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COMMENT

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Management of cytomegalovirus infections – Swedish recommendations 2023

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ABSTRACT

Cytomegalovirus (CMV) infection, which mostly causes a subclinical infection early in life, has important clinical consequences in certain patient groups. CMV is the most common congenital infection and can cause permanent disabilities such as hearing loss and motor- and cognitive deficits in affected infants. In allogeneic haematopoietic stem cell and solid organ transplant recipients, CMV still is an important infectious complication with a risk for life-threatening disease. The previous Swedish recommendations for the management of CMV infections were updated by an expert group under the guidance of The Swedish Reference Group for Antiviral Treatment (RAV) and published at the website of RAV in August 2023 (https://www.sls.se/rav/rekommendationer/cytomegalovirus/). We here provide a translation of the updated recommendations, with minor modifications regarding diagnosis of CMV pneumonia. In the present recommendations, we discuss aspects of old and new CMV antivirals, including dosing for different age groups, and cover the management of congenital infections and CMV in immunocompromised patients. The recommendations are evidence-graded in accordance with the Oxford Centre for Evidence-Based Medicine.

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Background

Cytomegalovirus (CMV) infection is predominantly acquired during childhood. In countries with a high standard of hygiene, primary infection commonly occurs in adults. The majority of CMV infections are subclinical or give rise to a non-specific febrile illness. Following primary infection, CMV establishes a lifelong persistence/latency. Reactivated CMV infections, and probably also re-infections, are common and usually asymptomatic in immunocompetent individuals. In immunosuppressed patients and children infected by the mother during pregnancy, CMV is of significant medical importance, as a disease of varying severity can result from both primary and reactivated infections [1].

Aetiology and epidemiology

CMV belongs to the family of Herpesviridae, which are enveloped DNA viruses that establish lifelong persistence/latency after primary infection. Although CMV can infect many different types of cells, macrophages and monocytes constitute the main reservoir for CMV [2]. The prevalence of CMV antibodies in the population varies between 50–95% depending on country, social class, and age group. In Sweden, 30–40% of children have antibodies against CMV at the age of one year, with 70% CMV seropositivity in women of childbearing age and 80% among individuals $>$ 50 years [3].

CMV can be transmitted through various body fluids such as urine, saliva, semen, cervical secretions, and breast milk. Another important route of transmission is through organ or allogenic haematopoietic stem cell transplantation (HCT) [1]. Previously, blood transfusion was also a source of infection, but since currently only leucocyte-reduced blood is used in Sweden, the risk of transmission of CMV *via* blood transfusion is minimal. Transmission from mother to child can occur during pregnancy, labour, and breastfeeding. In congenitally and postnatally CMV-infected children, viral shedding may continue for several years [4]. However, the risk of transmission to the environment is low if proper hand hygiene is maintained. After puberty, transmission is likely to occur mainly through exposure from young children or through sexual contact.

Congenital and postnatal CMV

Congenital CMV infection

Among the congenital infections, CMV infection is the most common. The incidence is reported to vary between 0.2–2% worldwide and increases with increasing seroprevalence in women of childbearing age. The incidence in Sweden is 0.2–0.5% [5,6].

Only a small proportion (10–15%) of infants born with congenital CMV-infection are symptomatic at birth. The clinical presentation is like that of other congenital infections. It may include symptoms and signs from many organs, such as the central nervous system (CNS) (microcephaly, seizures), liver (jaundice, hepatomegaly), spleen (splenomegaly) and bone marrow (anaemia, neutropenia, thrombocytopenia). Congenital CMV can also cause growth retardation. The clinical presentation varies from subclinical or mild to severe septic disease. The mortality rate has been reported to be 5–10% in children with symptoms in the neonatal period [7].

In approximately 10–15% of children with congenital CMV infection, permanent disabilities are seen, such as hearing loss, balance disorders, visual impairment, cerebral palsy, intellectual disability, autism, and epilepsy. Congenital CMV infection is the leading cause of non-genetic congenital sensorineural hearing loss [7].

CMV infection acquired in the postnatal period

Postnatal CMV infection rarely leads to symptomatic disease in moderately preterm and full-term infants. However, in infants with *severe combined immunodeficiency (*SCID), CMV can cause severe disease. Infants diagnosed with SCID should be protected from CMV infection by interrupting breastfeeding. They should also be investigated for the occurrence of congenital CMV infection.

