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# Cytomegalovirus infection after allogeneic hematopoietic stem cell transplantation: clinical significance and definitions

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## Abstract

***Introduction.*** *Cytomegalovirus infection is one of the critical and life-threatening infectious complications in patients after allogeneic hematopoietic stem cell transplantation. The most significant risk factors for the development of cytomegalovirus infection are cytomegalovirus serostatus of the donor and recipient and delayed reconstitution of cytomegalovirus-specific CD4+ and CD8+ T lymphocytes after allogeneic hematopoietic stem cells transplantation.*

*The infection may be asymptomatic or may lead to serious complications such as cytomegalovirus disease, which happens in 10-40% of cases. Cytomegalovirus infection has different impact on patients after hematopoietic stem cell transplantation. For instance, acute and chronic graft versus host disease may also be the risk factors for the development of cytomegalovirus infection. There is also information about the influence of cytomegalovirus infection on a graft failure. We also know that cytomegalovirus replication is associated with lower relapse risk in patients with acute myeloid leukemia and chronic myeloid leukemia.*

*Antiviral prophylaxis and preemptive therapy are good strategies to reduce the risk of the cytomegalovirus infection. Despite this, cytomegalovirus infection is still associated with decreased overall survival and increased non-relapse mortality in recipients of allogeneic stem cells.*

***Aim**. The aim of this review is to systematize modern concepts used in the management and treatment of cytomegalovirus infections in patients after hematopoietic stem cell transplantation.*

**Keywords:** hematopoietic stem cell transplantation, cytomegalovirus infection, resistant cytomegalovirus infection, refractory cytomegalovirus infection, cytomegalovirus disease

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allo-HSCT, allogeneic hematopoietic stem cell transplantation

ALT, alanine aminotransferase;

AML, acute myeloid leukemia

AST, aspartate aminotransferase;

BAL, bronchoalveolar lavage;

CMV DNA, cytomegalovirus deoxyribonucleic acid

CMV, cytomegalovirus

CNS, central nervous system,

DNA, deoxyribonucleic acid

EEG, electroencephalography

GIT, gastrointestinal tract;

GVHD, graft-versus-host disease/response

GVT response, graft-versus-tumor response

HSCs, hematopoietic stem cells

PCR, polymerase chain reaction

## Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is one of the stages of the treatment program for patients with hemoblastoses and non-tumor diseases of the blood system. The risk of the allo-HSCT procedure is associated not only with the toxicity of chemotherapy drugs used in conditioning programs, but also with complications that occur both in the early and late periods after allo-HSCT. One of the most serious and life-threatening complications is cytomegalovirus infection (CMV infection), and it is currently the leading cause of death among infectious diseases in patients after allo-HSCT, especially in the first 100 days after allo-HSCT [1-3].

The prevalence of CMV infection in the general population ranges from 40% to 100% and has a rather high variability depending on the region of residence. [4-5]. In immunocompetent people, cytomegalovirus (CMV) is under the control of the immune system, remaining in a latent state in the human body and not manifesting itself clinically.

In immunocompromised patients, namely, patients after transplantation of solid organs (SOs), hematopoietic stem cells (HSCs), patients with HIV, patients receiving immunosuppressive therapy, newborns, pregnant women, CMV can cause severe damage to various organs and tissues [6].

The most severe CMV infection occurs in allogeneic HSC recipients. Insufficient and/or delayed reconstitution of CMV-specific

CD4+ and CD8+ T lymphocytes after allo-HSCT predisposes to the development of CMV infection and CMV disease [7-8].

Variants of the course of CMV infection in allogeneic HSC recipients are different: from asymptomatic CMV infection to severe CMV disease with multiple organ damage [9-10]. In addition to organ damage, CMV infection in allo-HSCT can have a direct effect on the graft, namely, play a role in the development of graft failure, prolonged cytopenia leading to the development of other bacterial and fungal infections [11, 12].

The prevalence of CMV seropositivity in the general population (positive test for anti-CMV antibodies [anti-CMV-IgG]) varies geographically and is also associated with socioeconomic status. The CMV status of the donor and recipient (D/R) is a decisive factor in choosing a scheme for the prevention of graft-versus-host disease (GVHD), therefore, in conditions of searching for an unrelated donor, it is not always possible to choose a seronegative donor for an allogeneic HSC recipient [4].

According to various data, CMV infection is observed in approximately 60-70% of CMV-seropositive patients, and primary CMV infection affects from 20% to 30% of CMV-seronegative patients in whom allo-HSCT was performed from a seropositive donor [13].

In addition, the relationship of CMV infection with GVHD has been described, namely the fact that GVHD and the immunosuppressive therapy used to treat it increase the risk of developing CMV infection. Some studies also describe the opposite effect, when an episode of CMV infection was associated with a new onset of GVHD [14-15].

