Risk of relapse	Recommended Regimen (dose adjust for GFR)
+	-	High	Valganciclovir for 200 days (6 months) *__RESTART__ oral Valganciclovir prophylaxis for 100 days if patient subsequently receives intensified IS with ATG / Alemtuzumab / Rituximab
+	+	Intermediate	No Prophylaxis *__UNLESS__ patient subsequently receives intensified IS with ATG / Alemtuzumab / Rituximab, then start oral Valganciclovir for 100 days
-	+	Intermediate	
-	-	Low	No prophylaxis

Equivocal results: Where the CMV result is equivocal we recommend starting Valganciclovir as above until a definitive results is obtained. The sample must also be repeated in 1- 2 weeks to confirm.

Potential Adverse Effects

CMV prophylaxis can cause leucopoenia and diarrhoea in up to 52% patients which can lead to discontinuation of medication and risk of viral proliferation.

3.2.4 When to use a pre-emptive approach - This is not a 1st line approach because:

***i)* There are significant logistical challenges and risk around reviewing results**

***ii)* Requires weekly CMV PCR monitoring** until patient completes either 6 months or 3 months of monitoring as per above chemoprophylaxis table.

This approach can be used for patients where there are significant side-effects with valganciclovir. When active disease is detected treatment of CMV is given as per protocol below

3.3 Antiviral management - treatment of CMV viraemia

3.3.1 Treatment is offered after the appearance of CMV viraemia >745 IU (lower cut-off value at UHL). CMV viraemia can present as CMV viral syndrome or CMV disease. CMV disease can be divided in to mild, moderate or severe disease and should always be discussed with a consultant virologist.

3.3.2 For CMV viral syndrome or mild-moderate CMV disease, Valganciclovir is used first line at treatment dose. For severe CMV disease (neutropenia, significant UGI symptoms, tissue invasive and or life-threatening illness), ganciclovir IV is used first line and once patient makes clinical recovery, ganciclovir may be changed to treatment dose valganciclovir until treatment iscomplete.

3.3.3 The management of CMV disease involves reduction/withdrawal of antimetabolite therapy as the presence of CMV infection implies over-immunosuppression.

3.3.4 Oral Valganciclovir dosing

Valganciclovir (tablets) - Doses adjusted for renal function (using **Cockcroft- Gault formula**)

GFR (mL/min)	**Induction/Treatment** dose	**Maintenance/Prophylaxis** dose
≥ 60	900 mg twice daily	900 mg once daily
40-59	450 mg twice daily	450 mg once daily
25-39	450 mg once daily	450 mg every 48 hours
10-24	450 mg every 48 hours	450 mg twice weekly
< 10	450 mg twice weekly	450mg* once weekly

*manufacturer does not recommend tablets when GFR less than 10ml/min. In practice we recommend 450mg starting dose and titrate as GFR improves. If the patient remains haemodialysis dependent, continue 450 mg once weekly after haemodialysis

Valganciclovir – Oral Solution (50mg/ml): Doses adjusted for renal function (using **Cockcroft- Gault formula**)

Consider prescribing for patients unable to take tablets or need a low dose, depending on product availability.

GFR (mL/min)	**Induction/Treatment** dose	**Maintenance/Prophylaxis** dose
25-39	450 mg once daily	225mg once daily
10-24	225mg once daily	125mg once daily
Transplant patients who remain haemodialysis dependent GFR < 10ml/min	200mg three times a week after haemodialysis	100mg three times a week after haemodialysis

3.3.4 Intravenous Ganciclovir dosing: Doses adjusted for renal function (using **Cockcroft- Gault formula**)

GFR (mL/min)	**Induction/Treatment** dose	**Maintenance/Prophylaxis** dose
≥ 70	5 mg/kg twice daily	5 mg/kg once daily
50-69	2.5 mg/kg twice daily	2.5 mg/kg once daily
25-49	2.5 mg/kg once daily	1.25 mg/kg once daily
10-24	1.25 mg/kg once daily	0.625 mg/kg once daily
< 10	1.25 mg/kg three times a week after haemodialysis	0.625 mg/kg three times a week after haemodialysis

3.3.5 Length of course

In patients with proven CMV infection, treatment is given until the CMV PCR is negative on two occasions at least 2 weeks apart and then stopped. Prolonged induction treatment may increase the risk of bone marrow toxicity.

Treatment is followed by oral Valganciclovir prophylactic treatment for one month after resolution of CMV disease following mild illness, and for three months after severe illness, although there are no randomised trials to inform this strategy (BTS guidance)

4. Education and Training

No specific training required

5. Monitoring and Audit Criteria

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Key Performance Indicator	Method of Assessment	Frequency	Lead
CMV cases in patients transplanted for more than one year	Proton ILAB data	Annual	

6. Legal Liability Guideline Statement

See section 6.4 of the UHL Policy for Policies for details of the Trust Legal Liability statement for Guidance documents

7. Supporting Documents and Key References

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8. Key Words

Cytomegalovirus, CMV, renal transplant, valganciclovir, ganciclovir

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This table is used to track the development and approval and dissemination of the document and any changes made on revised / reviewed versions

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REVIEW RECORD			
DATE	**ISSUE NUMBER**	**REVIEWED BY**	**DESCRIPTION OF CHANGES (IF ANY)**
Dec 04	2	S Carr / G Hartley	Valganciclovir added
May 2006	3	S Carr/G Hartley	Aciclovir removed completely
March 2009	4	S Carr/M Fraser/G Hartley	Text reviewed and dosages adjusted
June 2010	5	S Carr/M Fraser	Introduction and Table amended
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May 2016	6	SM/MM/PT/SC	Reviewed and updated to new UHL template
May 2018	7	SC/MM/SM	Reviewed and updated to include new recommendations about duration of prophylaxis and use of pre-emptive monitoring Discussed at Tx MDT 040618
November 2020	8	MM	Updated dosing tables and specified dosing based on Cockcroft and Gault GFR calculation
July 2021	9	PT/MM	Added section 3.3.3

April 2023	10	MM/JJS	Minor edits. New reference added