Symptomatic infection can also occur in infants with low birth weight (less than 1500 g) and gestational age below 32 weeks. The clinical manifestations include hepatitis, pneumonitis, colitis, thrombocytopenia, and neutropenia. In rare cases, CMV can cause a severe sepsis-like disease [8,9], but death due to CMV is very uncommon.

CMV in immunocompetent individuals

Primary CMV infection in immune-competent patients usually has a subclinical course and rarely presents any significant symptoms. Long-term fever (usually one to five weeks, but in rare cases longer) is the predominant symptom in symptomatic CMV infection. Laboratory testing often reveals liver involvement and lymphocytosis with atypical lymphocytes. The total white blood cell count can range from leucopoenia (especially early in

the disease) to moderate leukocytosis. Occasionally, thrombocytopenia and anaemia occur. Unusual complications include enterocolitis, meningoencephalitis, myocarditis, interstitial pneumonia, and Guillain-Barré syndrome [1]. Severe CMV disease in immunocompetent individuals is uncommon and such cases should be investigated for possible underlying immunodeficiency.

CMV in transplant and other immunosuppressed patients

The risk of CMV disease in severely immunocompromised patients is mostly linked to suppressed T-cell function. Patients with mild to moderate immunosuppressed conditions rarely develop CMV disease, although it occasionally can occur, especially if the CMV infection is primary. The clinical manifestations of CMV are similar regardless of the underlying cause of the immunodeficiency. However, the risk of different types of organ involvement may vary between different patient groups. A distinction is made between CMV infection (presence of viral replication) and CMV disease (CMV infection with clinical manifestations), see Fact Box 1. For abbreviations of CMV serological status, see Fact Box 2. A summary of the clinical manifestations is presented in Table 1.

Fact Box 1. Definition of CMV infection and CMV disease. [10]

- CMV infection: evidence of CMV replication in blood, other body fluids, or tissues, regardless of symptoms.
- CMV disease: CMV infection with clinical manifestations.
  May present as CMV syndrome (fever, leucopoenia and/or thrombocytopenia), or organinvasive disease

Fact Box 2. Abbreviations for CMV serological status of recipient and donor.

R- = CMV-seronegative recipient
R+ = CMV seropositive recipient
D- = CMV-seronegative donor
D+ = CMV seropositive donor

CMV after allogeneic and autologous stem cells transplantation and in patients with hematological malignancy

Patients undergoing HCT are at high risk of developing CMV infection requiring treatment unless prophylaxis is administered. The most important risk factor is the patient's serological status. Patients who are seropositive for CMV-antibodies have higher transplant-related mortality and poorer survival than those who are seronegative [11,12]. Other risk factors for CMV reactivation after HCT are CMV infection shortly before the transplant, the use of anti-T-cell antibodies for T-cell depletion, T-cell depletion *in vitro*, graft-versus-host disease (GVHD), and HLA mismatch between donor and recipient [13]. The most common localisation of CMV disease in this patient group is the gastrointestinal tract, especially in cases of concurrent acute GVHD [13]. CMV pneumonitis is now less common but has still a high mortality rate [14]. Other forms of CMV disease, such as retinitis or encephalitis, are rare.

Patients undergoing autologous HCT for hematological malignancy have a low risk of CMV reactivation and CMV disease [15]. The most common signs of CMV reactivation are fever and gastrointestinal symptoms, while other organ manifestations are rare. Several recently introduced drugs for the treatment of hematological malignancy, such as idelalisib, CAR-T cells, bispecific antibodies, and dasatinib, have been associated with symptomatic CMV infection, although end-organ disease seems to be rare.

CMV in solid organ transplant recipients

CMV is one of the most common opportunistic infections in solid organ transplant (SOT) recipients. The risk of CMV disease is highest in CMV-seronegative recipients (R-) who receive organs from CMV-seropositive donors (D+; primary CMV infection in the recipient). Seropositive recipients (R+) are at moderate risk of reactivating CMV and acquiring CMV disease. The risk of developing CMV disease also depends on the type of SOT, with the highest risk observed in lung and intestinal transplant recipients. High levels of immunosuppression, such as treatment with anti-thymocyte globulin (ATG) or high doses of corticosteroids also increase the risk of CMV disease [16].

