Current Research in Translational Medicine 73 (2025) 103535

Contents lists available at ScienceDirect

Current Research in Translational Medicine

journal homepage: www.elsevier.com/locate/retram

Original article

Expert consensus on the management of cytomegalovirus infection in pediatric allogeneic hematopoietic stem cell transplantation

Simone Cesaro [a,*], Manuela Spadea [b], Franca Fagioli [b], Fulvio Porta [c], Marco Rabusin [d], Giulia Ferrando [e], Adriana Balduzzi [f,g], Arcangelo Prete [h], Marco Zecca [i], Maura Faraci [e]

[a] Pediatric Hematology Oncology, Department of Mother and Child, Azienda Ospedaliera Universitaria Integrata Verona, Italy
[b] Pediatric Oncohematology, Stem Cell Transplantation and Cell Therapy Division Regina Margherita Children's Hospital, University of Turin, Italy
[c] Pediatric Oncohaematology, Stem Cell Transplantation Unit Children's Hospital, Spedali Civili, Brescia, Italy
[d] Institute of Maternal and Child Health IRCCS "Burlo Garofolo", Trieste, Italy
[e] Hematopoietic Stem Cell Transplantation Unit, Department of Pediatric Hematology-Oncology, IRCCS, Istituto Giannina Gaslini, Genova, Italy
[f] Pediatrics, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy
[g] School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy
[h] Pediatric Hematology Oncology IRCCS-AOU di Bologna, University of Bologna, Bologna, Italy
[i] Pediatric Hematology / Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

ARTICLE INFO

Keywords:
Cytomegalovirus
Viral infection
Pediatric
Hematopoietic stem cell transplantation
Expert consensus

ABSTRACT

Cytomegalovirus (CMV) infection is the most frequent viral complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT). In the pediatric setting, several issues on its management are still debated due to the limited evidence compared to adults. The aim of this consensus was to promote harmonization of practices to improve prevention, control and treatment of CMV infection in children and adolescents.

Consensus was generated through voting by a panel of experts from 8 Italian pediatric transplant units who selected 11 topics on prevention of CMV infection and disease, risk factors, diagnosis, prophylaxis, pre-emptive, and therapeutic approaches and formulated 11 statements.

Statements were generated on impact of CMV infection on allo-HSCT outcome; risk factors for infection; monitoring of patients at risk; duration of infection risk; CMV prophylaxis and CMV pre-emptive strategies; choice of the antiviral therapy; use of CMV-IgG; antiviral combination therapy; role of adoptive cell therapy; therapeutic drug monitoring. All statements reached a mean score of ≥7 (agreement) at the first voting round and reached an even higher level of consensus at the second voting round after discussion and possible modification of some statements.

In conclusion, CMV infection is a risk factor for lower survival and higher non-relapse mortality. We propose a set of expert consensus-generated recommendations aimed at harmonizing the management of CMV infection in pediatric allo-HSCT. We recognize that this field has several unmet needs and emphasize the need for further specific clinical investigations.

1. Introduction

Cytomegalovirus (CMV) infection is the most frequent viral complication after allogeneic hematopoietic stem cell transplantation (HSCT), affecting 40–60 % of the patients within 3–4 months post-transplant [1, 2]. CMV infection is defined by increasing or persistent CMV replication in the blood (CMV viremia) without associated symptoms, while CMV disease is defined by the presence of signs or symptoms of systemic or organ involvement, such as fever, dyspnea, hypoxemia, retinitis, and enteritis. Both CMV infection and disease are risk factors for overall mortality in the first year after HSCT [3–5].

Over the last decade, several pharmacological innovations have been introduced in the management of CMV, resulting in significant changes in routine clinical practice. The introduction of letermovir significantly reduced the impact of CMV infection on early morbidity and mortality, as well as the weight of donor/recipient CMV serostatus in the choice of

* Corresponding author at: Pediatric Hematology Oncology, Department of Mother and Child, Azienda Ospedaliera, Universitaria Integrata Verona, Piazzale Aristide Stefani 1 37126 Verona, Italy.
E-mail address: simone.cesaro@aovr.veneto.it (S. Cesaro).

https://doi.org/10.1016/j.retram.2025.103535
Received 22 April 2025; Accepted 14 August 2025
Available online 15 August 2025

the graft source. In the adult setting, letermovir enabled a shift from the practice of CMV viremia-driven pre-emptive treatment to CMV prophylaxis [6,7].

A second significant step forward was the demonstration that maribavir, an anti-CMV drug, was more effective and less toxic than other antivirals (ganciclovir [GCV]/valganciclovir [Val-GCV], foscarnet [FSC], and cidofovir [CDV]) in the treatment of resistant and refractory CMV infections [8]. The benefit of these pharmacological innovations has not been extended so far to the pediatric transplanted population, due to the paucity of pediatric data and barriers to conducting pediatric trials. Maribavir received the market authorization in EU for patients 12 years of age or older and weighing $\geq$ 35 kg while letermovir is authorized only for patients aged 18 years or older. Although letermovir has been available since 2017, pediatric experience with these two drugs is limited to case series or retrospective studies reporting the off-label use on a named-patient basis [9–13].

Nevertheless, it is important to underline that pharmacokinetic parameters can be different in the pediatric population, especially in children <4 years old, than in the adult population, as observed with ganciclovir [14].

In a survey conducted in 2020 among transplant centers reporting to the European Society for Blood and Marrow Transplant (EBMT) Registry, the main difference between pediatric and adult centers was the percentage of centers using CMV prophylaxis, 62 % vs. 37 %, respectively, as well as the type of antiviral drugs used for prophylaxis: letermovir in 6 % vs.74 %, GCV/Val-GCV 50 % vs. 12 % and FSC 13 % vs. 0 %, respectively [15].

Apart from pharmacological innovations, another important issue is the role of adoptive immunotherapy in the management of CMV infection in the HSCT setting. Despite the recent recommendations for the management of CMV infection in stem cell transplant patients by the10th edition of European Conference on Infections in Leukemia (ECIL-10) do not differentiate the indications between the pediatric and adult patients [16], there are still controversial opinions on the management of pediatric CMV infection, and well as limited data regarding the optimal antiviral treatment that may undermine an early or individualized treatment. For these reasons, a national expert consensus was organized, along the lines of a modified Delphi method, with the aim of providing help in harmonizing and optimizing the prevention and control of CMV infections in the pediatric HSCT setting.

2. Methods

Delphi is a research survey technique used as a way of collecting data from respondents within their domain of expertise. Its aim is to deal with divergent opinions, uncertain or controversial issues to achieve consensus concerning real-world topics [17]. The methodology of Delphi Consensus was chosen because there is a clear lack of pediatric studies that can give robust evidence-based indications, which is a situation that determines heterogeneity and uncertainty in the routine practice.

The process of this consensus followed these steps:

1) the chairman (SC) of the infectious diseases working group (ID-WG) of the Italian Association of Pediatric Hematology and Oncology (AIEOP) invited a representative of pediatric hematologists from 8 AIEOP transplant units that performs at least 10 allo-HSCT per year (range 10–40/year): Each delegate had a long-lasting experience in the management of allo-HSCT and of transplant complications as Director of the transplant program (AB, AP, FF, FP, MZ, MF, MR) or expert in the subject (MS, GF) (July 2023);
2) the panelists convened for an in-person meeting and, after discussion, agreed on the most relevant topics that would deserve definition and/or harmonization: epidemiology, risk factors and diagnosis of CMV infection, management of patient at risk of CMV infection, therapy of CMV infection, and new frontiers for treatment (September 2023);
3) Each topic was assigned to panelists as follows: diagnosis of CMV infection FP, FF, MS; management of patients at risk of CMV infection (AR, SC, MR; therapy of CMV infection (MF, GF, SC); and new frontiers (AB, M, MR). The panelist reviewed the pediatric literature of the last ten years on the topics assigned to identify the references of main interest using as key words: cytomegalovirus, infection, disease, pediatric, allogeneic hematopoietic stem cell transplantation (September 2023).
4) virtual meetings followed by email-based focus group interactions allowed panelists to elaborate statements regarding the topics, based on evidence available and/or expert opinion, with contributions from each panelist; one statement was generated for each topic (October 2023- September 2024);
5) in a second final meeting, the statements were subjected to a first round of voting on a 1–9 scale; the presence of any disagreement during the first round of voting was discussed for revision, and prompted a second voting round until there was consensus (mean rating from 7 to 9 = agreement of all the experts), or no agreement (mean rating <7) (October 2024).