The "positive" phenomena of cytomegalovirus have also been described. CMV infection leads to potentiation of the antitumor effect (induces the graft-versus-tumor (GVT) response), which prevents the

development of relapse in patients with acute myeloid leukemia, chronic myeloid leukemia [16-17].

Despite the widespread implementation of the strategy for the prevention of CMV infection in recipients of allogeneic HSCs, preventive and targeted therapy for CMV infection, the mortality associated with it among recipients of hematopoietic stem cells is still high and, according to various data, makes 45–60 % [8].

This paper summarized modern concepts used in the assessment of CMV infection in patients after allo-HSCT. Based on the analysis of literature sources, we proposed schemes for the diagnosis of CMV infection, which make it possible to simplify the assessment of clinical and laboratory signs of CMV infection in allogeneic HSC recipients.

**The concept of CMV infection and CMV disease**

Currently, in clinical practice, for patients after allo-HSCT, the key concepts have been formed that are used in establishing the diagnosis and variant of CMV infection, assessing the response to therapy, and specifying the resistance to antiviral drugs [18]. Meanwhile, CMV infection in allo-HSCT has its own diagnostic features, which have been discussed in this review.

*CMV infection* (the equivalent term is *CMV replication*) is a condition characterized by isolating the virus and/or detecting viral proteins (antigen) and/or nucleic acids in any biological fluid or tissue of the body, regardless of the presence or absence of any clinical manifestations [18]. It is important to note that the diagnosis of CMV infection is not associated with the presence or absence of clinical symptoms and does not require the initiation of targeted therapy in all cases (not to be confused with preventive therapy).

*CMV disease* is a CMV infection that occurs with damage to target organs and has the documented molecular genetic, cultural, histological and/or immunohistochemical evidence of cytomegalovirus damage to a certain organ. The target organ can be any organ of the recipient. It is important to note that without detection cytomegalovirus in the tissue of the target organ, it is impossible to speak of CMV disease, even if the clinical improvement was achieved with the empirical administration of antiviral drugs.

**Current methods of detecting cytomegalovirus**

There are several basic methods for detecting cytomegalovirus.

*Polymerase chain reaction (PCR)*

Polymerase chain reaction is a widely available, fast and sensitive method for diagnosing CMV infection. The method detects and quantifies cytomegalovirus nucleic acids [19].

DNA can be extracted from whole blood, white blood cells, plasma or any other tissue (tissue samples) or fluid (urine, cerebrospinal fluid, bronchoalveolar lavage fluid, etc.). PCR analysis for CMV can be qualitative, when the presence or absence of CMV is confirmed in the test sample, or quantitative, in which the amount of viral DNA in the corresponding sample is measured [20-21].

The advantages of PCR are the ability to simultaneously process a large number of samples in a short period of time, the determination of viral load with high sensitivity, and the test feasibility despite cytopenia [19].

Based on the results of PCR diagnosis, a concept such as DNAemia is distinguished.

*DNAemia* is the detection of cytomegalovirus DNA in whole blood, plasma samples, serum, peripheral blood lymphocytes.

*Determination of CMV pp65 antigenemia*

The CMV pp65 antigen is a structural CMV protein that is detected in peripheral blood leukocytes during active CMV infection. To determine antigenemia, a monoclonal antibody specific for CMV pp65 antigen is used. Detection of pp 65 is made by the immunofluorescent staining. The result is reported as the number of pp65-positive cells per number of white blood cells counted.

In this way, *antigenemia* is the detection of cytomegalovirus pp65 antigen in peripheral blood leukocytes. Since the method detects a viral protein in leukocytes, it is not informative in patients with leukopenia. Quantitative PCR is preferred over antigen test for patients with leukopenia [19, 22, 23].

*Culture diagnostic methods*

The culture method consists of assessing the cytopathic effect of CMV on human fibroblasts [19]. In this approach, human biomaterial (blood and other biological fluids) is used, which is placed on a growth medium along with human fibroblast cells. Fibroblasts get infected with CMV, after that a direct cytopathic effect of CMV can be assessed over a period of 2 to 21 days (this cytopathic effect is directly related to the amount of virus in the sample). Worth to note the minus of this diagnostic method which requires 2-3 weeks of investigation, which is not applicable in patients in severe condition after allo-HSCT [19]. Also, the culture method has a lower specificity for the diagnosis of CMV infection compared to quantitative PCR and detection of the CMV pp 65 antigen [19].

Based on the results of culture diagnostic methods, the conclusion may sound like *viremia* that is the detection of CMV by culture methods.