Symptoms of CMV infection range from what is termed 'CMV-syndrome', characterised by low-grade fever, malaise, muscle and joint pain, leucopoenia, thrombocytopenia, and transaminase elevation, to severe end-organ disease such as pneumonitis, gastrointestinal ulcerations, hepatitis, nephritis, encephalitis, myocarditis, and retinitis. The most common organ manifestation is gastroenteritis. Lung involvement is also common in lung transplant recipients.

Table 1. Clinical manifestations and diagnosis of CMV in immunocompromised patients.

Organ/manifestation	Clinical manifestations	Diagnostic techniques	Comment
CMV syndrome	Fever, malaise, leucopoenia, thrombocytopenia, elevated transaminase levels.	CMV-DNA in blood	Common manifestation in solid organ transplant at recipients.
Gastritis/esophagitis	Vomiting, abdominal-retrosternal pain	Gastroscopy: immunohistopathology[1]	Less common. Can occur together with GVHD in HCT patients
Enterocolitis	Diarrhea, abdominal pain	Colonoscopy: Pathol. with immunohistochemistry[1]	Most frequent organ manifestation. Often coexisting with intestinal GVHD in HCT patients.
Hepatitis	Signs of liver inflammation	Liver biopsy: Pathol. with immunohistochemistry[1,2]	Less common. Important to exclude other viruses. Differential diagnosis can be drug toxicity, rejection or GVHD, respectively[2]
Pneumonia	Cough, fever, respiratory failure.	Solitary to widespread lung infiltrates. CMV-DNA quantification in BAL[3]	Uncommon. High negative predictive value if negative CMV-DNA in BAL. Important to exclude other agents.
Nephritis	Elevated creatinine levels	Kidney biopsy: Pathol. with immunohistochemistry[1]	Rare
Myocarditis	Heart failure, chest pain	Biopsy with immuno histochemistry[1]	Rare
Retinitis	Visual impairment	Eye examination, CMV-DNA in vitreous liquid.	Rare
Encephalitis	Headache, fever, photophobia, confusion seizures	CMV-DNA in cerebrospinal fluid.	Rare

GVHD, graft-versus-host disease; HCT, allogeneic haematopoietic stem cell transplantation.
[1]Detection of CMV-DNA on biopsies is not recommended since it is difficult to interpret.
[2]An important differential diagnosis is rejection in liver transplant patients and GVHD in HCT patients.
[3]There are some data on diagnostic levels in HCT patients [22]. For lung transplant patients, data have been mixed and less conclusive [23,24].

CMV in HIV-infected individuals

In the past, retinitis was the most common manifestation of CMV in patients with acquired immune deficiency syndrome (AIDS). Since the introduction of modern antiretroviral therapy, the incidence of CMV retinitis has dropped considerably, as retinitis almost exclusively occurs in patients with CD4 T-cell counts below 50×10^6/L [17].

Other manifestations of CMV in HIV-infected individuals are less common. CMV viremia may cause prolonged fever, and gastrointestinal CMV infection can cause esophagitis and colitis. Involvement of the central nervous system can manifest as encephalitis, polyradiculitis and polyneuropathy. Adrenalitis is also a possible manifestation of CMV infection [18].

CMV in inflammatory bowel disease (IBD)

Subclinical CMV reactivation is common in patients with IBD treated with immunosuppressive drugs. However, in most cases, the reactivation is transient even if the immunosuppressive treatment is continued. Therefore, screening for CMV is not recommended. In recent years, an increasing number of publications have highlighted a possible link between primary CMV infection and exacerbation of intestinal symptoms in patients with IBD [19–21].

Diagnostic methods for CMV

In immunocompetent individuals, the diagnosis is based on the detection of CMV IgM antibodies or a significant increase of IgG antibodies between acute and convalescent sera. For the diagnosis of congenital CMV in newborn infants, the use of PCR analysis in urine is a highly reliable method. If an infant tests positive for CMV before 14 days of age, the diagnosis is confirmed, while congenital CMV infection is excluded if no CMV is detected before 14 days of age (see Supplemental Document S1 for details about diagnosis of congenital CMV infection).

