

CHAPTER 7

Infectious complications and prevention

CHAPTER 7.1 Cytomegalovirus infection

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1 Cytomegalovirus and kidney transplantation

Despite recent advances, cytomegalovirus (CMV) infection remains one of the most common complications in solid organ transplant recipients, with an increased risk of complications, graft loss, morbidity, and mortality [1]. While adult and paediatric transplant recipients share common risk factors for CMV disease, children face unique challenges that increase their risk of exposure and infection. Because they are likely to be CMV-naïve at the time of transplantation, they are more likely to acquire primary CMV infection post-transplant. In addition, CMV donor (D)-negative and recipient (R)-negative paediatric kidney transplant recipients are at increased risk of de novo infection from community sources, such as day care. Prior to the introduction of prophylactic and preemptive therapy, CMV disease occurred in approximately 15% of paediatric kidney transplant recipients [2]. Antiviral prophylaxis and preemptive treatment strategies have reduced the burden of CMV disease, while standardized quantitative nucleic acid testing has allowed more effective monitoring [3]. In the current era, CMV DNAemia affects approximately 20% of paediatric kidney transplant patients, with 1–10% developing CMV disease and 14% experiencing late-onset disease [1, 4, 5]. In addition to established therapeutic agents such as

valganciclovir and ganciclovir, novel antiviral agents and adjunctive treatments such as virus-specific T cells offer promising options for safer and more effective prevention and treatment [3].

2 Definitions

CMV DNAemia: Detection of CMV DNA in the blood in the absence of clinical symptoms [3].

CMV infection: Evidence of CMV replication regardless of symptoms, defined as isolation of virus or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen [6], e.g., positive PCR, positive pp65 antigen, positive cell culture, and/or histopathological evidence.

CMV disease: Evidence of CMV infection accompanied by attributable symptoms. CMV disease can be further categorized as a CMV syndrome or as tissue invasive disease [1]

CMV syndrome: CMV replication plus one or more of the following criteria: Fever, malaise, leukocytopenia, thrombocytopenia.

Tissue invasive disease: CMV replication plus one or more of the following criteria: Gastrointestinal disease, pneumonia, hepatitis, central nervous system disease, retinitis, others (nephritis, cystitis, myocarditis, pancreatitis, etc.).

3 Pre-transplant CMV diagnostics

As in adults, the risk of CMV disease in paediatric transplant recipients depends on the donor and recipient serostatus (D/R). Pre-transplant CMV serostatus defines the risk of CMV after transplantation and guides decisions about either antiviral prophylaxis or active surveillance (with preemptive therapy) [1]. However, in infants younger than 12 months, interpretation of serostatus is complicated by maternal CMV antibodies transferred across the placenta and the intermittent shedding of CMV in saliva and urine [1]. Prior to the introduction of routine CMV prevention strategies, CMV-related disease in solid organ transplant (SOT) recipients typically occurred within the first three months

(early-onset). After discontinuation of early-onset post-transplant prophylaxis, complications are more likely to occur as late-onset CMV disease, particularly in high-risk CMV-positive donor/CMV-negative recipient (D+/R-) cases [7].

Risk categories are generally defined and treated as (exceptions, see further below):

- (D+/R-) High risk
- (D+/R+) Intermediate risk
- (D-/R-) Low risk
- (D-/R+) The risk associated with (D-/R+) serostatus and its management both depend whether or not the recipient has received induction therapy with lymphocyte-depleting antibodies.

We also recommend:

- Pre-transplant serological testing of all donors and recipients: Ideally prior to any necessary blood transfusion to avoid transmission of CMV antibodies. (Sample usually required: 1 mL of serum (or 2 mL of whole-blood) for CMV IgG serostatus determination)
- If the donor has received multiple transfusions prior to organ retrieval, consider possible CMV transmission and classify the donor as CMV IgG positive.
- For donors and recipients younger than 12 months of age, assume the highest possible CMV risk for the recipient due to possible maternal antibody transmission [1].

| Donor < 12 months | Recipient < 12 months | Highest risk categorization |
|-------------------|-----------------------|-----------------------------|
| + | + or - | D+/R-* |
| - | + | D-/R+ |
| - | - | D-/R- |

* If the recipient is confirmed positive by CMV culture or nucleic acid testing, assign D+/R+.