*Immunohistochemical diagnostic methods*

Using histological and immunohistochemical methods, CMV antigens can be detected, as well as cytopathic changes in tissue samples characteristic of CMV infection. The test is performed directly on tissue samples, which is very specific for the diagnosis of CMV disease. [19, 24]. The limiting factor of the study is the invasive nature of the procedure for obtaining the material; however, at present, this is crucial for establishing the diagnosis of CMV disease.

Immunohistochemical examination is performed mainly on tissue samples and/or biological fluids; as a rule, frozen sections of biopsy tissue samples and/or centrifugation of cells on a glass slide are used, then mono- or polyclonal antibodies specified to CMV antigens are applied and then visualized using standard techniques (immunoenzyme and immunofluorescence assays). This method is more sensitive and more highly specific than histological examination, but is very laborious and requires experienced staff [25].

**CMV infection in clinical practice**

The basic definitions for CMV infection were developed by "The CMV Drug Development Forum" for their use in recipients of transplanted solid organs and hematopoietic stem cells [26].

A recipient of allogeneic HSCs, donor, or both the donor and the recipient can be infected with cytomegalovirus. There are several conditions associated with CMV, namely, primary CMV infection, reinfection, CMV reactivation, and recurrent CMV infection [27].

*Primary CMV infection* is a newly diagnosed CMV infection in a patient in whom the presence of CMV was not proven by either molecular or serological diagnostic methods before allo-HSCT.

*Reinfection with CMV* is a variant of CMV infection when a new strain of cytomegalovirus different from the originally present is found in the recipient. Sequencing methods are used for confirmation. Without this confirmation, the establishment of reinfection is impossible.

*CMV reactivation* is a variant of CMV infection, which is characterized by the detection of viral strains (previously detected and current) that are indistinguishable when sequencing regions of the viral genome [18]. The risk of reactivation is higher in conditions of immunosuppression , and is also associated with a high risk of developing CMV disease with the involvement of target organs, graft failure, leukopenia, post-transplant lymphoproliferative diseases, and high mortality [28, 29].

Without performing viral genome sequencing we cannot talk about the fact of CMV reactivation.

Taking into account the importance of correct terminology and, consequently, choosing adequate tactics for managing and treating the condition developed alongside CMV infection, we based on the analysis of literary sources [26, 27] and formulated the scheme to define the concepts of reactivation, reinfection, and an episode of CMV infection, which are shown in the figure.

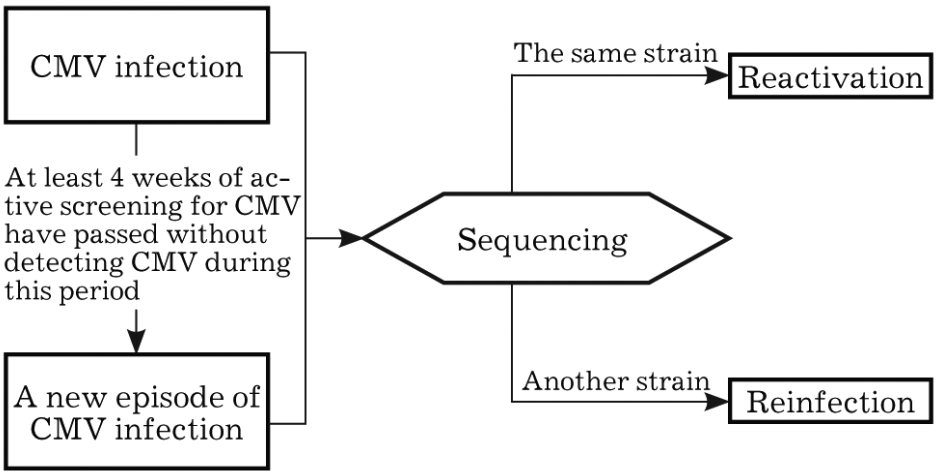


**Fig. 1. Differentiating the cytomegalovirus infection types [26, 27]**

*Recurrent CMV infection* refers to the detection of a new CMV infection in a patient with a previously diagnosed and treated CMV infection after at least 4 weeks of active observation after the moment of cure. Recurrent CMV infection may result from reactivation of a latent virus (reactivation) or being repeatedly infected (reinfection) [18].

The current understanding of CMV infection emphasizes that reinfection occurs quite often. But the "clinical" use of the terms "reinfection" and "reactivation" in routine practice is actually impossible, since sequencing of CMV DNA samples is performed very rarely [30].

Based on this, in clinical practice, the use of the terms "reactivation" and "reinfection" is not possible, except in cases where sequencing of archival and current samples is performed and similarity or difference with previous strains can be proved.

**CMV disease**

CMV disease develops in 10–40% of patients undergoing allo-HSCT [31-33].