No human subject data were collected and the manuscript adheres to ethical standards for non-interventional literature-based work.

3. Results

The content of the statements elaborated for the consensus was: (1) impact of CMV infection on the outcome of pediatric allogeneic HSCT; (2) risk factors for CMV infection in pediatric HSCT; (3) how to monitor patients at risk for CMV infection; (4) how to identify the duration of CMV infection risk in pediatric patients; (5) when is a CMV prophylaxis strategy recommended (6) when is a pre-emptive strategy recommended and at which threshold of viremia should therapy be started; (7) how to choose the appropriate antiviral therapy; (8) are CMV-IgG indicated? (9) Is antiviral combination therapy indicated? (10) What is the role of adoptive cellular therapy? (11) What is the role of therapeutic drug monitoring (TDM) in the management of antiviral therapy for CMV infection?

At the first voting round, all 11 statements reached a mean score of $\geq$7. After the discussion, 7 statements were modified and achieved a higher level of consensus in the second voting round. The complete list of statements with the results of the first and second rounds of voting and the changes made is shown in Table 1. The final statements with final ratings are discussed below.

4. Discussion

4.1. . Impact of CMV infection on the outcome of pediatric HSCT

Statement 1: CMV infection is a risk factor for lower survival and higher non-relapse mortality in pediatric transplantation. [Final mean score: 8.9]

Historically, CMV infection has been the major viral complication in HSCT patients, with a death rate of almost 100 % in untreated patients and 10–70 % of mortality in patients with CMV diseases (pneumonia, enteritis, retinitis), despite antiviral treatment [18]. Over the last three decades, early detection of CMV infection in the asymptomatic phase has been made possible, first by antigenemia, and then by the more sensitive quantitative PCR, which has allowed early diagnosis and treatment of presymptomatic CMV infection. In patients at high-risk of CMV infection, despite the adoption of antiviral prophylaxis or of PCR-based pre-emptive treatment with GCV or FSC, several studies demonstrated that CMV infection continued to be associated with lower survival and higher non-relapse mortality (NRM), especially in HSCT with unrelated cord blood or haploidentical donor [19–22]. In a recent retrospective study on 1035 HSCT patients younger than 18 years, CMV

Table 1
Consensus statements for the management of cytomegalovirus infection in pediatric allogeneic hematopoietic stem cell transplantation.

TOPICS AND STATEMENTS	ROUND 1 Mean score (SD)	FINAL VERSION	ROUND 2 Mean score (SD)
1. Impact of CMV infection on the outcome of pediatric allo-HSCT *CMV infection is a risk factor for lower survival and higher non-relapse mortality in pediatric transplantation.*	8.9 (0.4)		No
2. Risk factors for CMV infection in pediatric allo-HSCT *The strongest risk factor for the development of CMV infection in the early post-engraftment period of HSCT is the CMV serological status of the recipient/donor pair.*	8.7 (0.7)	*The strongest risk factor for the development of CMV infection in the early post-engraftment period of HCT is the CMV* ***positive*** *serological status of the* ***recipient or donor.***	8.7 (0.7)
3. How to monitor the patient at risk of CMV infection *Quantitative CMV-DNAemia, performed at least once a week, is the most sensitive test to diagnose early CMV infection. Monitoring may have variable duration depending on patient's clinical status, type of HSCT, and grade of immune reconstitution, but is mandatory for the first 3 months after HSCT.*	9.0 (0.0)		No
4. How to identify the duration of the risk of CMV infection in pediatric patients *The sequential monitoring of patient's immune reconstitution by quantitative flow cytometry analysis is recommended alongside with CMV-specific immunity for the first year after allo-HSCT or until full recovery of CMV immunity is documented.*	8.6 (1.3)	*The sequential monitoring of patients' immune reconstitution by quantitative flow cytometry analysis is recommended for the first year after allo-HSCT or until immune recovery is documented.* ***CMV-specific immunity testing may be useful in refractory patients.***	8.9 (0.3)
5. When is CMV prophylaxis recommended *Universal prophylaxis is recommended in all children undergoing allogeneic-HSCT, with preferred agent acyclovir or valacyclovir. Anti-CMV specific prophylaxis is recommended for very high-risk patients (D-/R+ CMV serostatus, haploHSCT with* in vivo *or ex vivo T-cell depleted, cord blood HSCT, acute or chronic GvHD).*	7.4 (1.9)	*Anti-CMV specific primary prophylaxis is recommended for very high-risk patients (R+CMV serostatus, haploHSCT with* in vivo *or ex vivo T-cell depleted, cord blood HSCT).* *General herpes prophylaxis, with acyclovir or valacyclovir, is recommended in all children undergoing allogeneic-HSCT but may have only limited activity against CMV.*	8.8 (0.4)
6. When is a pre-emptive strategy recommended and at what threshold of viremia should therapy be started *Pre-emptive therapy, based on the detection of CMV DNA in plasma or whole blood, is the standard of care for patients after an allo-HSCT; the threshold of 1000 copies/ml or 1000 IU/ml is one of the most commonly used, although there is no homogeneous strategy.*	8.3 (0.9)	*Pre-emptive therapy, based on the detection of CMV DNA in plasma or whole blood, is the standard of care for patients after an allo-HSCT; although there is no homogenous strategy, the threshold of 1000 IU/ml is one of the most commonly used,* but it may vary ***depending on the degree of the immunosuppression****, (note that for the centers that use copies/ml as measure unit, the threshold most used is of 1000 copies/ml)*	9.0 (0.0)
7. How to choose the appropriate antiviral therapy *Ganciclovir, valganciclovir or foscarnet are the recommended first-line treatments for CMV infection or CMV disease, while maribavir (with age limits), cidofovir and adoptive immunotherapy are options for clinically refractory or drug-resistant infections.*	9.0 (0.0)		No
8. Are CMV-IgGs indicated? *The use of CMV-IgGs has limited evidence-based data of efficacy, and the definition of their role would require future research in the setting of HCT.*	8.2 (1.0)	***Although CMV-IgGs are used in HSCT in clinical practice****, evidence-based efficacy data are limited and defining their role would require future research.*	8.9 (0.3)
9. Is anti-viral combination therapy indicated? *The combination of antivirals with different mechanisms of action may be considered in selected patients affected by recurrent-refractory infection difficult to treat after assessment of the risk-benefit ratio for efficacy and side effects.*	8.3 (1.4)	*The combination of antivirals with different mechanisms of action may be considered in selected patients affected by a difficult-to-treat recurrent-refractory infection after assessment of the benefit-risk ratio in terms of efficacy and side effects.*	9.0 (0.0)
10 What is role of therapeutic drug monitoring (TDM) in the management of antiviral therapy for CMV infection *Therapeutic drug monitoring is recommended for pediatric patients treated with ganciclovir and valganciclovir due to the high intra- and*	8.4 (0.9)		No

(*continued on next page*)

Table 1 (*continued*)

TOPICS AND STATEMENTS	ROUND 1 Mean score (SD)	FINAL VERSION	ROUND 2 Mean score (SD)
inter-patient drug variability and the lower probability of achieving the therapeutic target.			
11 What is the role of adoptive cell therapy? *Adoptive cell therapy is an option for patients with refractory or resistant CMV infection or poorly responding CMV disease and poor or delayed immune recovery after HSCT, although its large-scale applicability is hampered by manufacturing bottlenecks and limited availability of cell products.*	9.0 (0.0)		No

viremia was observed in 25 % of the patients, of whom 15 % had received grafts from matched family donors and 30 % from matched unrelated donors, 41 % T-replete and 14 % T-deplete haploidentical HSC grafts [23]. In this study, CMV infections were significantly associated with all-cause mortality and increased risk of mortality due to graft versus host disease (GVHD). Moreover, CMV infections with high CMV-DNA load or refractory or recurrent are associated with a greater risk of death and inferior overall survival [24,25]. For this reason, preventing CMV infection has the potential to reduce the risk of overall and non-relapse mortality in the first year after allo-HSCT [3].