4 Post-transplant CMV decisions: Prophylaxis vs. pre-emptive strategy

Given the high incidence of primary CMV infection and reactivation in paediatric solid organ transplantation, preventive strategies play a crucial role in enhancing transplant success and improving clinical outcomes. The choice between prophylaxis and pre-emptive strategies depends on the CMV risk profile of the patient and the level of immunosuppression administered [1]. These strategies help to mitigate the risk of CMV infection and disease, while also reducing the associated indirect effects of CMV infection [1, 6, 7]. Similar to adults, paediatric evidence supports the use of serostatus-guided antiviral prophylaxis in paediatric kidney transplant recipients. However, its use in young children is limited due to the risk of bone marrow suppression and the lack of comprehensive pharmacokinetic data for valganciclovir. Universal prophylaxis involves the administration of antiviral medication to all patients or a selected group of high-risk patients, starting within the first 10 days post-transplant and continuing for a defined period, typically 3 to 6 months [1].

On the other hand, preemptive therapy reduces antiviral-related toxicity but requires frequent viral load monitoring [1]. Effective preemptive therapy (PET) relies on routine blood monitoring for CMV at regular intervals (e.g., weekly CMV viral load testing) to detect viral replication at an early stage. Once a predefined assay threshold is reached – ideally before clinical symptoms emerge – antiviral treatment is initiated to prevent progression to clinical disease. Advances in assay availability and standardization have made this approach increasingly feasible. However, due to differences in diagnostic specimen types (whole-blood vs. plasma) and variability in assay platforms, a universally applicable threshold for initiating therapy has yet to be established [1, 8, 9].

Definitions:

- Prophylaxis: Administration of valganciclovir (or ganciclovir) for 3–6 months post-transplant.
- Preemptive strategy: Regular CMV PCR surveillance post-transplant and initiation of antiviral therapy (double prophylactic dose) if CMV DNAemia is detected by PCR, irrespective of clinical symptoms.

We recommend:

- Patients at high CMV risk (CMV D+/R–) or intermediate risk (CMV D+/R+) receive valganciclovir prophylaxis.

- CMV S-/E+ patients receiving ATG/Thymoglobulin®: treat as high CMV risk (valganciclovir prophylaxis)
- CMV S-/E+ patients without ATG/Thymoglobulin® therapy follow a pre-emptive strategy approach (CMV PCR surveillance, initiation of antiviral therapy at relevant CMV DNAemia).
- Low risk patients (CMV S-/E-) are followed clinically; if CMV infection is suspected, PCR testing is performed.

Duration of prophylaxis:

The duration of prophylaxis depends on the intensity of immunosuppressive therapy.

- For patients receiving standard immunosuppression (dual/triple therapy), we recommend 3 months of prophylaxis.
- For patients receiving ATG/Thymoglobulin® induction or treatment, we recommend 6 months of prophylaxis.
- Patients on methylprednisolone pulse therapy: 3 months prophylaxis, if high or intermediate risk category.

Valganciclovir prophylactic dosage

- Single daily dose (mg/day) = $7 \times \text{BSA (m}^2) \times \text{eGFR (ml/min/1.73 m}^2\text{)}^a$
- Maximum eGFR value to use in formula: 150 mL/min/1.73 m² (to avoid overdosing)^b
- Maximum prophylactic daily dose: 900 mg
- Valganciclovir available as: 450 mg tablets or 50 mg/ml suspension
- For persistent anuria post-transplant: Start intravenous ganciclovir (0.625 mg/kg 3 × weekly after haemodialysis) or valganciclovir suspension according to product guidelines at 48 h post-transplant.

^a Calculation of eGFR using $k = 0.413$ [10].