In immunocompromised patients, the diagnosis of CMV infection is usually based on the detection of CMV-DNA in blood since the development of an antibody response frequently is absent or delayed. The diagnosis of CMV disease is established with a combination of symptoms, clinical signs and detection of CMV in blood (CMV syndrome) and/or detection of CMV with immunohistochemistry (or histopathology) from the organ involved. The detection of CMV-DNA in tissue samples is insufficient for diagnosing CMV end-organ disease. An exception is the detection of CMV-DNA in bronchoalveolar lavage (BAL) in HCT patients, for whom an increasing level of CMV-DNA in BAL could be associated with CMV pneumonitis [22]. The same may be the case for lung transplant patients [23]. Detection of CMV-DNA in cerebrospinal fluid (in the absence of blood in the sample) indicates CMV encephalitis. Retinitis can be diagnosed by fundus examination, and in unclear cases, analysis of CMV-DNA in the vitreous fluid verifies the diagnosis.

A brief summary of the diagnostic criteria for CMV disease in immunocompromised patients is presented in Table 1.

Antiviral drugs

The antiviral drugs ganciclovir, valganciclovir, cidofovir, foscarnet, and maribavir can be used for the treatment of CMV infections. Letermovir is the preferred prophylaxis against CMV after HCT in adults. High-dose aciclovir and its prodrug valaciclovir can be considered for prophylaxis in some cases but are less effective than the other CMV antivirals [25]. Suggested dosage of the different drugs is presented in Table 2.

Ganciclovir and valganciclovir are first-line options for treating CMV and for prophylaxis against CMV in solid organ transplant patients [16]. Ganciclovir and valganciclovir commonly cause bone marrow suppression, and especially HCT patients are at risk of pronounced neutropenia. Furthermore, ganciclovir can be nephrotoxic, and the dose must be adjusted according to renal function.

Foscarnet is an alternative in cases of ganciclovir-resistant CMV. Foscarnet can also be used instead of ganciclovir/valganciclovir for treating patients with profound and persistent bone marrow suppression. However, foscarnet has the disadvantage of significant nephrotoxicity, can cause electrolyte dysregulation, and can only be administered intravenously. The risk of renal toxicity can be reduced by dosing based on renal function and with concurrent hydration.

Maribavir was 2022 approved in the EU for the treatment of refractory CMV infection, including ganciclovir-resistant CMV in adults and has in the US also been approved for children from 12 years of age [26,27]. Maribavir is orally available and has a generally favorable safety profile. Maribavir may, therefore, be an important alternative for the treatment of refractory CMV infection. However, there are data indicating that maribavir has a low barrier of resistance, and this potential issue needs to be closely followed [28]. Notably, maribavir has low penetrance to the central nervous system and, therefore, should not be used in CMV retinitis or encephalitis cases. Maribavir interacts with several immunosuppressive drugs (including tacrolimus and cyclosporine), requiring close monitoring of the serum concentration and dose adjustment of these when used in conjunction.

Cidofovir is an option for treating CMV but is rarely used for this indication due to significant nephrotoxicity. However, it has a place in the co-treatment of adenovirus and CMV in HCT patients. Simultaneous hydration and treatment with probenecid are important to reduce the risk of renal toxicity.

Letermovir is approved for prophylaxis for CMV infection in high-risk HCT [29], and since 2023 for high-risk kidney transplant recipients [30], but not for treatment of CMV or for use in children.

Table 2. Dosage of different CMV drugs in adults and children (except preterm infants or congenital infection). Note possible dose adjustment in renal failure.

Drug	Prophylaxis in adults	Treatment of adults	Prophylaxis in children	Treatment of children
Ganciclovir	5 mg/kg q24h	5 mg/kg q12h[1]	5 mg/kg q24h	5 mg/kg q12h[1]
Valganciclovir	900 mg q24h[2]	900 mg q12h[1]	16 mg/kg q24h[3], max 900 mg q24h	16 mg/kg q12h[1,3], max 900 mg q12h
Foscarnet	–	Induction:[4] 60 mg/kg q8h or 90 mg/kg q12h, Maintenance: 90 mg/kg q24h	–	Induction:[4] 60 mg/kg q8h or 90 mg/kg q12h, Maintenance: 90 mg/kg q24h
Cidofovir[5]	–	Induction: 3–5 mg/kg once a week, Maintenance: 3–5 mg/kg every 14 days	–	Induction: 3–5 mg/kg once a week, Maintenance: 3–5 mg/kg every 14 days
Letermovir	480 mg q24h (in combination with ciclosporin 240 mg q24h)	–	–	–
Maribavir	–	400 mg q12h	–	Approved in the USA (but not EU) from 12 years (minimum 35 kg): 400 mg q12h
Valaciclovir	Option after kidney transplant, see below for dosage[6]	–	Option after kidney transplant, see below for dosage[7]	–