4.2. . Risk factors for CMV infection in pediatric allo-HSCT

Statement 2: The strongest risk factor for CMV infection in the early post-engraftment period of HSCT is the CMV-positive serological status of the recipient or donor. [8.7]

CMV infection is diagnosed in 20–50 % of allo-HSCTs. The development of CMV infection is strongly influenced by previous CMV exposure of the recipient/donor (R/D) pair, assessed by their serological status. The CMV *R+/D-* combination has the highest risk of CMV infection (approximately 50 %), followed by CMV *R+/D+* (30–40 %), and CMV R-/D+ (14–20 %) [3,26]. To prevent CMV infection, current guidelines recommend, when possible, combining a CMV D- with an R-, a combination associated with an almost null risk of CMV infection [27]. Another major risk factor for CMV infection is the severity of immunosuppression, induced by either GVHD prophylaxis and/or treatment, and type of donor. Multiple lines of immunosuppressants may be needed for the treatment of moderate-severe acute GVHD or to prevent GVHD when the donor is partially compatible or haploidentical. Moreover, recipients of cord blood stem cells experience a delayed recovery of CMV-specific T-cell immunity compared to recipients of bone marrow or peripheral donor HCT, thus being at higher risk of CMV infection [26,28]. Although the risk of CMV infection is highest in the early post-transplant course, late CMV infection, after day +100, may occur in about 10–20 % of patients and is associated with higher overall mortality. Risk factors for late CMV infection are prior CMV infection and treatment for acute GVHD [29].

4.3. . How to monitor the patient at risk of CMV infection

Statement 3: Quantitative CMV-DNAemia, performed at least once a week, is the most sensitive test to diagnose early CMV infection. Monitoring may have a variable duration depending on the patient's clinical status, type of HSCT, and grade of immune reconstitution, but it is mandatory for the first 3 months after HSCT. [9.0]

Over the last two decades, quantitative PCR for detecting CMV-DNA load in blood or plasma has replaced the detection of pp65 protein in neutrophils for the early diagnosis of CMV infection in the presymptomatic phase. In the EBMT CMV management survey, which included adult centers, pediatric centers, and centers with a joint adult and pediatric transplant program, CMV monitoring was performed by blood or plasma PCR in 97 % of 180 responding centers, and of these, 97 % used a quantitative method. No significant differences were observed between adult-only centers, pediatric-only centers, and joint adult/pediatric centers. Additionally, 95 % of centers had performed CMV monitoring for all HSCT types and only 4 % of centers had limited it to HSCTs considered at high risk for CMV infection (such as unrelated HSCTs, related and unrelated cord blood-HSCTs, T-cell replete or *ex-vivo* depleted haploidentical HSCTs, and HSCTs from recipient and/or donor with positive CMV serology). The frequency of CMV-PCR testing was variable, but most centers (61 %) performed it at least once weekly until day +100, while 29 % of the centers performed it twice weekly during the hospitalization for transplant and then once a week after discharge (4 %). The period of close CMV monitoring generally included the first hundred days after HSCT, but most centers declared to extend this monitoring beyond day 100 in the presence of risk factors for late CMV infection, such as active treatment for GVHD, immunosuppressive or steroid therapy, a CD4 count $<0.25\times10^9$/L, or a lymphocyte count $<0.3\times10^9$/L [15].

4.4. . How to identify the duration of the risk of CMV infection in pediatric patient

Statement 4: The sequential monitoring of patients' immune reconstitution by quantitative flow cytometry analysis is recommended for the first year after allo-HSCT or until immune recovery is documented. CMV-specific immunity testing may be useful in refractory patients. [8.9]

Assessing the speed and quality of immune reconstitution (by CD3+, CD4+, CD8+, CD19+, NK cell levels) after allo-HSCT provides information on the patient's anti-infective and immunological competence. Knowing the status of CMV-specific cell-mediated immunity (CMV-CMI) at a critical time point could be crucial in deciding the duration of antiviral prophylaxis or assessing a patient's risk of recurrent CMV infection [30]. So far, limited evidence exists about clinical applicability and significance of different methods – e.g., ELISPOT CMV and QUANTIFERON—CMV – to evaluate CMV-CMI, especially in the pediatric setting [31,32]. However, both these methods showed very high negative predictive value (NPV) and sensitivity and were found not to be interchangeable [33]. Further studies are needed before a clear recommendation can be made about which method, if any, may be best for monitoring CMV-CMI. In the meantime, clinicians should use the one available at their institution to assess the duration of the risk of CMV infection after HSCT. Although the optimal timing of these tests has not yet been defined, clinicians should tailor the frequency of CMV monitoring to each patient's clinical history (e.g. these tests should be repeated, even if a patient has achieved full CMV-specific immune reconstitution, whenever the patient presents with a complication that could potentially undermine his/her immune recovery). Moreover, considering the impact of late CMV infections on morbidity and mortality after allo-HSCT, this monitoring should cover at least the first year after transplantation or could be shortened if full CMV-CMI recovery is documented in the absence of further complications.

4.5. . When is CMV prophylaxis recommended?

Statement 5: Anti-CMV specific primary prophylaxis is recommended for very high-risk patients (R+CMV serostatus, haploidentical HSCT with in vivo or ex vivo T-cell depletion, cord blood HSCT). General herpes prophylaxis,

with acyclovir or valacyclovir, is recommended in all children undergoing allogeneic-HSCT, but may have only limited activity against CMV. [8.8]

Two recently published systematic reviews demonstrated the overall efficacy of antiviral prophylaxis against CMV after HSCT, in terms of reducing both CMV infection and disease, especially when performed with GCV and letermovir [34,35]. The latter was the only drug that demonstrated a reduction in all-cause mortality (week-24 OR, 0.59; 95 % CI, 0.38–0.98) in a phase 3 trial [35]. However, the use of GCV cannot be universally recommended, due to the associated risk of myelotoxicity, whereas letermovir cannot be officially prescribed to all patients because it is still off-label in pediatric patients. Prophylaxis with acyclovir or valacyclovir is still recommended, but the main objective is to reduce HSV or VZV infection because the efficacy against CMV is limited [27]. Considering the greater risk of CMV infection and disease in CMV-seropositive children having a CMV-seronegative donor, in recipients of haploidentical (including PT-Cy) [36] or cord-blood transplantation, and in patients presenting acute or chronic GvHD requiring systemic corticosteroids, several pediatric centers have started using prophylaxis with letermovir as local policy or off-label use on a named-patient basis [9,11,37–40]. Moreover, letermovir is also recommended in pediatric patients in the latest edition of recommendations for CMV infection by the 10th edition of European Conference on Infections in Leukemia (ECIL-10) [16].

More data are expected to be published in the coming years, and a pediatric trial program is underway to determine the best dosage for patients younger than 18 years.

