Cytomegalovirus in paediatric transplantation

Fields marked with * are mandatory.

Cytomegalovirus infection and disease in Paediatric transplantation

In pediatric patients, the main risk factor for the development of post-transplantation cytomegalovirus (CMV) is the absence of specific immunity to the virus in the pre-transplantation period. CMV infection has become less of a problem in pediatric organ transplant (SOT/HSCT) recipients mainly due to the availability of sensitive diagnostic techniques, the development of prevention strategies, and the possibility of starting effective antiviral treatments.

Historically, prophylaxis with antivirals, either universal or in those patients selected in order to the risk of acquiring the infection, has been the most used preventive strategy. Possible negative effects of it such as the delay in the acquisition of individual immunity against the virus, the development of late disease, the acquisition of viral resistance to drugs or the risk of toxicity have promoted alternative strategies of prevention such as anticipated treatment. The selection between these types of prevention as well as some specific aspects related to its application or to the treatment once the infection is confirmed are still subjects to discussion and remain unsolved.

The purpose of this survey, like that of the rest of the clinical audits promoted by the **Transplantchild Healthcare Working Group**, seeks to identify the clinical reality of the centres and programs included in the ERN on this topic related to CMV infection and disease.

Please, share this survey with your colleagues who may be interested in answering it.

Thank you for your valuable input. If you have any concerns or questions about this survey, please contact us (HelpDesk or Medical Advisor).

* **Please, insert a valid email:**

* **Institution:**

- AUSTRIA - Centre for Pediatric Lung Transplantation, Medical University of Vienna
- BELGIUM - Princess Elisabeth Children's Hospital, Gent
- BELGIUM - University Hospital Saint-Luc, Brussels
- CROATIA - University Hospital Centre Zagreb
- DENMARK - Odense University Hospital
- DENMARK - Rigshospitalet University Hospital, Copenhagen
- ESTONIA - Tartu University Hospital
- FINLAND - HUS Helsinki University Hospital
- FRANCE - Hôpital Bicêtre - Hôpitaux de Paris
- FRANCE - Hôpital Necker Enfants Malades - Hôpitaux de Paris
- GERMANY - Medizinische Hochschule Hannover
- GERMANY - University Medical Center Hamburg-Eppendorf (UKE), Hamburg
- HUNGARY - Semmelweis University, Budapest
- IRELAND - Children's Health Ireland (CHI)
- ITALY - AOU Città della Salute e della Scienzia di Torino
- ITALY - Azienda Ospedaliera di Padova
- ITALY - ISMETT Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione, Palermo
- ITALY - Ospedale Papa Giovanni XXIII, Bergamo
- ITALY - Ospedale Pediatrico Bambino Gesù, Rome
- LATVIA - Children’s Clinical University Hospital, Riga
- LITHUANIA - Vilnius University Hospital Santaros Klinikos
- LUXEMBOURG - Centre Hospitalier du Luxembourg
- MALTA - Mater Dei Hospital, Malta
- NORWAY - Oslo University Hospital
- Other
- POLAND - Children's Memorial Health Institute, Warsaw
- PORTUGAL - Centro Hospitalar de Lisboa Norte
- PORTUGAL - Centro Hospitalar do Porto
- PORTUGAL - Centro Hospitalar e Universitário de Coimbra
- SPAIN - Hospital Infantil Universitario Niño Jesús, Madrid
- SPAIN - Hospital Sant Joan de Déu, Barcelona
- SPAIN - Hospital Universitario Gregorio Marañón, Madrid
- SPAIN - Hospital Universitario La Paz, Madrid
- SPAIN - Hospital Universitario Virgen del Rocío, Sevilla
- SPAIN - Hospital Universitari Vall d’Hebron, Barcelona
- SWEDEN - Karolinska University Hospital
- SWEDEN - Sahlgrenska Universitetssjukhuset, Göteborg
- SWEDEN - Skåne University Hospital, Lund
- THE NETHERLANDS - Erasmus UMC Rotterdam
- THE NETHERLANDS - UMC Amsterdam
- THE NETHERLANDS - UMC Utrecht
- UK - King's College Hospital NHS Foundation Trust, London

Please, specify other institution name:

* **Which transplantation program is your unit dedicated to?**

- [ ] Hematopoietic stem cell
- [ ] Heart
- [ ] Kidney
- [ ] Intestinal
- [ ] Lung
- [ ] Liver
- [ ] Pancreas

* **Choose your profile:**

- ( ) Transplantation (surgeon or paediatrician)
- ( ) Paediatric infectious diseases

Data protection policy

Please, download and read the data protection policy:

210428_Survey_clause.pdf

- [ ] I accept your Terms

PRE-TRANSPLANTATION

* **1. Donors are selected according to donor / recipient CMV serostatus?**

- ( ) Yes
- ( ) No

* **2. In the case of recipients < 12 months of age, a pretransplant positive CMV-IgG is considered by you in terms of defining risk as:**

- ( ) Seronegative CMV recipient with pasive transference of maternal CMV IgG
- ( ) Seropositive CMV recipient
- ( ) A confirmatory test is needed and performed

If a confirmatory test is needed and performed, please select:

- [ ] CMV PCR in urine
- [ ] CMV PCR in blood
- [ ] Both
- [ ] Other

Other confirmatory test:

3. Do you assess the recipient's CMV-specific T-cell response before SOT?

- [ ] No
- [ ] Yes with QuantiFERON-CMV
- [ ] Yes with CMV ELISPOT
- [ ] Yes with other method

Please, describe other method:

4. During SOT procedure, CMV-negative blood products are used in seronegative recipients?

- ( ) Yes
- ( ) No

POSTRANSPLANTATION

Definitions:

CMV Infection: isolation of the virus or the detection of viral proteins (antigenemia) or CMV DNA / mRNA in any body liquid or tissue.

CMV disease: evidence of symptoms or signs coupled with the detection of CMV infection in the blood.

Prophylaxis: antiviral treatment started to prevent CMV infection/disease, after transplantation procedure and prior viremia is detected. Regardless of its duration time.

Preemptive treatment is defined as the administration of an antiviral agent with CMV activity (e.g.: valganciclovir, ganciclovir, cidofovir, etc) after the date of CMV infection and prior to the date of progression to CMV disease (i.e.: Only after transplant surveillance of CMV infection with periodical monitorization of CMV viremia and initiation of antiviral drugs upon the detection of viremia - any value or a pre-established cut-off of the viral load)

Assessment and prevention of CMV infection/disease

* **1. In your programme, the current strategy to prevent CMV infection/disease is:**

- ( ) Only prophylaxis
- ( ) Only preemptive treatment
- ( ) Blended protocol (prophylaxis followed by preemptive therapy)
- ( ) Both options, depending individual estimated risk of CMV infection
- ( ) Different to above mentioned

Please specify your strategy:

2.a What was the main reason to select prophylaxis as your current preventive strategy?

- Higher efficacy in preventing CMV disease
- Avoiding more frequent blood collection for viremia screening required in preemptive strategy

2.b Prophylaxis is applied:

- All patients (universal)
- Only those patients considered at high risk *(please specify)*

High risk criteria *(the answer could be multiple):*

- CMV status: Donor positive / Recipient negative
- CMV status: Donor positive / Recipient positive
- CMV status: Donor negative / Recipient positive
- T-cell depletion
- Other criteria

Please specify other criteria of high risk:

2.c CMV prophylaxis drugs *(the answer could be multiple):*

- Oral valganciclovir
- Intravenous ganciclovir
- IV ganciclovir followed by oral valganciclovir
- Oral acyclovir or valacyclovir
- Other (e.g. anti-CMV specific immunoglobulin, foscarnet, etc)

Please, describe other drugs used in CMV prophylaxis:

2.d Prophylaxis duration:

Only values between 1 and 52 are allowed

weeks

Please, describe if:

1.Your program follows other prophylaxis duration.

2. You are reporting more than one transplantation program and they have different prophylaxis duration.

3. The prophylaxis duration depends on estimated risk of CMV infection/disease.

2.e How often do you screen the CMV infection during prophylaxis? Please, describe:

2.f What was the main reason to select preemptive treatment as your current preventive strategy?

- Higher efficacy in preventing CMV disease
- Avoiding potential toxicity of antivirals
- Better prevention of late CMV disease and/or CMV antiviral-resistance

2.g How often do you screen the CMV infection during preemptive strategy? Please, describe:

2.h Upon detection of CMV infection (positive viral load without related symptoms/signs):

- Any positive CMV viremia is treated
- Only a viral load above a preset cut-off value is treated

Cut-off value used to start treatment *(please add units):*

2.i Anti-viral used to treat CMV infection *(multiple choice)*:

- Oral valganciclovir
- Intravenous ganciclovir
- IV ganciclovir followed by oral valganciclovir
- Other

Please, describe other anti-viral treatment:

2.j CMV infection treatment duration:

- Fixed (established) duration
- Until viremia is cleared
- Until reducing viremia below a preset value

Please, describe the preset value:

2.k If it is necessary to increase the immunosuppressive treatment (e.g. bolus of steroids, T-cell depletion, etc):