q24h, once daily; q12h, twice daily; q8h, three times daily; q6h, four times daily.
[1]Consider analysis of the ganciclovir-concentration, especially in renal failure, treatment failure or side effects.
[2]Half dose is used in some transplant centres for lower risk transplants (kidney, liver) [31,32] but may be associated with break-through infections and evolvement of ganciclovir resistance, especially in D+/R- transplants [33].
[3]Details on paediatric valganciclovir dosing can be found in the Supplementary Document, S2.
[4]For pre-emptive treatment of adults and children: Foscarnet 60 mg/kg q12h, Maintenance: 90 mg/kg q24h [34].
[5]Probenecid and extra hydration must always be given at the same time as cidofovir.
[6]Valaciclovir 2 g q6h is the most documented dose, but it may be difficult to tolerate this dose. Valaciclovir 1 g q8h gave comparable results in one study [35]. Less effective than ganciclovir [25].
[7]Valaciclovir is approved from the age of 12 in Sweden but can be considered from the age of 3 months in the dose of 20 mg/kg (up to 1000 mg) q8h. In a pharmacokinetic study, valaciclovir 20 mg/kg q8h was given to children 3 months-11 year which gave the equivalent AUC as valaciclovir 1000 mg q8h in adults [36].

Treatment and prophylaxis

Treatment for congenital CMV infection

Treatment during pregnancy for suspected or confirmed foetal infection is currently not recommended. Postnatal treatment is only recommended in infants with CNS disease (microcephaly, calcifications, chorioretinitis, white matter alteration or other MRI abnormality consistent with congenital CMV) *or* other serious manifestations (life-threatening CMV disease or single/multi-organ failure) (grade B recommendation). There is no consensus on recommending treatment in infants with hearing loss or chorioretinitis as the only CMV manifestation. There is also no support for treating infants with asymptomatic CMV infection.

The recommended treatment strategy is oral valganciclovir 16 mg/kg twice daily for six months, starting in the first month of life (grade B recommendation). Intravenous ganciclovir can be used if the drug cannot be administered orally or in case of decreased intestinal absorption. A known side effect is neutropenia. Monitoring should be done regarding blood cell count, transaminases, creatinine and electrolytes once a week for the first four weeks, then once a month. In case of neutropenia $<0.5 \times 10^9$/l, half the dose is recommended. The treatment has not been studied in infants< 32 weeks of gestation. Long-term effects are not known [7].

Treatment of preterm infants with postnatally acquired CMV infection

Treatment of postnatal CMV infection aims to reduce the severity and duration of symptoms. There is currently no indication for long-term antiviral therapy to reduce the potential future harm of postnatally acquired CMV infection.

Treatment can be considered for:

- Preterm births (< 32 weeks of gestation) who have established severe postnatally acquired CMV disease.
- Severe organ disease, including hepatitis, bone marrow suppression (anaemia, neutropenia, thrombocytopenia), severe intestinal manifestations, pneumonitis, or possibly exacerbated bronchopulmonary dysplasia.
- Sepsis-like disease (grade B recommendation)

The treatment aims to reduce the amount of virus, and thereby the symptoms, and is provided as intravenous ganciclovir or oral valganciclovir (see dosage in Table 3). The treatment should normally last two weeks but maybe extended in individual cases [9] (grade C recommendation).

Treatment of CMV infection in immunocompetent patients

The available data on CMV infection in immunocompetent individuals do not support antiviral treatment. This also applies to pregnant women. However, in rare cases with severe disease and organ involvement, treatment may be considered, primarily with intravenous ganciclovir. One problem with ganciclovir (as with cidofovir) is the risk of teratogenicity. Pregnant women should, therefore, only be treated if they are severely ill (grade D recommendation).

Treatment and prophylaxis of CMV after transplantation and in patients with hematological malignancies

A well-planned preventive strategy against CMV disease is important for all solid organ transplant and HCT patients. This may involve antiviral prophylaxis, pre-emptive therapy or a combination of both (grade A recommendation) (Fact Box 3).

Fact Box 3. Definitions of treatment/prophylaxis.