Over the past few decades, significant advances have been made in the diagnosis and treatment of CMV infection and CMV disease. In the

course of clinical studies, the need for widespread use of a unified terminology to define conditions and complications associated with CMV has become apparent.

As the first attempt to develop unified approaches to the diagnosis and treatment of CMV infection, the main provisions and definitions were published in the materials of the 4th International Conference on CMV in France in 1993 [34]. These definitions were updated later at the 5th International Conference on CMV in Stockholm in 1995 [34] and were used until 2002, when P. Ljungman and colleagues have published updated and expanded definitions of CMV infection for use in transplant patients and other immunocompromised patients [34]. These definitions are widely used by clinicians in different countries and have no alternatives.

CMV disease includes two clinical forms: CMV disease per se with involvement of target organs and CMV syndrome.

*CMV syndrome* is a condition that is diagnosed only in solid organ transplant recipients [35]. It includes the signs of CMV infection, fever over 38°C for at least 2 days, increasing general weakness, leukopenia, neutropenia, thrombocytopenia, and elevations in hepatic aminotransferases greater than two normal values (not applicable to liver transplant recipients). In CMV syndrome, detection of CMV in tissues is not mandatory, but it is still required to confirm CMV infection [18, 36]. The concept of CMV-syndrome cannot be applied to recipients of allogeneic HSCs, as there might be other causes that could lead to similar clinical and laboratory manifestations as those at CMV syndrome, even despite the fact that in some cases, the use of antiviral drugs in the patients after allo-HSCT helps reach clinical improvements (body temperature decrease, cytopenia resolution, etc.). Thus, if CMV DNA is detected in blood and clinical manifestations typical of CMV syndrome

are present in recipients of allogeneic HSCs, we can speak only of CMV infection, rather than of CMV syndrome.

Signs and symptoms of CMV disease with the involvement of target organs can be difficult to recognize. To confirm CMV disease with target organ involvement, the presence of clinical symptoms consistent with target organ damage, as well as the CMV detection in a target organ biopsy, is required.

When establishing the diagnosis of CMV disease with target organ damage, additional definitions to the diagnosis used, namely the concepts of proven (confirmed), probable and possible CMV disease. It should be noted that this classification is not applicable to absolutely all organs.

The concept of "proven CMV disease with involvement of target organs" is applicable only for the diagnosis of CMV pneumonia, CMV disease with involvement of the gastrointestinal tract. Variants of proven and probable CMV disease are used both for previous conditions and for the diagnosis of CMV encephalitis. For the above described variants of CMV disease, as well as that with the involvement of other target organs, the diagnosis reads "probable CMV infection".

The most common variants of CMV disease involving target organs are listed in Table 1. Other forms of CMV disease are not listed in the table, given the rarity of developing CMV disease involving other organs. The approach to diagnosing CMV disease of another target organ is similar to the diagnostic algorithm proposed in the Table.

## Table 1. Criteria for the diagnosis of cytomegalovirus disease

| CMV disease of the target organ | Documented (confirmed) | Probable | Possible |
|---|---|---|---|
| **CMV pneumonia** | - Clinical presentation of pneumonia<br>- Detection of CMV DNA **in tissue (biopsy)** | - Clinical presentation of pneumonia<br>- Detection of CMV DNA **in BAL fluid** | - Detection of CMV DNA **in tissue (biopsy) or BAL fluid** |
| **CMV with gastrointestinal involvement** | - Clinical symptoms of the upper and / or lower gastrointestinal tract involvement<br>- Detection of CMV DNA **in tissue (biopsy)**<br>- Histological abnormalities characteristic of CMV, regardless of the GVHD presence or absence (giant infected cells with a modified nucleus, have a typical "owl's eye" appearance) | - Clinical symptoms of the upper and / or lower gastrointestinal tract involvement<br>- Detection of CMV DNA **in tissue (biopsy)** | - Detection of CMV DNA **in tissue (biopsy)** |
| **CMV hepatitis** | - Clinical presentation of hepatitis and laboratory abnormalities (increase in ALT, AST, total bilirubin)<br>- Detection of CMV DNA **in tissue (biopsy)**<br>- Exclusion of other causes of hepatitis | - | - |
| **CMV retinitis** | - Ophthalmological pattern, typical for CMV<br>- Detection of CMV DNA **in vitreous fluid** | - | - |
| **CMV encephalitis, -ventriculitis** | - Clinical presentation of CNS involvement<br>- Detection of CMV DNA **in tissue (biopsy)** | - Clinical presentation of CNS involvement<br>- Detection of **CMV DNA in CSF** (excluding contamination with blood)<br>- EEG results | - |
| **CMV nephritis** | - Clinical presentation of nephritis<br>- Detection of CMV DNA **in tissue (biopsy)**<br>- Histological abnormalities characteristic of CMV (giant infected cells with a modified nucleus, have a typical "owl's eye" appearance) | - | - |
| **CMV cystitis** | - Clinical presentation of cystitis<br>- Detection of CMV DNA **in tissue (biopsy)** | - | - |