4.6. . When is a pre-emptive strategy recommended, and at what threshold of viremia should therapy be started

Statement 6: Pre-emptive therapy, based on the detection of CMV DNA in plasma or whole blood, is the standard of care for patients who have undergone an allo-HSCT; although there is no homogenous strategy, the threshold 1000 IU/ml is one of the most commonly used, but it may vary depending on the degree of the immunosuppression (note that for the centers that use copies/ml as measure unit, the threshold most used is of 1000 copies/ml) [9.0]

Pre-emptive therapy, based on the detection of CMV DNA in plasma or whole blood by RT-qPCR, is the standard of care for pairs where the recipient or donor or both are CMV seropositive, regardless of the use of antiviral prophylaxis [27]. CMV viral load monitoring is also applied to the CMV seronegative D/R pair, because of the risk of CMV primary transfusion-acquired infection, although it is unclear whether it is a cost-effective strategy [41]. The use of whole blood instead of plasma should be preferred, considering that plasma DNAemia may persist despite adequate viral control, leading to inappropriate antiviral overtreatment [42]. There is no validated and shared quantitative DNAemia threshold to start pre-emptive therapy, and in the pediatric population, the same indications as for adults are used. ECIL 7 guidelines recommend adapting the decisional threshold value on the patient's baseline characteristics and transplant risk factors and monitoring the patient over time using the same sample and the same method for DNA extraction, RT-qPCR assay, given the high variability between commercial assays and *in-house* methods [27]. To reduce the variability of PCR assays, the results should be reported as International DNA Units (IU) rather than DNA copies. In an expert consensus, the start of pre-emptive therapy has been set at $> 10^4$ CMV genomic copies/mL of whole blood or at $> 10^3$ CMV genomic copies/mL of plasma, but a lower cut-off should be considered for high risk patients. A survey on CMV practices and management reported that 59 % of centers used the threshold of $>10^3$ copies/mL or $>10^3$ IU/mL to initiate pre-emptive therapy, for both manipulated and unmanipulated HSCT, while a lower threshold, $> 10^2$, or a higher threshold, $> 10^4$, was used in the 17 % and 9 % of the centers for unmanipulated allograft and in the 25 % and 8 % for manipulated allograft, respectively [43]. In addition to the threshold value, a shorter doubling time of CMV load is important in deciding on a more rapid initiation of pre-emptive therapy [15].

Typically, pre-emptive therapy is recommended for at least 2 weeks or until CMV DNAemia clears, whereas the need for a longer treatment period due to slower or no reduction in CMV load may suggest a clinically refractory CMV infection associated to a poor immune recovery [27,41,42].

4.7. . How to choose the appropriate antiviral therapy

Statement 7: GCV, Val-GCV, or FSC are the recommended first-line treatment for CMV infection or disease, while maribavir (with age limits), CDV, and adoptive immunotherapy are options for clinically refractory or drug-resistant infections. [9.0]

GCV, Val-GCV – the oral pro-drug of GCV – and FSC are the antivirals recommended as first-line treatment of CMV infection and disease [27]. In the pre-emptive treatment setting, GCV and FSC are equally effective, but their different toxicity profiles influence the choice. Considering that neutropenia is the most relevant side effect of GCV, in addition to liver toxicity, FSC may be preferred during the peri-engraftment period. In the post-engraftment period, the recommended first-line therapy for CMV infection or disease is GCV (5 mg/Kg twice a day for at least 2 weeks or until CMV-PCR becomes negative, whichever occurs last). GCV-associated neutropenia occurs after 10–14 days of treatment and can be managed by G-CSF administration, while the reduction of the dose is not recommended to avoid the emergence of resistance. FSC (90 mg/kg twice a day) may be an alternative to GCV or be used as second-line therapy in patients with recurrent CMV reactivation [15,27,44]. The renal toxicity profile of FSC (renal tubular failure, electrolyte imbalance, urethritis) requires hyperhydration, monitoring of renal function and avoidance of concomitant nephrotoxic drugs [41,42]. In patients with recurrent CMV infections or poorly responsive to GCV or FSC, testing for drug resistance genes is recommended. In these types of infections, maribavir, an innovative anti-CMV drug, has been recently approved, but with different age limits: in patients > 12 years by the Food and Drug Administration (FDA) and >18 years by the European Medicines Agency (EMA) [8,12]. CDV, a broad-spectrum antiviral agent, is also an alternative to GCV or FSC in CMV infections caused by GCV- or FSC-resistant strains, but limited efficacy data and a significant renal toxicity profile make its use occasional or limited to selected individual patients [44].

Adoptive immunotherapy with CMV-specific cytotoxic T-lymphocytes from donors or third parties is indicated as an adjuvant to antiviral therapy, especially in cases of recurrent infections in patients with poor immune reconstitution [15,27].

4.8. . Is CMV-IgG indicated?

Statement 8: Although CMV-IgG is used in HSCT in clinical practice, evidence-based efficacy data are limited, and defining its role would require future research. [8.9]

The use of polyclonal CMV-specific hyperimmunoglobulin preparations (CMV-IgG) has been reported by several authors in the last three decades, alone or together with antivirals, in the prophylaxis or pre-emptive treatment of CMV infection or as adjunctive therapy for CMV disease. The rationale for the use of CMV-IgG is based on their ability to neutralize CMV viral particles and their immunomodulatory and inhibitory effect on T-cell replication and dendritic cell maturation, which in solid organ transplantation has been associated with a reduced risk of graft rejection [45]. However, robust evidence regarding CMV-IgG efficacy is lacking [46], and their use is generally not recommended by guidelines in prophylaxis and pre-emptive treatment; they are considered as a mild adjunctive therapeutic option only for CMV pneumonia [27,41,43]. Several retrospective studies showed that CMV-IgG is safe and well tolerated. In a series of 23 patients, of whom 7 were treated with CMV-IgG in monotherapy prophylaxis and 16 received CMV-IgG combined with an antiviral as pre-emptive therapy,

the response rate was 78 %, and the 100-day overall survival was 70 % from the start of CMV-IgG administration [47]. Similar results were obtained in a retrospective series of 92 patients, where 14 patients who received CMV-IgG as prophylaxis were completely protected from CMV infection, while 65 % of the patients (51/78) who received CMV-IgG with antivirals as pre-emptive treatment achieved the complete clearance of CMV viremia [48]. The pre-emptive use of CMV-IgG together with antivirals was assessed in a group of 73 patients with CMV viremia post-allo-HSCT. The patients were divided in two groups, based on the total dose of anti-thymocyte globulin (ATG) received in the conditioning regimen (low ATG dose: ⟨ 6 mg/kg; high ATG dose ⟩ 6 mg/kg). The combination of CMV-IgG and anti-CMV drugs was associated with a 100 % response rate, while early use of CMV-IgG significantly accelerated CMV clearance (14 vs. 21 days), especially in the high-dose ATG group (14 vs. 23 days), improved the 2-week response rate and reduced the 2-week reactivation rate [49]. In a retrospective study on 35 patients with CMV proven-probable disease (pneumonia 26, enteritis 9), the association of CMV-IgG with antivirals (GCV or FSC) was feasible and safe, although the mortality rate remained as high as 49 % [50]. In conclusion, CMV-IgG preparations may have a role in the prophylaxis and treatment of CMV infection due to their immunomodulatory activity combined with an adequate safety profile. However, further studies are warranted to evaluate the role of CMV-IgG especially in the setting of prophylaxis and pre-emptive therapy.

4.9. . Is anti-viral combination therapy indicated?