^b Other centers have adopted lower age-dependent upper eGFR limits in children to avoid over-exposure to valganciclovir [11]

5 Post-transplant CMV diagnostics

In immunosuppressed patients, seroconversion during primary infection may be delayed or absent. Therefore, antibody detection is only useful for determining pre-transplant CMV serostatus, but not for diagnosing active CMV infection

after transplantation [7]. As CMV DNA concentrations may vary between whole blood and plasma, surveillance should be performed consistently using the same sample type for each patient [7].

We recommend:

- 10 days post-transplant (except for D-/R- patients and those under prophylaxis): 2 ml EDTA-treated blood for CMV quantitative PCR testing.
- In cases of clinical suspicion or unexplained leukocytopenia/neutropenia, CMV PCR testing should also be considered during ongoing prophylaxis.

Post-transplant, quantitative nucleic acid amplification testing is the preferred method for diagnosing CMV infection, guiding preemptive strategies, and monitoring response to therapy [1, 12]. Although there is no universally accepted threshold for initiation of therapy, a clinically significant increase in CMV DNA viral load is currently defined as at least a threefold increase ($\geq 0.5 \log_{10}$ copies/mL) in viremia within one week [7]. Another issue that remains controversial is routine surveillance for breakthrough CMV DNAemia during antiviral prophylaxis. While studies in paediatric SOT recipients have reported breakthrough CMV DNAemia during valganciclovir prophylaxis, its clinical significance remains uncertain [3]. It has been associated with adverse outcomes such as graft rejection, secondary infections, and potential valganciclovir/ganciclovir resistance. However, the respective paediatric data are inconclusive and causality has not been firmly established. Furthermore, progression from breakthrough CMV DNAemia to CMV disease is rare [3]. In accordance with the German guideline on S2k guideline on the management of viral infections in organ transplantation, we currently do not recommend routine screening for CMV DNAemia during prophylaxis unless there is clinical suspicion of CMV replication [7].

We recommend the following monitoring schedule:

- For patients after 3 months of prophylaxis, we recommend the following schedule:
 - Months 3–6: twice a month
 - Months 6–12: once a month
 - After 12 months: twice per year and if clinical symptoms or graft dysfunction occur.
- For patients after 6 months of prophylaxis, we recommend the following schedule:
 - Months 6–9: twice a month

- Months 9–12: once a month
- After 12 months: twice a year and if clinical symptoms or graft dysfunction occur.
- For patients following a preemptive strategy, we recommend the following schedule:
 - Months 0–4: once a week
 - Months 4–12: once a month
 - After 12 months: twice a year and if graft dysfunction occurs.

Regarding the diagnostic workup after solid organ transplantation, it has to be mentioned that a negative CMV DNA test does not necessarily rule out tissue invasive CMV disease [13, 14]. Higher CMV DNA levels in tissue compared to peripheral blood suggest tissue invasion, which is particularly relevant in pulmonary or intestinal involvement. In such cases, histological and immunohistochemical analyses are essential for diagnosis [14–17].

6 Treatment of CMV replication and CMV disease after paediatric kidney transplantation

Both oral valganciclovir and intravenous ganciclovir can be used for non-life-threatening CMV disease; valganciclovir is generally preferred if feasible because of its oral formulation, which can help to reduce or avoid hospital stays and reduce the risk of infectious and vascular complications associated with intravenous therapy. Conversely, intravenous ganciclovir is the preferred option for the initial treatment of life-threatening CMV disease, as it ensures optimal drug exposure when immediate and effective antiviral activity is critical [1, 18]. Antiviral treatment should be given for at least two weeks and continued until both clinical symptoms have resolved and CMV DNAemia falls below a defined threshold (lower limit of quantification < 200 IU/mL) in two consecutive weekly tests [1, 7]. Once clinical improvement is achieved, intravenous ganciclovir can be switched to valganciclovir in patients who can tolerate oral therapy. In cases of leukopenia, it is not recommended to discontinue or substitute (val)ganciclovir before considering the use of granulocyte colony-stimulating factor and/or discontinuing other myelosuppressive medications [1].