| | | | |
|---|---|---|---|
| | - Histological abnormalities characteristic of CMV (giant infected cells with a modified nucleus, have a typical "owl's eye" appearance) | | |
| **CMV myocarditis** | - Clinical presentation of myocarditis<br>- Detection of CMV DNA **in tissue (biopsy)**<br>- Histological abnormalities characteristic of CMV (giant infected cells with a modified nucleus, have a typical "owl's eye" appearance) | - | - |
| **CMV syndrome** | - | - Detection of CMV in blood and the presence of at least two symptoms:<br>1. Fever > 38°C for at least 2 days<br>2. New or increased malaise (Severity Grade 2) or new or increased fatigue (Severity Grade 3)<br>3. Leukopenia, neutropenia by two measurements at least 24 hours apart<br>4. >5% atypical lymphocytes<br>5. Thrombocytopenia<br>6. Increase in hepatic aminotransferases by more than two norms (not applicable to liver transplant recipients) | - |

CMV DNA, cytomegalovirus deoxyribonucleic acid; BAL, bronchoalveolar lavage; GIT, gastrointestinal tract; GVHD, graft-versus-host disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system, EEG, electroencephalography; CSF, cerebrospinal fluid

The issue of detection of CMV DNA in the bone marrow deserves special attention. Following the diagnostic criteria proposed by P. Ljungman et al, CMV disease of the target organ may be verified if there organ damage, which is manifested by the corresponding clinical symptoms, and if CMV DNA has been detected by a molecular method in

the biopsy sample and/or CMV histologically confirmed [18]. According to the accepted classifications and definitions, the bone marrow is a tissue [37], and therefore the concept of CMV disease involving the bone marrow is not applied in clinical practice. Thus, in case of the development of cytopenias and the detection of CMV at histological examination, one can speak only of CMV infection, rather than of CMV disease.

**The concepts of prophylaxis, preemptive therapy, and targeted therapy of CMV infection and CMV disease**

Currently, there are no unified guidelines for strategies for monitoring and preventing CMV infection and CMV disease. In particular, there are no standard thresholds for initiation of therapy in assessing DNAemia while monitoring CMV infection.

There are several approaches to the control of CMV infection: prophylaxis, preemptive therapy and targeted therapy.

*Prophylaxis of CMV infection*

Prophylaxis of CMV infection is the implementation of measures aimed at preventing CMV infection in seropositive recipients, as well as preventing the development of primary CMV infection, CMV reactivation or recurrent CMV infection.

The prophylaxis strategy means the administration of antiviral drugs to all recipients of allogeneic HSCs for a long period as a universal prophylaxis of viral infections. The main goal of this approach is to prevent the development of CMV infection and CMV disease.

In addition to antiviral drugs for the CMV infection prophylaxis, blood components from CMV-seronegative donors or leukocyte-reduced

blood components should be used as replacement blood transfusion therapy [38-40].

*Preemptive therapy*

Preventive therapy is a strategy in which antiviral drugs are given for asymptomatic CMV infection detected by a screening test [41]. At present, preemptive therapy based on blood CMV DNA monitoring by PCR is the basis for improving post-transplant parameters, but the use of this strategy remains at the discretion of the transplant center and depends on its resources [42].

Preemptive therapy includes regular PCR testing of blood samples and the administration of antiviral drugs when CMV DNA is detected, which prevents the development of CMV disease [38].

In some studies, preemptive therapy was started when PCR detected CMV DNA less than 1500 IU/mL (=1000 copies/mL) [43]. In another prospective study, a threshold of 3.983 IU/mL and above was considered an indication for initiating a preemptive therapy in solid organ recipients [44]. But the threshold for the therapy initiation varies from center to center, depending on the method of detecting CMV infection and assessing patient's risk factors.

The duration of preventive therapy should be at least 2 weeks, and it is considered effective if there is at least one negative PCR test [38, 41].

An increase in viral load during the first 2 weeks of therapy does not require a change in therapy. If cytomegalovirus is detected after 2 weeks of preventive therapy by PCR, a longer antiviral therapy should be considered [38].

In case of repeated CMV DNA isolation by PCR, the preemptive therapy can be provided with the same drug. It should also be noted that

the therapy efficacy can be enhanced by reducing the dose of immunosuppressive drugs [38].

Preemptive therapy has been shown to be effective in preventing the development of CMV disease and has the advantage of limiting the toxicity and costs early after allo-HSCT [42, 45]. Preemptive therapy can be used as a standalone strategy or in combination with antiviral prophylaxis [38].