Statement 9: The combination of antivirals with different mechanisms of action may be considered in selected patients affected by a difficult-to-treat recurrent-refractory infection after assessment of the benefit-risk ratio in terms of efficacy and side effects. [9.0]

The rationale of combining anti-CMV drugs is to enhance the antiviral effect by targeting multiple CMV replication sites and preventing the selection of CMV-resistant strains, potentially associated with monotherapy. The most frequently used combination is GCV with FSC, which has shown superior efficacy to monotherapy for CMV retinitis in HIV patients [26,40]. Both GCV and FSC inhibit CMV DNA polymerase, which is essential for CMV replication, but with different mechanisms. In vitro and in vivo data have shown that the combination of GCV and FSC is slightly synergistic [51,52]. Actually, there is a lack of data showing that the combination has a superior efficacy to monotherapy. In a retrospective study on 242 haploidentical HSCT patients, no difference was found regarding the duration of CMV infection, the incidence of CMV disease, the rate of recurrence of CMV infection, and 1-year survival in the group of 65 patients treated with the combination of GCV and FSC and the group of 156 patients treated with monotherapy (GCV or FSC) [53]. The combination of anti-CMV drugs has been suggested by experts as a second- or third-line approach for refractory or resistant CMV infections, especially when the choice of the antiviral combination is guided by the results of genotyping on the phosphotransferase-gene (UL97) and the DNA polymerase-gene (UL54) [54]. This indication is partially overcome by the recent approval of maribavir for the treatment of refractory/resistant CMV infection in patients aged 12 years or older. In a randomized phase III study, maribavir (2 × 400 mg/daily for 8 weeks) was superior to investigator-assigned best therapy (GCV/Val-GCV, FSC, CDV) in CMV clearance and symptom control, with lower hematological and renal toxicity and treatment discontinuation rate [8,55]. The combination of GCV and FSC has also been used to reduce the side effects of each antiviral by combining them at half daily dose every other day. In a retrospective study of 57 pediatric HSCT patients, the use of alternate-day GCV and FSC administered at half the full daily dose was associated with 100 % efficacy in preventing CMV infection, although 5 % and 25 % of patients discontinued GCV and FSC for hematological and renal toxicity, respectively [56].

4.10. . What is the role of therapeutic drug monitoring (TDM) in the management of antiviral therapy for CMV infection

Statement 10: Therapeutic drug monitoring is recommended for pediatric patients treated with GCV and Val-GCV, due to the high intra- and inter-patient drug variability and the lower probability of achieving the therapeutic target. [8.4]

GCV and, to a lesser extent, the prodrug Val-GCV are the first-choice antivirals for the treatment of CMV infection and disease [15]. In the pediatric population, the pharmacokinetics of GCV is characterized by a high intra- and inter-patient variability, increasing the risk of undertreatment and drug resistance, especially in patients younger than 6 years who have a more rapid renal clearance [57]. While GCV underdosing may lead to treatment failure with progression to CMV disease and emergence of drug resistance, overexposure to GCV may result in severe myelotoxicity with the risk of bacterial or fungal infection, and the need of platelet transfusions and dose reduction or discontinuation of therapy. This risk of underexposure to GCV and Val-GCV is higher in the pediatric population where the dosage calculation is commonly based on body weight. Simulations based on population pharmacokinetic models suggest that the use of a formula combining body surface area (BSA) and creatinine clearance calculated by the Schwartz method (CrCLS) allows to achieve an area under the concentration-time curve (AUC_{0-24}) of 40–60 ug – hour/mL, which is considered effective to prevent CMV infection across the different pediatric age groups. The formula for intravenous GCV is dose mg = 3 x BSA x CrCls; while for oral Val-GCV is: mg = 7 x BSA x CrCLS [58]. TDM of GCV is advisable in children due to the high interindividual variability and the low probability of achieving the therapeutic target compared to adults. The therapeutic trough level of GCV is between 0.5 and 3 μg/mL, and a trough level < 0.5 μg/mL is an indication to increase the dosage. In patients at higher risk of myelotoxicity, generating an AUC_{0-24} curve, with pre-dose sampling and 4–5 post-dose samplings, is more precise than the simple determination of the trough level to define the need for dose adjustment [59]. Determination of blood FSC level has been less studied in pediatric patients and has been used primarily in HIV patients to investigate renal toxicity or resistance in clinically refractory patients [60,61]. TDM is not required with letermovir, a drug that has shown relatively stable trough levels in adult patients with GvHD or gastrointestinal symptoms, while the higher trough levels expected by drug interaction with posaconazole or cyclosporin can be managed by a daily-dose reduction [62]. Data regarding the pharmacokinetics and pharmacodynamics of letermovir in pediatric age are limited and require future research.

4.11. . What is the role of adoptive cell therapy?

Statement 11: Adoptive cell therapy is an option for patients with refractory or resistant CMV infection or poorly responsive CMV disease and poor or delayed immune recovery after HSCT, although its large-scale applicability is hampered by manufacturing bottlenecks and limited availability of cell products. [9.0]

Despite recent advances in antiviral drug prophylaxis and treatment of refractory and resistant CMV infection, delayed or poor immune reconstitution in the post-HSCT period remains a major obstacle to achieving a rapid and adequate recovery from CMV infection. Moreover, poor immune function is a predisposing factor for recurrent or persistent CMV infection and a cause of progression to CMV disease. The use of adoptive cell therapy with CMV-specific T lymphocytes (CMV-T cells) to enhance CMV-directed cellular immunity has been explored by several authors over the past three decades. In the 2020 EBMT survey, 28 % of participating centers reported using adoptive CMV-T cell therapy, primarily for the treatment of recurrent/refractory disease or in the context of clinical trials [15]. A meta-analysis, including 40 studies published between 1995 and 2023, evaluating 953 patients who received CMV adoptive cellular therapy for therapeutic purposes, showed an overall

response rate of 90.16 % and a complete response rate of 82.59 %. Factors associated with response were the degree of HLA matching between donor and recipient, the use or not of steroids in the recipient, the source of CMV-T cells (better in donor-derived vs. third-party ones), and age (better in adult than in pediatric patients). The safety profile was acceptable, with acute GvHD, usually mild to moderate, reported in 24.32 % of patients, while no adverse events were reported in 9 studies [62]. One of the main challenges of this approach is its large-scale feasibility due to the cost and complexity of manufacturing in academic centers and the availability of commercial products. CMV-T cell production can be obtained by direct selection of CMV-T cells from the CMV seropositive stem cell donor by interferon-gamma capture system or CMV tetramers/streptamers, followed by *ex vivo* expansion by stimulation with cytokines; alternatively, a third-party donor can be used to obtain CMV-T cells to expand *ex vivo* by cytokine stimulation and subsequently cryopreserved and stored. Thereafter, these third-party donor CMV-T cells can be used upon demand, after identification of the best HLA-matched product for the patient who needs it. Importantly, the use of stored third-party donor CMV-T cells has the potential to shorten the time from clinical indication to treatment with CMV-T cells. Both transplant donor-derived and third-party donor CMV-T cells are associated with variable viral clearance and clinical efficacy [63–65].

In the prophylactic setting, a phase II study based on Posoleucel®, a third-party multivirus-specific T-cell product, showed safety and efficacy in preventing CMV and other viral reactivations/diseases in the early phase after HSCT [66]. However, the subsequent phase III trial, which enrolled allo-HSCT recipients considered at high risk for CMV infection, failed to meet the efficacy endpoints at interim analysis and was stopped in December 2023. Thus, the prophylactic efficacy of antiviral cellular products in the setting of HSCT remains to be further tested.

5. Conclusions

CMV infection is a risk factor for lower survival and higher non-relapse mortality in the pediatric transplant setting. The main pre-transplant factor predicting the risk of CMV infection and disease is CMV seropositivity of the recipient and/or donor, as well as the degree of immunosuppression, while the early post-engraftment period is the period at highest risk of CMV infection.

Quantitative monitoring of CMV-DNAemia by molecular techniques is the most sensitive method to identify subclinical CMV infection. Letermovir prophylaxis has radically changed the negative impact of recipient/donor CMV seropositivity on morbidity and mortality from CMV infection, and its marketing authorization for the pediatric population is highly anticipated. Pre-emptive therapy with GCV or FSC is still the standard of care to prevent the development of CMV disease in children. Maribavir represents a new option for CMV refractory-resistant infection due to its favorable efficacy and safety profile already shown in adolescents aged 12 years and older and adult patients. In addition to innovative antiviral drugs, TDM also represents a tool for management improvement, considering the limited availability of pharmacokinetic data in the pediatric population. The other main indications that emerged from the consensus are the need for monitoring post-HSCT immune reconstitution by quantitative flow cytometry and the need to focus further clinical research on adoptive cell therapy.

