# Prevention and Treatment of CMV Infection (and Other Herpes Viruses)

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## 6.1 Prevention and Treatment of Cytomegalovirus (CMV) Infection

### 6.1.1 Description of the Pathogen

CMV is a double-stranded DNA virus of the *Herpesviridae* family that has the capacity to produce primary infection or reactivation in SOT recipients.

### 6.1.2 Definitions

- *Infection or replication*: Isolation of the virus or the detection of viral proteins (antigenemia) or CMV DNA/mRNA in any body liquid or tissue. In SOT recipients, latent infection (i.e., seropositivity for CMV) is generally considered to be a separate entity.
- *Antigenemia*: Direct detection of the CMV pp65 antigen in peripheral blood leukocytes, mainly neutrophils.
- *DNAemia*: Detection of CMV DNA in plasma or whole blood.
- *CMV disease*: Evidence of symptoms or signs together with the detection of CMV infection in blood or tissue. CMV disease can be classified as a viral syndrome (see below) or tissue-invasive disease (in case of end organ disease such as CMV gastrointestinal disease or pneumonitis). Proven CMV disease requires

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the presence of CMV in tissue. A new category of probable CMV disease has been proposed in case of compatible symptoms of end-organ disease, but without confirmation by biopsy.

- *Viral syndrome*: Presence of fever and/or malaise associated with the presence of leukopenia and thrombocytopenia or an increase in transaminases. This is considered a type of CMV disease.
- *Universal prophylaxis*: Administration of an effective antiviral drug to prevent the development of CMV replication and/or disease in at-risk patients.
- *Preemptive therapy*: Regular monitoring for CMV replication followed by initiation of antiviral treatment in patients displaying asymptomatic CMV replication in order to prevent progression to CMV disease.

### 6.1.3 Diagnosis

Although antigenemia is still used, a quantitative real-time nucleic acid amplification-based assay or polymerase chain reaction (PCR) is recommended for the diagnosis and monitoring of CMV infection after transplantation. Viral loads can be determined in both plasma and whole blood samples, but the same type of sample should be used when comparing viral loads or following a given patient. There are also differences between viral loads obtained in different centers, thus making an international standard reference necessary. Of note, an improvement on the agreement between viral load values has been obtained with the calibration of tests using the World Health Organization (WHO) international standard. There is a direct association between viral load values and the likelihood that an individual will develop active disease. Moreover, the rate of increase of viral loads is also a predictor of developing disease. Due to the variability of the results among laboratories, a single test should be used for monitoring patients over time. Laboratories should establish their own cutoffs and audit clinical outcomes to verify the trigger points used for treatment.

Viral resistance depends on the existence of mutations in the CMV genome. Plasma or whole blood is the sample of choice. Genotypic assays (PCR amplification) are available for clinical use. Two genomic regions must be studied: UL97 kinase gene involved in the initial phosphorylation of ganciclovir (codons 400–670) and the UL54 polymerase gene (codons 300–1000). Common UL97 and UL54 mutations are shown in Table 6.1. A web-based search tool, www.informatik.

**Table 6.1** Levels of ganciclovir resistance with the most common UL97 mutations

| Mutations or deletions | Ganciclovir $IC_{50}$ mutant strain/ wild type | Interpretation |
|---|---|---|
| M460V/I/T, H520Q, A594V/G, L595S/W, C603W | 5–15 | High-grade resistance |
| C592G | 2–5 | Low-grade resistance |

For other less frequent mutations, search the web-based tool, www.informatik.uni-ulm.de/ni/staff/HKestler/hcmv/

uni-ulm.de/ni/staff/HKestler/hcmv/, has been developed that links the sequence to a database containing all published UL97 and UL54 mutations and corresponding antiviral drug susceptibility phenotypes. If mutations only appear in the UL97 gene, viruses are resistant only to ganciclovir. UL54 mutations typically added to pre-existing UL97 mutations, increasing the level of ganciclovir resistance and commonly conferring different levels of cross-resistance to other CMV antivirals such as foscarnet or cidofovir. In the future, next-generation sequencing (NGS) technologies may enable the detection of far smaller viral subpopulations and may therefore improve the detection of drug resistance emergence.