*Targeted therapy for CMV infection*

Targeted (etiotropic) therapy for CMV infection is the administration of antiviral drugs for the treatment of the CMV infection associated with clinical symptoms. The duration of therapy varies and depends on the prescribed drug, dose, and response to antiviral therapy [38].

The duration of treatment is determined individually, based on clinical symptoms and the type of CMV infection, but as a rule, targeted treatment is carried out for at least 2 weeks [38].

**Criteria for assessing the response to antiviral therapy**

When assessing the inefficacy of ongoing antiviral therapy, the following concepts are used: refractory and resistant CMV infection.

Refractory and resistant CMV infection in HSC recipients remains a difficult problem due to the limited number of available antiviral drugs in the Russian Federation and the serious toxic effects associated with them [46, 47]. Considering the response to antiviral therapy and the clinical course of the disease, the CMV Resistance Working Group defined the concepts of recurrent and refractory CMV infection [18, 26].

*Refractory CMV infection* is a variant of CMV infection in which the amount of DNA in the blood increases (at least 10 times) after at least

two weeks of adequate (at recommended doses) antiviral therapy. It is important to note that in the first two weeks from the start of antiviral therapy, an increase in viral load is not considered as refractoriness, since active cytomegalovirus replication continues during this period. That is, monitoring in the first 14 days after the start of therapy does not provide additional information about refractoriness or the presence/absence of response to therapy. In addition, if the doses of antiviral drugs are not appropriate (subtherapeutic doses) then an increase in viral load in this case cannot be regarded as refractoriness.

*Probable refractory CMV* infection is the persistence of a CMV viral load lasting for at least two weeks after the start of adequate antiviral therapy at recommended doses. However, CMV DNA persistence of less than 1000 IU/mL should not be considered a refractory CMV infection.

*Resistant CMV infection* is a decreased susceptibility to one or more antiviral drugs due to a genetic mutation of the virus. As a rule, viral mutations affect genes involved in the anabolism of antiviral drugs, for example, mutations in the genes UL54, UL97, UL56/89/51, etc. [46] . Viral mutations are detected only by viral genome sequencing methods [26]. Dose-increase of antivirals may be an option for the treatment of resistant CMV infection. In addition, it is important to reduce the doses of immunosuppressive therapy also given to the patient. In world practice, alternative antiviral drugs that are not currently registered in the Russian Federation, for example, maribavir, are used as guidelines for the treatment of resistant CMV infection [38, 48].

Despite strategies for prophylaxis, preemptive therapy, and targeted therapy for CMV infection, the antiviral drug resistance remains a serious problem in allogeneic HSC recipients. According to various data, resistance to antiviral drugs develops in 1-40% of patients after allo-

HSCT and usually leads to the prolongation of antiviral drug administration. [38, 49].

Antiviral drug resistance may be suspected when antigenemia or the number CMV copies increases on laboratory tests, a clinical deterioration of the target organ CMV disease occurs, and in situation of no response to ongoing treatment after 2 weeks of therapy [38].

Thus, the difference between the definitions of "refractory CMV infection" and "resistant CMV infection" is that refractoriness is a clinical definition based on the criteria for response to antiviral therapy, while resistant CMV infection is a concept based on a laboratory determination of drug-resistant genotype or mutations that are responsible for resistance to antiviral drugs.

Due to the increase in the number of allo-HSCTs performed and, consequently, the complications associated with them, we reviewed publications about management of patients with CMV infection [18, 26, 27]. Based on these works, we propose a scheme that illustrates step by step the algorithm and strategy for diagnosing CMV infection and CMV disease in patients after allo-HSCT, as well as the variants of an effective and ineffective antiviral therapy. The scheme is shown in Fig. 2.