Prophylaxis
Preventive treatment of all patients assessed to be at risk of developing CMV infection/disease.
Targeted prophylaxis
Preventive treatment for certain groups at particularly high risk of CMV disease, such as D+/R- organ transplant patients or D-/R + stem cell transplant patients.
Pre-emptive therapy
Initiation of antiviral therapy after detection of CMV by quantitative PCR monitoring in an asymptomatic patient.
Treatment
Antiviral therapy in a patient with CMV disease.

CMV prevention after allogeneic haematopoietic stem cell transplantation

In adult CMV IgG-positive patients, prophylaxis with letermovir is recommended for at least three months after

Table 3. Dosage in congenital infection and in preterm infants.

Drug	Congenital	Preterm< 32 w
Ganciclovir	5–6 mg/kg q12h	5–6 mg/kg q12h (careful monitoring of drug concentration and side effects)
Valganciclovir	16 mg/kg q12h for 6 months	16 mg/kg q12h (careful monitoring of drug concentration and side effects)

q12h, twice daily.

HCT [15] (grade A recommendation). Recent data from a randomised controlled trial shows that a longer duration of prophylaxis in high-risk patients is safe and can be considered on an individual basis [37]. It is also possible to use letermovir as secondary prophylaxis after treatment of CMV reactivation (grade C recommendation). Monitoring of CMV-DNA should be performed at least weekly for the first three months after HCT in all patients, including those receiving antiviral prophylaxis. An exception is seronegative patients with a seronegative donor, where monitoring can be done every two weeks since these patients have a low risk for CMV infection. After three months, an individual assessment of the need for monitoring should be performed for each patient. Continued monitoring over a more extended period is recommended for patients who have had repeated CMV infections, patients with acute GVHD requiring immunosuppressive therapy, and seropositive patients transplanted from seronegative donors.

Antiviral treatment of allogeneic haematopoietic stem cell transplant patients and patients with hematological malignancies

Since the techniques used for CMV monitoring vary and the risk of CMV complications also varies, it is not possible to specify an exact CMV-DNA cut-off level for when antiviral treatment should be initiated. However, there is experience from several transplant centres to initiate treatment at CMV-DNA at approximately 1000–2000 IU/ml blood or plasma [38]. For high-risk patients (especially those with cord blood or haploidentical donors and patients with severe GVHD), treatment is often initiated at lower levels of CMV-DNA. The primary choice of treatment is valganciclovir (grade B recommendation). In severe disease, or if the gastrointestinal uptake is uncertain, intravenous ganciclovir should be used. Serum concentration measurements of ganciclovir may be considered, especially in cases of renal dysfunction or if side effects are suspected. Most patients respond and become CMV-DNA negative after two to three weeks of treatment. The risk of new reactivations is high in patients transplanted from a CMV seronegative donor or in those having other risk factors such as acute GVHD. Repeated antiviral treatments increase the risk of antiviral resistance and drug toxicity, especially bone marrow suppression. However, it is important to note that a rise in blood CMV-DNA levels early after initiation of treatment is usually not a sign of drug resistance. A minimum of two weeks of treatment is normally recommended before second-line treatment should be considered. In ganciclovir-resistant or refractory CMV infection, foscarnet and maribavir are possible alternatives. The choice of second-line treatment should be made individually depending on, among other things, the side effect profile (see section about antiviral drugs).

The same drugs that can be used in pre-emptive treatment can also be used in treating CMV disease. However, a longer duration of treatment is usually needed and must be decided individually depending on the efficacy and toxicity of the given treatment.

Limited data exist on the treatment of CMV in patients after autologous HCT or those treated for hematological malignancy. CMV disease is rare in these patients but can occur, and it should be treated similarly to allogeneic HCT patients.

CMV prevention after solid organ transplantation

Primary prophylaxis or pre-emptive treatment is recommended after organ transplantation, depending on the type of organ and the CMV serological status of the donor and recipient (grade A recommendation). Pre-emptive treatment requires are liable monitoring system and is usually not suitable for organ recipients at high risk of infection. As a rule, prophylaxis should be started within the first week after transplantation and, in high-risk cases, within the first few days. The duration of prophylaxis depends on the type of organ, the degree of immunosuppression and the CMV serological status of the donor and recipient (Table 4). Oral valganciclovir is the first-line choice for primary prophylaxis. Letermovir is an alternative for adult kidney recipients [30]. Valaciclovir may also

Table 4. Recommended CMV prophylaxis in organ transplantation.