Author contributions

All authors contributed to the design of the work, output definition, writing, revision and final approval of the manuscript. All authors agree to be accountable for all aspects of the work.

Funding

This work was unconditionally supported by Grifols

Grifols had no role in the design of the study; in the collection, analyses, interpretation of data; or in the decision to publish the results. In addition, the funder did not play a role in the process or influence the decisions reached.

Declaration of interest

SIMONE CESARO

Simone Cesaro received writing assistance by Havas Life Rome S.r.L.

ARCANGELO PRETE

Arcangelo Prete is board membership of Jazz Pharmaceuticals.

FRANCA FAGIOLI, MAURA FARACI, GIULIA FERRANDO, FULVIO PORTA, MARCO RABUSIN, MANUELA SPADEA, ADRIANA BALDUZZI, MARCO ZECCA:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors are grateful to Havas Life Italy S.r.l. for its supervision and coordination of the project and to Renata Perego, MD, for her help in drafting the manuscript and editorial support. Eugenio Rosado, PhD, CMPP (Grifols) is acknowledged for reviewing the manuscript.

References

[1] Marty FM, Ljungman P, Chemaly RF, Maertens J, Dadwal SS, Duarte RF, et al. Letermovir prophylaxis for Cytomegalovirus in hematopoietic-cell transplantation. N Engl J Med 2017;377:2433–44. https://doi.org/10.1056/NEJMoa1706640.

[2] Marty FM, Ljungman P, Papanicolaou GA, Winston DJ, Chemaly RF, Strasfeld L, et al. Maribavir prophylaxis for prevention of cytomegalovirus disease in recipients of allogeneic stem-cell transplants: a phase 3, double-blind, placebo-controlled, randomised trial. Lancet Infect Dis 2011;11:284–92. https://doi.org/10.1016/S1473-3099(11)70024-X.

[3] Green ML, Leisenring W, Xie H, Mast TC, Cui Y, Sandmaier BM, et al. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. Lancet Haematol 2016;3:e119–27. https://doi.org/10.1016/S2352-3026(15)00289-6.

[4] Hill JA, Mayer BT, Xie H, Leisenring WM, Huang ML, Stevens-Ayers T, et al. The cumulative burden of double-stranded DNA virus detection after allogeneic HCT is associated with increased mortality. Blood 2017;129:2316–25. https://doi.org/10.1182/blood-2016-10-748426.

[5] Hill JA, Mayer BT, Xie H, Leisenring WM, Huang ML, Stevens-Ayers T, et al. Kinetics of double-stranded DNA viremia after allogeneic hematopoietic cell transplantation. Clin Infect Dis 2018;66:368–75. https://doi.org/10.1093/cid/cix804.

[6] Ljungman P, Schmitt M, Marty FM, Maertens J, Chemaly RF, Kartsonis NA, et al. A mortality analysis of letermovir prophylaxis for Cytomegalovirus (CMV) in CMV-seropositive recipients of allogeneic hematopoietic cell transplantation. Clin Infect Dis 2020;70:1525–33. https://doi.org/10.1093/cid/ciz490.

[7] Su Y, Stern A, Karantoni E, Nawar T, Han G, Zavras P, et al. Impact of Letermovir primary Cytomegalovirus prophylaxis on 1-year mortality after allogeneic hematopoietic cell transplantation: a retrospective cohort study. Clin Infect Dis 2022;75:795–804. https://doi.org/10.1093/cid/ciab1064.

[8] Avery RK, Alain S, Alexander BD, Blumberg EA, Chemaly RF, Cordonnier C, et al. Maribavir for refractory Cytomegalovirus infections with or without resistance post-transplant: results from a phase 3 randomized clinical trial. Clin Infect Dis 2021;75(4):690–701. https://doi.org/10.1093/cid/ciab988.

[9] Galaverna F, Baccelli F, Zama D, Tridello G, Masetti R, Soncini E, et al. Letermovir for Cytomegalovirus infection in pediatric patients undergoing allogenic hematopoietic stem cell transplantation: a real-life study by the Infectious Diseases Working Group of Italian Association of Pediatric Hematology-Oncology (AIEOP). Bone Marrow Transpl 2024;59(4):505–12. https://doi.org/10.1038/s41409-024-02209-2.

[10] Kuhn A, Puttkammer J, Madigan T, Dinnes L, Khan S, Ferdjallah A, et al. Letermovir as Cytomegalovirus prophylaxis in a pediatric cohort: a retrospective analysis. Transpl Cell Ther 2023;29:62. https://doi.org/10.1016/j.jtct.2022.10.005. e1-e4.

[11] Chen TT, David AP, Barthelmess EK, MacBrayne CE. Letermovir for Cytomegalovirus prophylaxis in pediatric hematopoietic stem cell transplantation. Pediatr Blood Cancer 2023;70:e30608. https://doi.org/10.1002/pbc.30608.

[12] Fisher JE, Mulieri K, Finch E, Ericson JE. Use of Maribavir for multidrug resistant cytomegaloviremia in a pediatric oncology patient. J Pediatr Hematol Oncol 2024;46(3):e244–7. https://doi.org/10.1097/MPH.0000000000002841.

[13] Aldalati AY, Hussein AM, Balbaa E, Hammadeh BM, Idrees M, Aloudat O, et al. Efficacy and safety of Letermovir for Cytomegalovirus prophylaxis in pediatric