For the treatment of asymptomatic CMV replication and CMV syndrome we recommend:

- Therapeutic dose of valganciclovir: The prophylactic dose given two times a day.
- Maximum therapeutic daily dose: 900 mg twice daily (total 1800 mg/d).
- Reduce maintenance immunosuppressive therapy if possible.
- Frequent clinical monitoring and weekly CMV DNAemia testing by PCR
- If CMV DNAemia recurs, consider switching to an everolimus-based immunosuppressive therapy
- During CMV replication, pneumocystis jirovecii pneumonia prophylaxis should be maintained for the duration of viremia.

For the treatment of tissue invasive CMV disease we recommend:

- IV ganciclovir: 10 mg/kg/day divided into two doses as a short infusion for 14 days. Followed by 5 mg/kg/day once daily as a short infusion until clinical resolution and two consecutive negative CMV PCR results. Minimum treatment duration: 3 weeks. Caution: Dose adjustments required for GFR < 70 mL/min/1.73 m² (see Table 1).
- For CMV pneumonitis or enterocolitis, consider adding 100 mg/kg b.w. of hyperimmune globulin, depending on the patient's condition.
- CMV DNAemia testing by PCR: Twice weekly.
- Reduce maintenance immunosuppressive therapy if possible.
- Depending on immunosuppressive regimen, secondary prophylaxis with valganciclovir for 1–3 months may be considered.

Ensuring the correct dose of antiviral medication is critical to the effective management of CMV disease (Table 1). Inadequate dosing may lead to treatment failure and increase the risk of resistance development, while excessive doses may increase the risk of toxicity. To optimize therapy, renal function should be closely monitored by regular assessment of serum creatinine levels [1, 19, 20]. We recommend the following adjustments to the dose and dosing interval of i.v. ganciclovir in relation to kidney function.

Table 1 Dosage of i.v. ganciclovir in relation to kidney function

| Creatinine clearance (according to Schwartz) (mL/min·1.73 m ²) | Initial therapy | | Maintenance therapy | |
|--|-----------------------------------|---------------------------|-----------------------------------|---------------------------|
| | Dose (mg/ kg BW ¹) | Dosing interval (h) | Dose (mg/ kg BW ¹) | Dosing Interval (h) |
| ≥ 70 | 5.0 | 12 | 5.0 | 24 |
| 50–69 | 2.5 | 12 | 2.5 | 24 |
| 25–49 | 2.5 | 24 | 1.25 | 24 |
| 10–24 | 1.25 | 24 | 0.625 | 24 |
| < 10 | 1.25 | 3 × per week ² | 0.625 | 3 × per week ² |

¹ body weight; ² after haemodialysis

Regarding dosing of oral valganciclovir please refer to section 4.

7 Management of treatment-resistant CMV disease

Drug resistance is characterized by viral genetic mutations that reduce susceptibility to one or more antiviral drugs, often resulting in persistent or increasing viral load or symptomatic disease despite adequate treatment. It can manifest in varying degrees, from asymptomatic cases that resolve without intervention to severe or even fatal organ disease [21, 22]. The development of resistance is strongly associated with increased morbidity and mortality, highlighting the importance of early detection and treatment [1, 23, 24].

We recommend:

- If the CMV viral load is not reduced by 50% after 2 weeks of therapy, resistance testing by RT-PCR genotyping (UL97 and UL54 mutations) should be performed.
- If necessary, biopsy material or bronchoalveolar lavage (BAL) fluid should also be tested for CMV mutation.
- After consultation with virology/infectious disease specialists, alternative agents such as foscarnet may be used (caution: nephrotoxicity).

In paediatric kidney transplantation, the use of everolimus in combination with low-dose cyclosporine A has been associated with a significantly lower incidence of CMV disease compared with mycophenolate mofetil (MMF) with standard-dose calcineurin inhibitors. Although data on switching to mTOR inhibitors during active CMV infection are lacking, an mTOR-based immunosuppressive regimen may be considered in cases of recurrent CMV viremia [7, 25].

8 Exposure prophylaxis and hospital hygiene

- Patient isolation: not generally required.
- Precautions: Avoid contact with pregnant women, neonates and immunosuppressed patients (see hospital hygiene guidelines).

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