Type of organ	CMV antibody status	Level of risk	Prophylaxis[1,2]
All	D-/R-	low	No-CMV prophylaxis[3]
Kidney	D+/R-	high	6 months
	R+	medium	3 months
Pancreas	D+/R-	high	3–6 months
	R+	medium	3 months
Liver	D+/R-	high	3–6 months
	R+	medium	3 months
Heart	D+/R-	high	3–6 months
	R+	medium	3 months
Lung	D+/R-	high	12 months
	R+	high	6 months
Visceral[4] (gut)	D+/R-	high	6–12 months
	R+	high	3–6 months

CMV, Cytomegalovirus; D, donor; R, recipient; +, CMV IgG positive; -, CMV IgG negative.

[1]Monitoring CMV-DNA in blood and pre-emptive therapy is an option for seropositive (R+) kidney, liver, or heart recipients but not for lung or visceral recipients at high risk of CMV disease (16).

[2]Monitoring should be considered after prophylaxis is completed, especially in patients at high risk of CMV disease.

[3]Prophylaxis with acyclovir/valacyclovir against other herpes viruses is recommended.

[4]In the first 7–14 days after transplantation, IV ganciclovir is recommended for everyone. Absorption from the gut may be poor.

be used for adult kidney recipients but is less effective than valganciclovir [25].

Treatment of CMV in organ transplantation

Reduction of the patient's immunosuppression should always be considered. This is particularly important in severe CMV disease and when there is possible drug resistance. CMV disease (symptomatic infection) should always be treated (grade A recommendation). In asymptomatic patients, detection of CMV-DNA in blood must be related to the risk of developing CMV disease in the individual patient. Factors such as time after transplantation, degree of immunisation against the donor, level of immunosuppression, and whether it is a primary infection or reactivation of CMV should be considered. A primary infection should normally be treated (grade B recommendation). Detection of CMV-DNA in blood in individuals who are CMV IgG positive (R+) implies reactivation. Whether a reactivation should be treated or continued close monitoring is sufficient depends on the CMV-DNA level, the CMV replication dynamics and the immunosuppression level. The exact level of CMV-DNA in blood prompting treatment has not been established. Moreover, the risk of CMV disease may be more related to the rate of CMV-DNA level increase rather than the absolute level [39]. In some studies, including mainly CMV IgG-positive kidney and liver transplant recipients, 2500–4000 IU/mL plasma or whole blood has been used as a threshold level to initiate treatment [16]. See proposal for management of positive CMV-DNA in blood, as shown in Figure 1.

The first-line treatment alternatives are intravenous ganciclovir or oral valganciclovir (grade A recommendation). The duration of the treatment for asymptomatic CMV infection (pre-emptive treatment) or CMV syndrome should be, at minimum, two weeks. CMV disease with organ manifestation should be treated for at least three weeks, often longer if there is no rapid decline of CMV-DNA levels or if signs of organ involvement have not been resolved. Following treatment, secondary prophylaxis should be considered, especially if the infection/disease is recurrent or if the level of immunosuppression cannot be reduced.

Symptoms or laboratory findings should improve during antiviral treatment, and CMV-DNA in the blood should be reduced. An initial, transient increase in blood CMV-DNA is often seen, but the level should gradually decrease