hematopoietic stem cell transplantation recipients: a systematic review, meta-analysis, and meta-regression. Transpl Infect Dis 2025:e70006. https://doi.org/10.1111/tid.70006.
[14] Yang W, Irwin A, Weerdenburg H, McWhinney B, Cole T, Lei A, et al. Serum ganciclovir drug exposure in children receiving standard ganciclovir dosing. Antimicrob Agents Chemother 2024;68(10):e0052524. https://doi.org/10.1128/aac.00525-24.
[15] Cesaro S, Ljungman P, Tridello G, Mikulska M, Wendel L, Styczynski J, et al. New trends in the management of cytomegalovirus infection after allogeneic hematopoietic cell transplantation: a survey of the Infectious Diseases Working Party of EBMT. Bone Marrow Transpl 2023;58:203–8. https://doi.org/10.1038/s41409-022-01863-8.
[16] Ljungman P, Alain S, Chemaly RF, Einsele H, Galaverna F, Hirsch HH, et al. Recommendations from the 10th European Conference on Infections in Leukaemia for the management of cytomegalovirus in patients after allogeneic haematopoietic cell transplantation and other T-cell-engaging therapies. Lancet Infect Dis 2025. https://doi.org/10.1016/S1473-3099(25)00069-6. S1473-3099(25)00069-6.
[17] de Villiers MR, de Villiers PJT, Kent AP. The Delphi technique in health sciences education research. Med Teach 2005;27(7):639–43. https://doi.org/10.1080/13611260500069947.
[18] Erard V, Guthrie KA, Seo S, Smith J, Huang M, Chien J, et al. Reduced mortality of Cytomegalovirus pneumonia after hematopoietic cell transplantation due to antiviral therapy and changes in transplantation practices. Clin Infect Dis 2015;61(1):31–9. https://doi.org/10.1093/cid/civ215.
[19] Matthes-Martin S, Lion T, Aberle SW, Fritsch G, Lawitschka A, Bittner B, et al. Pre-emptive treatment of CMV DNAemia in paediatric stem cell transplantation: the impact of recipient and donor CMV serostatus on the incidence of CMV disease and CMV-related mortality. Bone Marrow Transpl 2003;31:803–8. https://doi.org/10.1038/sj.bmt.1703927.
[20] Klejmont LM, Mo X, Milner J, Harrison L, Morris E, van de Ven C, et al. Risk factors associated with survival following ganciclovir prophylaxis through day +100 in Cytomegalovirus At-Risk pediatric allogeneic stem cell transplantation recipients: development of Cytomegalovirus viremia associated with significantly decreased 1-year survival. Transpl Cell Ther 2024;30. https://doi.org/10.1016/j.jtct.2023.09.025. 103.e1-e8.
[21] Yi ES, Lee JW, Kim YJ, Sung KW, Koo HH, Yoo KH. Risk factors and outcomes of cytomegalovirus infection in children post cord blood transplantation with focus on impact of graft-versus-host disease and immunosuppressants. Ann Hematol 2022;101:409–19. https://doi.org/10.1007/s00277-021-04707-5.
[22] Hiwarkar P, Gaspar HB, Gilmour K, Jagani M, Chiesa R, Bennett-Rees N, et al. Impact of viral reactivations in the era of pre-emptive antiviral drug therapy following allogeneic haematopoietic SCT in paediatric recipients. Bone Marrow Transpl 2013;48:803–8. https://doi.org/10.1038/bmt.2012.221.
[23] Chakraborty S, Swaminathan VV, Ganesan K, Duraisamy S, Meena S, Jayakumar I, et al. Cytomegalovirus reactivation as a risk factor for all-cause mortality in children undergoing hematopoietic stem cell transplantation: experience over two decades from a tertiary referral center in India. Indian J Hematol Blood Transfus 2024;40:91–6. https://doi.org/10.1007/s12288-023-01654-1.
[24] Silcock R, Mitchell K, Fraser C, Clark J. Epidemiology and outcome for viremia in children undergoing bone marrow transplant: a retrospective cohort study. Transpl Infect Dis 2021;23:e13580. https://doi.org/10.1111/tid.13580.
[25] Szmit Z, Frączkiewicz J, Salamonowicz-Bodzioch M, Król A, Ussowicz M, Mielcarek-Siedziuk M, et al. The impact of high CMV viral load and refractory CMV infection on pediatric HSCT recipients with underlying non-malignant disorder. J Clin Med 2022;11:5187. https://doi.org/10.3390/jcm11175187.
[26] Heston SM, Young RR, Tanaka JS, Jenkins K, Vinesett R, Saccoccio FM, et al. Risk factors for CMV viremia and treatment-associated adverse events among pediatric hematopoietic stem cell transplant recipients. Open Forum Infect Dis 2022;9:ofab639. https://doi.org/10.1093/ofid/ofab639.
[27] Ljungman P, de la Camara R, Robin C, Crocchiolo R, Einsele H, Hill JA, et al. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the. In: 2017 European Conference on Infections in Leukaemia (ECIL 7). Lancet Infect Dis. 19; 2019. e260–72. https://doi.org/10.1016/S1473-3099(19)30107-0.
[28] Jaing TH, Chang TY, Chen SH, Wen YC, Yu TJ, Lee CF, et al. Factors associated with cytomegalovirus infection in children undergoing allogeneic hematopoietic stem-cell transplantation. Medicine 2019;98:e14172. https://doi.org/10.1097/MD.0000000000014172.
[29] Rowe RG, Guo D, Lee M, Margossian S, London WB, Lehmann L. Cytomegalovirus infection in pediatric hematopoietic stem cell transplantation: risk factors for primary infection and cases of recurrent and late infection at a single center. Biol Blood Marrow Transpl 2016;22:1275–83. https://doi.org/10.1016/j.bbmt.2016.04.004.
[30] Chemaly RF, El Haddad L, Winston DJ, Rowley SD, Mulane KM, Chandrasekar P, et al. Cytomegalovirus (CMV) cell-mediated immunity and CMV infection after allogeneic hematopoietic cell transplantation: the REACT study. Clin Infect Dis 2020;71(9):2365–74. https://doi.org/10.1093/cid/ciz1210.
[31] Lee SM, Kim YJ, Yoo KH, Sung KW, Koo HH, Kang ES. Clinical usefulness of monitoring Cytomegalovirus-specific immunity by quantiferon-CMV in pediatric allogeneic hematopoietic stem cell transplantation recipients. Ann Lab Med 2017;37:277–81. https://doi.org/10.3343/alm.2017.37.3.277.
[32] Seo E, Choi ES, Kim JH, Kim H, Koh KN, Im HJ, et al. Immunologic monitoring of cytomegalovirus (CMV) enzyme-linked immune absorbent spot (ELISPOT) for controlling clinically significant CMV infection in pediatric allogeneic hematopoietic stem cell transplant recipients. PLoS One 2021;16(2):e0246191. https://doi.org/10.1371/journal.pone.0246191.
[33] Callens R, Colman S, Delie A, Schauwvlieghe A, Lodewyck T, Selleslag D, et al. Immunologic monitoring after allogeneic stem cell transplantation: T-SPOT.CMV and QuantiFERON-CMV, are they the same? Transpl Cell Ther 2023;29(6):392. https://doi.org/10.1016/j.jtct.2023.03.018. e1-e7.
[34] Gagelmann N, Ljungman P, Styczynski J, Kröger N. Comparative efficacy and safety of different antiviral agents for Cytomegalovirus prophylaxis in allogeneic hematopoietic cell transplantation: a systematic review and meta-analysis. Biol Blood Marrow Transpl 2018;24:2101–9. https://doi.org/10.1016/j.bbmt.2018.05.017.
[35] Chen K, Cheng MP, Hammond SP, Einsele H, Marty FM. Antiviral prophylaxis for cytomegalovirus infection in allogeneic hematopoietic cell transplantation. Blood Adv 2018;2(16):2159–75. https://doi.org/10.1182/bloodadvances.2018016493.
[36] Goldsmith SR, Abid MB, Auletta JJ, Bashey A, Beitinjaneh A, Castillo P, et al. Posttransplant cyclophosphamide is associated with increased cytomegalovirus infection: a CIBMTR analysis. Blood 2021;137:3291–305. https://doi.org/10.1182/blood.2020009362.
[37] César T, Le MP, Klifa R, Castelle M, Fournier B, Lévy R, et al. Letermovir for CMV prophylaxis in very high-risk pediatric hematopoietic stem cell transplantation recipients for inborn errors of immunity. J Clin Immunol 2023;44(1):6. https://doi.org/10.1007/s10875-023-01617-1.
[38] Yan B, Sun G, Wu Y, Wu W, Song K, Cheng Y, et al. Letermovir prophylaxis reduced cytomegalovirus reactivation and resistance post umbilical cord blood transplantation. Br J Haematol 2024;204:2378–89. https://doi.org/10.1111/bjh.19451.
[39] Körholz KF, Füller MA, Hennies M, Holterhus M, Hagedorn S, Ahlmann M, et al. Letermovir for prophylaxis and pre-emptive therapy of Cytomegalovirus infection in paediatric allogeneic haematopoietic cell transplant patients. Paediatr Drugs 2023;25:225–32. https://doi.org/10.1007/s40272-022-00547-6.
[40] Groll AH, Schulte JH, Antmen AB, Fraser CJ, Teal VL, Haber B, et al. Pharmacokinetics, safety, and efficacy of Letermovir for Cytomegalovirus prophylaxis in adolescent hematopoietic cell transplantation recipients. Pediatr Infect Dis J 2024;43(3):203–8. https://doi.org/10.1097/INF.0000000000004208.
[41] Hakki M, Aitken SL, Danziger-Isakov L, Michaels MG, Carpenter PA, Chemaly RF, et al. American Society for Transplantation and Cellular Therapy Series: #3-prevention of Cytomegalovirus infection and disease after hematopoietic cell Transplantation. Transpl Cell Ther 2021;27:707–19. https://doi.org/10.1016/j.jtct.2021.05.001.
[42] Girmenia C, Lazzarotto T, Bonifazi F, Patriarca F, Irrera G, Ciceri F, et al. Assessment and prevention of cytomegalovirus infection in allogeneic hematopoietic stem cell transplant and in solid organ transplant: a multidisciplinary consensus conference by the Italian GITMO, SITO, and AMCLI societies. Clin Transpl 2019;33:e13666. https://doi.org/10.1111/ctr.13666.
[43] Bontant T, Sedlaçek P, Balduzzi A, Gaspar B, Cesaro S, Einsele H, et al. Survey of CMV management in pediatric allogeneic HSCT programs, on behalf of the inborn errors, infectious diseases and pediatric diseases working parties of EBMT. Bone Marrow Transpl 2014;49(2):276–9. https://doi.org/10.1038/bmt.2013.164.
[44] Piret J, Boivin G. Management of Cytomegalovirus infections in the era of the novel antiviral players, Letermovir and Maribavir. Infect Dis Rep 2024;16:65–82. https://doi.org/10.3390/idr16010005.
[45] Barten MJ, Baldanti F, Staus A, Hüber CM, Glynou K, Zuckermann A. Effectiveness of prophylactic Human Cytomegalovirus hyperimmunoglobulin in preventing Cytomegalovirus infection following transplantation: a systematic review and meta-analysis. Life (Basel) 2022;12(3):361. https://doi.org/10.3390/life12030361.
[46] Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in hematopoietic stem cell transplantation: systematic review and meta-analysis. J Clin Oncol 2009;27(5):770–81. https://doi.org/10.1200/JCO.2008.16.8450.
[47] Alsuliman T, Kitel C, Dulery R, Guillaume T, Larosa F, Cornillon J, et al. Cytotect®CP as salvage therapy in patients with CMV infection following allogeneic hematopoietic cell transplantation: a multicenter retrospective study. Bone Marrow Transpl 2018;53:1328–35. https://doi.org/10.1038/s41409-018-0166-9.
[48] Malagola M, Greco R, Santarone S, Natale A, Iori AP, Quatrocchi L, et al. CMV management with specific immunoglobulins: a multicentric retrospective analysis on 92 allotransplanted patients. Mediterr J Hematol Infect Dis 2019;11:e2019048. https://doi.org/10.4084/MJHID.2019.048.
[49] Zhang P, Yang D, Tian J, Feng S, Jiang E, Han M. A clinical study of lyophilized intravenous human immunoglobulin containing high-titer cytomegalovirus-neutralizing antibody for the treatment of cytomegalovirus viremia after allogeneic hematopoietic stem cell transplantation. Ann Palliat Med 2021;10:5533–40. https://doi.org/10.21037/apm-21-1069.
[50] Alexander BT, Hladnik LM, Augustin KM, Casabar E, McKinnon PS, Reichley RM, et al. Use of cytomegalovirus intravenous immune globulin for the adjunctive treatment of cytomegalovirus in hematopoietic stem cell transplant recipients. Pharmacotherapy 2010;30:554–61. https://doi.org/10.1592/phco.30.6.554.
[51] Cai H, Kapoor A, He R, Venkatadri R, Forman M, Posner GH, et al. In vitro combination of anti-cytomegalovirus compounds acting through different targets: role of the slope parameter and insights into mechanisms of action. Antimicrob Agents Chemother 2014;58:986–94. https://doi.org/10.1128/AAC.01972-13.
[52] Drew WL. Is combination antiviral therapy for CMV superior to monotherapy? J Clin Virol 2006;35:485–8. https://doi.org/10.1016/j.jcv.2005.09.021.
[53] Ma R, He Y, Xu LP, Zhang XH, Wang Y, Liu KY, et al. Clinical analysis of the efficacies of ganciclovir plus foscarnet and a single antiviral drug for the treatment of cytomegalovirus infection after haploidentical stem cell transplantation].

