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# Management of CMV Viremia in Renal Transplant Patients from Perspective of Clinical Practice within United Kingdom

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## Abstract

Immunosuppression is an important aspect of management after kidney transplantation for maintenance of graft function. Cytomegalovirus infection in renal transplant patients is reactivation of the latent virus under the influence of immunosuppression. CMV viral load should be regularly monitored and treatment instituted with twice daily dosing if it is above the threshold of 10,000 copies/ml and when a patient is symptomatic. Severe refractory cases can be treated with CMV immune globulin or IVIG. New antiviral treatments like maribavir and brincidofovir are novel drugs that can be used for refractory disease. However, their use is limited, and more studies are currently needed before their widespread use.

**Keywords: Renal transplant; Immunosuppression; Viremia; Ganciclovir**

## Abbreviations

CMV: Cytomegalovirus; CrCl: Creatinine Clearance; r-ATG: rabbit-Anti Thymocyte Globulin; PCR: Polymerase Chain Reaction; BTS: British Transplant Society; GCSF: Granulocyte Colony Stimulating Factor; KDIGO: Kidney Disease Improving Global Outcomes

## Introduction

Immunosuppression is an important aspect of management after kidney transplantation for maintenance of graft function. This treatment being a double-edged sword however predisposes patients to reactivation of latent infection from cytomegalovirus. This is of clinical importance due to the risk of graft dysfunction and multi organ failure.

The seroprevalence of cytomegalovirus across the developing and developed world is between 40 and 100% in the general population [1].

After kidney transplantation the risk of reactivation develops if either the donor kidney or recipient is IgG positive from past CMV exposure. Donor positive and recipient positive groups (D+/R+) or donor positive recipient negative groups (D+/R-) have shown worse outcomes both in terms of graft survival and patient survival compared to donor negative and recipient positive (D-/R+) as evidenced by a study of more than 24,000 cadaveric renal transplants in the United States [2].

It is interesting to note that approximately 8% of cases renal transplant recipients can acquire symptomatic infection according to one observation [3].

CMV can follow two distinct clinical courses including an asymptomatic infection called CMV infection with detectable viral load and CMV disease which involves viremia associated with presence of symptoms like fever, chills or involvement of end organs including bone marrow suppression, hepatitis, pneumonitis, nephritis, gastroenteritis, encephalitis or retinitis [4].

The time of greatest vulnerability is the time when the immunosuppression is at its peak which is the first three months after transplant. As mentioned above, CMV infection or disease both confer a mortality risk and risk of graft loss and hence should be promptly addressed in all transplant recipients [5].

## Management Strategies

In the United Kingdom, the British Transplant Society (BTS) has given recommendations and suggestions for both prevention and treatment of CMV in solid organ transplants. These guidelines

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are practiced across all transplant centers in the country.

**According to the guidelines:** All organ donors and recipients should be screened for CMV status prior to, or at the time of transplantation (1 A). For renal transplant recipients, the recommended management strategy is one of: Oral valganciclovir for at least 100 days (1 A), or Oral valganciclovir for 200 days (2 B) [6].

The 2009 KDIGO guidelines share similar recommendations and suggest that all patients before the transplant of solid organs should be screened for CMV IgG and if it is negative this should be repeated before the time of transplantation. It also recognizes two high risk category patients; those who are seronegative and receive an organ from seropositive donor and those who receive rabbit Anti Thymocyte Globulin (r-ATG) for induction any time after transplantation and where either the donor or recipient is positive [7].

In major hospitals of the UK, valganciclovir dose is calculated based upon Creatinine Clearance (CrCl) from Cockcroft Gault equation. For CrCl above 60 the dose is 900 mg once daily, this dose is continued for 3 months in standard risk patients and for 6 months for those who are considered high risk as defined above. Combined kidney pancreas recipients are also considered high risk if they are either donor or recipient positive.

For patients who are found to be having CMV infection without the symptoms, a few strategies can be employed. This can include watchful monitoring of viral PCR load on weekly basis and reduction in immunosuppression mainly antimetabolites while continuing calcineurin inhibitors and steroids. Treatment is started in asymptomatic patients if the viral PCR load increases to more than >10,000 copies/ml on two occasions.

As per the BTS recommendations and common practice, the treatment should continue for at least 14 days and until the viral load is less than 300 copies/ml. The same holds for CMV disease where patients are symptomatic with viral high viral load.

For patients who are severely symptomatic and need admission to hospital the recommended treatment is to use IV ganciclovir. Once the viremia is settled, oral valganciclovir is to be continued for another 1 to 3 months and regular viral PCR checks are carried out for any sign of reactivation.

## Special Consideration

Treatment with valganciclovir or ganciclovir is associated with bone marrow suppression mainly affecting white cell count and platelets and hence these should be closely monitored, and dose adjusted accordingly.

Once the acute treatment phase has finished, secondary prophylaxis with oral valganciclovir is recommended for up to three months. However according to a retrospective cohort study of 170 solid organ transplant recipients which included 79 renal transplants, secondary prophylaxis only covered re infection for 6 weeks after cessation of prophylaxis [8].

It is also worthy of note that CMV itself causes bone marrow suppression and hence in presence of active viral load, abrupt cessation of antiviral drugs be avoided as this might promote resistance. Co-existing prophylactic drugs like co-trimoxazole should also be considered as a cause and use of Granulocyte Colony Stimulating Factors (GCSF) to boost marrow can also be considered.

As mentioned above during treatment for CMV the antimetabolites like azathioprine or mycophenolate should be either dose reduced or stopped as CMV reactivation only happens due to immunosuppression. However, it should be borne in mind that CMV also predisposes to acute rejection episodes and hence it is important to maintain optimal levels of calcineurin inhibitors and steroid doses should be doubled.

Under dosing with valganciclovir or ganciclovir can result in resistance which is defined as lack of fall in viral load by 10-fold after two weeks of treatment. According to a study of more than 1,200 kidney transplant patients the incidence of developing resistance was around 2% and mainly in the donor positive recipient negative group who received treatment dose 900 mg once daily of valganciclovir rather than twice daily [9]. Management of such cases is with either foscarnet or cidofovir. However, these regimens have their own nephrotoxic potential which needs to be considered and performing genetic testing to detect CMV mutations is beneficial in guiding the treatment. UL97 mutations can be treated with foscarnet while UL54 mutations are resistant to both foscarnet and cidofovir.

Severe refractory cases can be treated with CMV immune globulin or IVIG.

## Conclusion

In summary, cytomegalovirus infection in renal transplant patients is reactivation of the latent virus under the influence of immunosuppression. Prophylaxis with once daily valganciclovir for at least 3 months should be given if the donor or recipients are IgG positive for the virus, and for 6 months in high-risk patients. An ideal approach would be to match the recipients with donors regarding their CMV status; however, this is not practical in view of shortage of organs.

CMV viral load should be regularly monitored and treatment instituted with twice daily dosing if it is above the threshold of 10,000 copies/ml and when a patient is symptomatic.

Severity of treatment means admission in the hospital for IV ganciclovir with an understanding about resistance which should lead to consideration of genetic testing and alternate antiviral drugs or immune globulins.

New antiviral treatments like maribavir and brincidofovir are novel drugs that can be used for refractory disease. However, their use is limited, and more studies are currently needed before their widespread use.

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