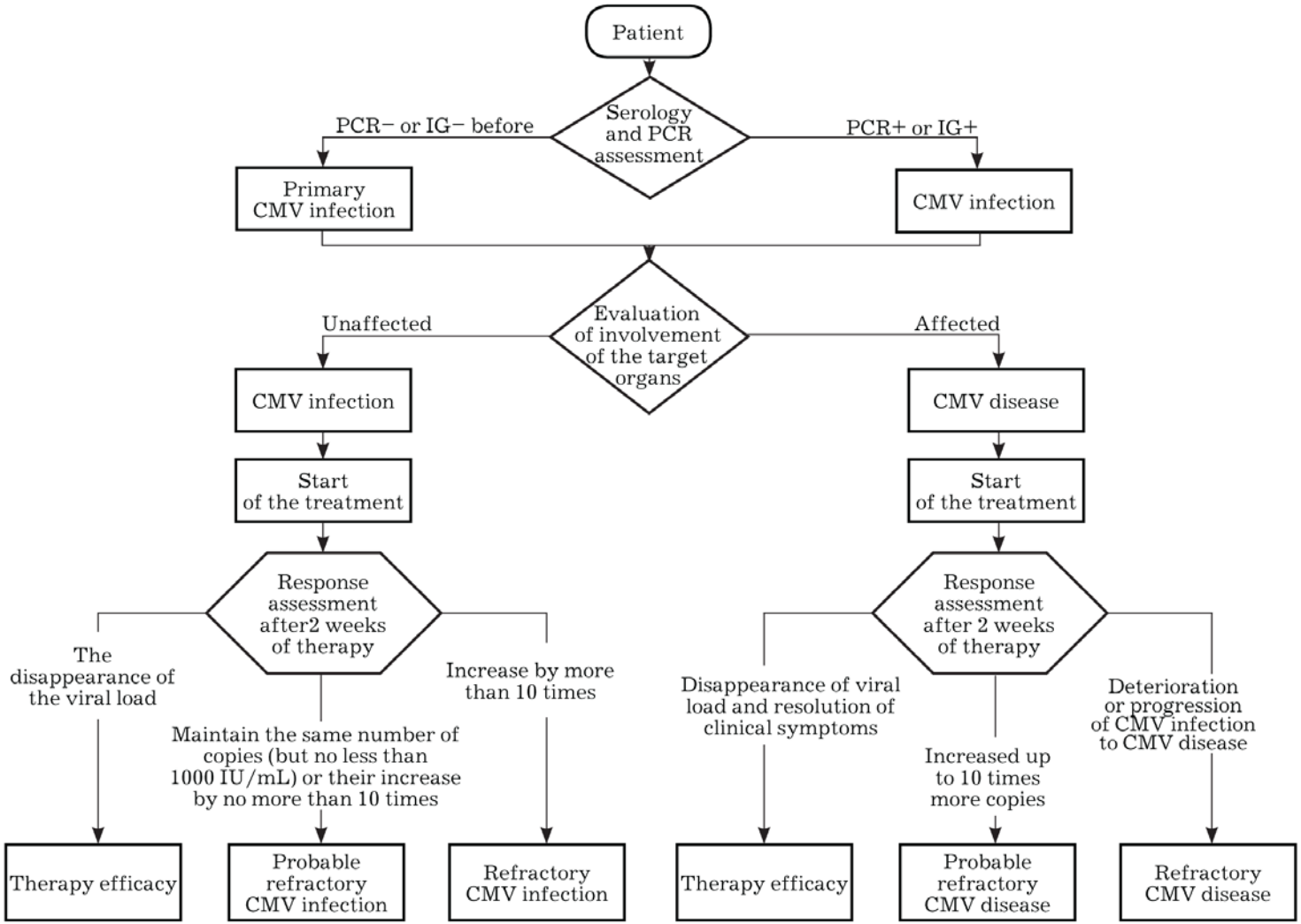


**Fig. 2. Algorithm for the diagnosis and management of cytomegalovirus infection and cytomegalovirus disease [18, 26, 27]**

**Criteria for evaluating the response to antiviral therapy in establishing the diagnosis of CMV disease**

As part of the CMV disease treatment, the options of response to therapy are also distinguished.

Thus, *refractory CMV disease* is the worsening of clinical symptoms consistent with target organ damage after two weeks of antiviral therapy at recommended doses. When determining the refractoriness of CMV disease, it is necessary to exclude other causes that could have led to organ damage (for example, another infectious agent, graft-versus-host disease, etc.).

*Probable refractory CMV disease* is an “insufficient” improvement in the clinical symptoms of target organ damage at least two weeks after the start of antiviral therapy at recommended doses.

**Cytomegalovirus infection and graft-versus-host disease**

CMV infection has long been shown to play a role in increasing the risk of developing GVHD [14, 15]. According to A. Grefte et al. CMV-infected endothelial cells begin to produce pro- inflammatory cytokines, such as interleukin-6, which is crucial in the initial phase of GVHD development, which leads to an increased incidence of this alloimmune complication [50].

In addition, immunosuppressive therapy used to treat GVHD has also been shown to increase the risk of CMV infection [51]. In acute grade II-IV GVHD accompanied by systemic glucocorticosteroid therapy, the risk of developing CMV infection is 61%. This is significantly higher than that in acute grade I GVHD without systemic therapy with glucocorticosteroids, being 35% [51]. In other studies, such as that by P.Teira et al. who found that early detection of CMV replication after

allo-HSCT was not associated with the likelihood of developing chronic GVHD [2].