Zhonghua Nei Ke Za Zhi 2023;62:76–83. https://doi.org/10.3760/cma.j.cn112138-20220118-00058.
[54] El Chaer F, Shah DP, Chemaly RF. How I treat resistant cytomegalovirus infection in hematopoietic cell transplantation recipients. Blood 2016;128:2624–36. https://doi.org/10.1182/blood-2016-06-688432.
[55] Gourin C, Alain S, Hantz S. Anti-CMV therapy, what next? A systematic review. Front Microbiol 2023;14. https://doi.org/10.3389/fmicb.2023.1321116.
[56] Shereck EB, Cooney E, van de Ven C, Della-Lotta P, Cairo MS. A pilot phase II study of alternate day ganciclovir and foscarnet in preventing cytomegalovirus (CMV) infections in at-risk pediatric and adolescent allogeneic stem cell transplant recipients. Pediatr Blood Cancer 2007;49:306–12. https://doi.org/10.1002/pbc.21043.
[57] Vethamuthu J, Feber J, Chretien A, Lampe D, Filler G. Unexpectedly high inter- and intrapatient variability of ganciclovir levels in children. Pediatr Transpl 2007;11:301–5. https://doi.org/10.1111/j.1399-3046.2006.00669.x.
[58] Jorga K, Reigner B, Chavanne C, Alvaro G, Frey N. Pediatric dosing of Ganciclovir and Valganciclovir: how model-based simulations can prevent underexposure and potential treatment failure. CPT Pharmacomet Syst Pharmacol 2019;8:167–76. https://doi.org/10.1002/psp4.12363.
[59] Duval X, Lemaitre F, Pertuisel S, Probert J, Gandemer V, Verdier MC, et al. The need for area under the curve measurements in the field of ganciclovir therapeutic drug monitoring in children: a case report. BMC Infect Dis 2021;21:1143. https://doi.org/10.1186/s12879-021-06828-8.
[60] Jr Balfour HH, CV Fletcher, Erice A, Henry WK, Acosta EP, Smith SA, et al. Effect of foscarnet on quantities of cytomegalovirus and human immunodeficiency virus in blood of persons with AIDS. Antimicrob Agents Chemother 1996;40(12):2721–6. https://doi.org/10.1128/AAC.40.12.2721.
[61] Wagstaff AJ, Foscarnet Bryson HM. A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with viral infections. Drugs 1994;48(2):199–226. https://doi.org/10.2165/00003495-199448020-00007.
[62] Taherian MR, Azarbar P, Barkhordar M, Toufani S, Aliabadi LS, Bahri T, et al. Efficacy and safety of adoptive T-cell therapy in treating cytomegalovirus infections post-haematopoietic stem cell transplantation: a systematic review and meta-analysis. Rev Med Virol 2024;34:e2558. https://doi.org/10.1002/rmv.2558.
[63] Neuenhahn M, Albrecht J, Odendahl M, Schlott F, Dössinger G, Schiemann M, et al. Transfer of minimally manipulated CMV-specific T cells from stem cell or third-party donors to treat CMV infection after allo-HSCT. Leukemia 2017;31:2161–71. https://doi.org/10.1038/leu.2017.16.
[64] Prokoph N, Larose H, Lim MS, Burke GAA, Turner SD. Treatment options for paediatric anaplastic large cell lymphoma (ALCL): current standard and beyond. Cancers (Basel) 2018;10:E99. https://doi.org/10.1002/rmv.2558.
[65] Roex MCJ, van Balen P, Germeroth L, Hageman L, van Egmond E, Veld SAJ, et al. Generation and infusion of multi-antigen-specific T cells to prevent complications early after T-cell depleted allogeneic stem cell transplantation-a phase I/II study. Leukemia 2020;34:831–44. https://doi.org/10.1038/s41375-019-0600-z.
[66] Pfeiffer T, Tzannou I, Wu M, Ramos C, Sasa G, Martinez C, et al. Posoleucel, an allogeneic, off-the-shelf multivirus-specific T-cell therapy, for the treatment of refractory viral infections in the post-HCT setting. Clin Cancer Res 2023;29(2):324–30. https://doi.org/10.1158/1078-0432.CCR-22-2415.