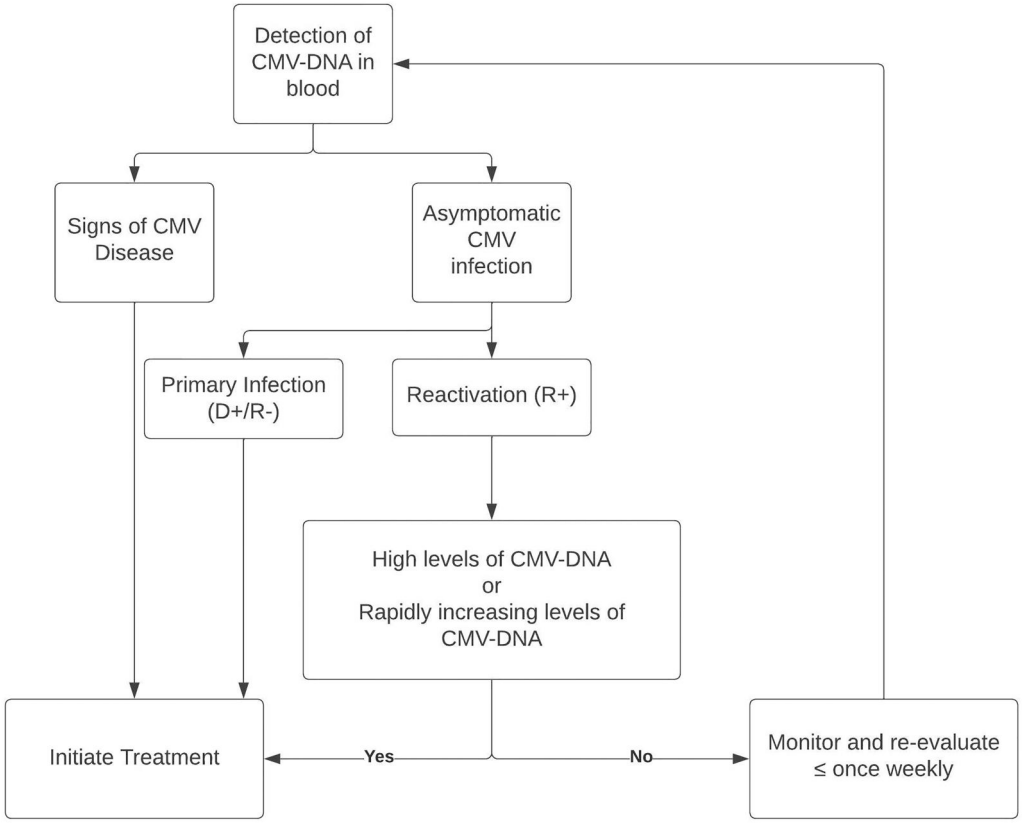

Figure 1. Proposed management of organ transplant patients with positive CMV-DNA in blood.
CMV, Cytomegalovirus; D, donor; R, recipient; +, CMV IgG positive; -, CMV IgG negative.

after that and ideally be undetectable at the end of treatment. Despite adequate treatment, it may take up to two weeks before CMV-DNA in the blood decreases.

If the treatment effect is suboptimal, compliance with the treatment, dosage, and the possibility of resistance development should be evaluated. In case of non-response or relapse during treatment, the CMV strain should be tested for drug resistance, and analysis of the serum concentration of ganciclovir should be considered.

Foscarnet and maribavir are possible alternatives in cases of ganciclovir-resistant and refractory CMV. The selection of second-line treatment should be made individually depending on, among other things, the side effect profile, see section about antiviral drugs.

Treatment of CMV in patients with HIV

In HIV-positive patients on antiretroviral therapy, the immunological status is usually good, and CMV disease is, therefore, rare in this population. Treatment of CMV is the same as in other immunosuppressed patients. For treatment of CMV retinitis, see Supplementary Document S3.

Treatment of CMV in patients with IBD

In patients with steroid-resistant IBD, CMV colitis should be ruled out, and if CMV antigen is detected by immunohistochemistry in intestinal biopsies, antiviral treatment should be considered (grade C recommendation).

If CMV colitis is diagnosed, reducing or stopping immunosuppressive therapy until symptoms resolve can be considered (Grade D recommendation).

Quality grading of evidence
1a Systematic analysis (with homogeneity) of randomised controlled trials
1b At least one large randomised controlled trial.
1c 'All or nothing' is ascertained when all patients died before treatment became available, but some survive with the treatment, or –some survive without treatment, but with treatment, all survive
2a Systematic analysis (with homogeneity) of cohort studies
2b Individual cohort studies, including randomised controlled studies with low evidence value (poor quality, wide confidence intervals, low inclusion of some subgroups in a study etc.).
2c 'Outcomes research'
3a Systematic analysis (with homogeneity) of case-control studies
3b Individual case-control studies
4 Case series with case-control studies and cohort studies with low quality
5 Expert opinions without critical analysis or based on physiology etc.

Grading of recommendations
A Based on quality grading of evidence 1a, b or c
B Based on quality grading of evidence 2a, b or c, 3a or b
C Based on quality grading of evidence 4
D Based on quality grading of evidence 5

Evidence and recommendation grading (www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009).

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