**Cytomegalovirus infection and relapse**

For the first time B. Lounnqvist in 1986 described the potential impact of CMV infection on reducing the likelihood of leukemia recurrence in patients after allo-HSCT [52]. Later on, other studies were published. So, in the study of N. Cantoni et al., CMV seropositivity of the donor and recipient were associated with a lower likelihood of recurrence in children with acute leukemia after allo-HSCT [53]. In the study by A. Elmaagacli et al., that included the patients with acute myeloid leukemia (AML), the relapse rates in patients with and without CMV infection were 9% and 42%, respectively [54]. In a publication by M. Green et al. on the study that included a large cohort of patients, it was shown that the CMV infection development in the first 100 days after allo-HSCT was associated with a moderate reduction in the risk of early relapse in patients with AML [55]. According to P. Teira et al., CMV seropositivity of the donor and recipient was also associated with a lower rate of AML recurrence [2]. In the publication by S. Ito et al. showed that CMV infection occurring up to day 100 after allo-HSCT was an independent factor associated with a decreased likelihood of recurrence in patients with chronic myeloid leukemia (CML) [56]. For patients with acute lymphoblastic leukemia, myelodysplastic syndrome and lymphoproliferative diseases, no such association was found [16, 57].

The observed antileukemic effect may be mediated by cytomegalovirus-induced expansion of donor NKG2C+ NK cells and γδT cells, as well as CD8+ cells co-expressing CD56+ and CD57+. NKG2C+ NK cells, NKG2C+ T cells, KIR-expressing NK cells, and γδT cells activate cytotoxic T cells and NK cells, which are more likely to attack

CMV-infected tumor cells, thus enhancing GVT response, which, in turn, leads to a decreased likelihood of recurrence [58].

Other mechanisms have also been described when, during CMV infection, the expansion of the mature NK cells CD56dimNKG2C+ CD57+ can occur, which increase the production of interferon gamma and mediate GVT response [59], as well as the mechanisms of cross-reaction of γδT cells recognizing CMV peptides and reacting against tumor cells [60].

Thus, the response of the immune system to CMV infection may reduce the likelihood of relapse in patients with acute myeloid leukemia, chronic myeloid leukemia [61]; however, it is worth taking into account the fact that in patients with CMV infection after allo-HSCT, the mortality not related to relapse remains high [49] and according to C. Solano et al. makes 23% within 1 year after allo-HSCT [62]. Also, despite a sufficient number of publications on the relationship between CMV infection and relapse, a number of authors have suggested that CMV-specific T-cell immunity per se does not affect the risk of relapse occurrence, and it is more likely that the rate and adequacy of the immune system reconstitution after allo-HSCT generally play a key role [63, 64].

**Cytomegalovirus infection and graft failure**

Graft failure is a serious complication after allogeneic hematopoietic stem cell transplantation, and is defined as the absence of initial acceptance of donor cells (primary graft failure) or loss of donor hematopoiesis after initial graft acceptance (secondary graft failure) [65]. Risk factors for graft failure include HLA incompatibility, AB0, the use of low-intensity conditioning modes, the diagnosis of the disease (aplastic anemia, hemoglobinopathies, MDS, myelofibrosis), the use of bone

marrow as a source of HSC, dose of CD34+ cells, the use of T-cell depletion [66, 67].

The role of CMV in the development of graft failure continues to be debated. Evidence-based studies supporting the impact of CMV infection on the graft failure in allogeneic HSC recipients are scarce. S-Y. Cho et al. noted that CMV infection might be associated with the development of cytopenia and, consequently, the development of a graft failure, but no direct relationship was established in their study [11].

In the study by C. Solano et al. in a large number of patients, no relationship was shown between early replication and such a complication as a graft failure [68]. In more detail, the issue of "failure" was studied in recipients of solid organs. Donor CMV infection led to rejection in the recipients of liver [69-71], kidneys [72-74]. Also, in patients after kidney transplantation, the mechanism of graft rejection has been described, when infection of vascular endothelial cells with cytomegalovirus leads to vasculopathy and rejection [72]. Based on the described mechanisms for the development of graft failure in solid organ recipients, it can be assumed that failure in allogeneic HSC recipients occurred with a similar development mechanism, i.e. CMV infection of the donor's hematopoietic cells and the immune response associated with this can potentially cause the graft failure in patients after allo-HSCT, but no confirmation of these assumptions has been described in the literature yet.

## Conclusion

Despite the introduction of strategies for prophylactic, preventive, targeted therapy, cytomegalovirus infection is still associated with high mortality and frequent detectability, especially at early stages after transplantation of allogeneic hematopoietic stem cells.

The schemes we have proposed to determine the variant of cytomegalovirus infection and diagnostic strategies, as well as the further development of clear algorithms for the diagnosis and treatment of cytomegalovirus infection and cytomegalovirus disease in transplant centers, will probably help improving transplantation outcomes.

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