- Increase the frequency of CMV screening
- Restart prophylaxis (if previously stopped)
- No change is made

* **3. In your centre, the screening of CMV infection is based on:**

- Quantitative PCR in blood
- Quantitative PCR in plasma
- CMV pp65 antigenemia assay
- Serology
- Other

Please, describe other screening test:

* **4. PCR values are reported in:**

- International Units per milliliter (IU/mL), WHO 2010
- Copies/mL

Treatment of CMV disease

* **1. First line treatment of CMV disease (CMV-related signs/symptoms with detected viremia):**

- Oral valganciclovir
- Intravenous ganciclovir
- IV ganciclovir followed by oral valganciclovir
- Other

Please, describe other drug used:

* **2. Treatment duration:**

- Fixed duration
- Until viremia is cleared

CMV viremia clearance definition:

- One negative viremia control
- Two negatives viremia controls
- Other

Please, describe other definition:

* **3. Prescription of anti-CMV specific immunoglobulin:**

- In all cases with CMV disease
- Only in those cases with Pneumonitis
- Only in those cases with other condition
- Not prescribed

Please, describe other condition:

Please, specify anti-CMV specific immunoglobulin dose, frequency, and duration:

* **4. When you prescribe IV ganciclovir or oral valganciclovir either as prophylaxis or as treatment of CMV infection/disease, the dose is the same for both situations?**

- Yes (both)
- Yes, only for IV ganciclovir
- Yes, only for oral valganciclovir
- No, we use different doses for prophylaxis and treatment

IV ganciclovir dose:

- Prophylaxis 5 mg/kg/day; treatment 5mg/kg/12 hours (adjusted to GFR)
- Other

Please, specify other dose:

Among these formulas to dose oral valganciclovir, which one do you use?:

- Valganciclovir dose (mg/dose) = 7 x BSA (m2) x Creatinine Clearance Rate (ml/min/1,73 m2) *Vaudry W,. Am J Transpl 2009*
- Valganciclovir dose (mg/dose) = 14 – 16 mgr / kg (adjusted for creatinine clearance rate) *Villeneuve D Pediatr Transplantation 2013*
- Valganciclovir dose (mg/dose) = weight (kg) x (0,07 x GFR ml/min + k) *Asberg A, Pediatr Transplantation 2014*
- Valganciclovir dose = 520 mg/m2 (adjusted to GFR)
- Other

Please, specify other dose:

Oral valganciclovir frequency of dosing:

- ○ Prophylaxis every 24 h; treatment every 12 hours
- ○ Other

Please, specify other frequency:

* **5. Do you monitor ganciclovir /valganciclovir trough levels?**

- ○ Yes
- ○ No

When? *(multiple choice)*

- ☐ All patients
- ☐ Lack of efficacy
- ☐ Suspected toxicity
- ☐ Other situations

Valganciclovir target trough levels *(please add units)*:

Ganciclovir target trough levels *(please add units)*:

Describe other situations:

* **6. Faced with a lack of efficacy of antiviral treatment, do you investigate potential resistance to ganciclovir and valganciclovir?**

- ○ Yes
- ○ No

Why? *(multiple choice)*

- ☐ Test not available
- ☐ It is not useful
- ☐ Other reason

Please, describe other reason:

7. In case of suspected or confirmed resistance to valganciclovir/ganciclovir, what is your strategy?

* Increasing IV ganciclovir dose
- Switch to an alternative drug
- Other strategy

Alternative drug:
- Foscarnet
- Letermovir
- Other

Please, describe other strategy or other alternative drug:

* **8. Do you assess the CMV-specific T-cell response after SOT & HSCT as a routine or in selected patients?**
- Yes in all patients
- Yes in selected cases
- No

Please, describe the criteria for selected cases:

Which test do you use?
- QuantiFERON-CMV
- CMV ELISPOT
- Other method

Please, describe other method:

* **9. Do you have any experience with adoptive T-cell immunotherapy for the treatment of CMV disease refractory to conventional treatment?**
- Yes
- No

Please, describe:

CMV infection/disease cases: quick overview

This is a quick survey related to CMV infection and / or disease episodes state of art across ERN-TransplantChild members.

Please, include the last **10** transplant recipients who met these **criteria** for each Transplantation program:

1. Age at transplantation procedure: 0-18 years old.

2. Follow up after transplantation: at least 1 year.

Please, download the CMV cases template. **Definitions** are described in "Definitions sheet". **Options** are predetermined in most cases (just click on the cell and select your answer from the list).

CMV_cases.xlsx

Please upload your file(s):

Thank you for your time!

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