### 6.1.4 Immunological Monitoring

Testing for anti-CMV IgG antibodies should be performed before transplantation in donors and recipients for the purposes of risk stratification. In recipient CMV negative (R−) patients, testing should be repeated at the time of transplantation. Donor serostatus should also be performed to stratify the subsequent risk of CMV infection and disease.

The use of CMV specific cell-mediated assays may also be clinically useful. The characteristics of different technics available for immunological monitoring are reviewed in Table 6.2. If available, pretransplant CMV-specific cell-mediated

**Table 6.2** Available methods for monitoring of CMV-specific T-cell-mediated immune response

| Characteristic | Intracellular cytokine staining | ELISpot | QuantiFERON-CMV | MHC-tetramer staining |
|---|---|---|---|---|
| Turnaround time | 8–10 h | 24–48 h | 24 h | 1–2 h |
| Functional analysis | Yes | Yes | Yes | No (unless associated to intracellular cytokine staining) |
| Differentiation between $CD8^+$ and $CD4^+$ T cells | Yes | No | No (detects mostly $CD8^+$ T cells) | Yes |
| Commercially available test | No | Yes | Yes | Yes |
| Advantages | Gold standard. Potential for freezing PBMCs | Potential for freezing PBMCs, can be used in presence of lymphopenia | Standardized | Specificity |
| Limitations | Lack of technical standardization. Expert laboratory is needed | Lack of technical standardization. Expert laboratory is needed | Limitations in patients with lymphopenia | Lack of technical standardization. Expert laboratory is needed |

*CMV* cytomegalovirus, *ELISpot* enzyme-linked immunosorbent spot assay, *PBMCs* peripheral blood mononuclear cells

immunity may better stratify the risk of CMV infection after transplantation as compared to serology, particularly in R+ recipients. After transplantation, the potential utility of monitoring CMV-specific cell-mediated immunity has been investigated in various clinical scenarios. Overall, a reactive test has a high negative predictive value for detecting risk of CMV replication, supporting the safety of discontinuing prophylaxis in high-risk patients above the protective threshold. Alternatively, patients with no evidence of protective response at the end of the prophylaxis period could benefit from the so-called hybrid approach (in which preemptive monitoring is initiated after completing prophylaxis). On the other hand, immune monitoring in intermediate-risk patients managed preemptively may be useful in guiding the frequency for surveillance of CMV infection and the thresholds for initiating antiviral therapy, or in case of treatment failure after appropriate antiviral therapy. However, interventional clinical trials are required to evaluate protocolized interventions based on the posttransplant kinetics of CMV-specific responses before including these assays in the routine clinical practice.

### 6.1.5 Prevention

Two major strategies have been used to prevent CMV infection: universal prophylaxis and preemptive therapy. Both are effective in the prevention of CMV disease.

Universal prophylaxis may be preferable in scenarios of rapid viral dynamics (lymphocyte-depleting therapy, potent immunosuppression, D+/R− setting). Oral valganciclovir is currently the preferred antiviral drug for the prevention of CMV infection, although intravenous ganciclovir can be used early after transplant if oral absorption is compromised. High-dose valacyclovir is an alternative option in renal transplantation. Letermovir is a promise drug that is currently under clinical development.

Late-onset CMV disease, defined as disease occurring after discontinuation of prophylaxis, is a common finding when using universal prophylaxis in D+/R− transplant recipients, developing in 20–36% of patients, depending on the type of organ transplant. A 200-day prophylaxis regimen has been shown to reduce the incidence of late-onset CMV disease, and it is recommended in D+/R− kidney transplant patients and, by extension, in other high-risk transplant recipients (e.g., heart, pancreas). In R+ patients, 3-month regimens are preferred. In lung and intestinal transplant recipients, the majority of the clinicians extend prophylaxis over 6 to 12 months after transplantation for both D+/R− and R+ patients. In recipients receiving alemtuzumab as induction therapy, monitoring of $CD4^+$ T lymphocytes has been used to continue prophylaxis (for at least 6 months) until CD4 T lymphocytes are over 200 cell/$mm^3$, although the efficacy of this strategy has not been tested on clinical trials.

In a preemptive strategy, viral load is typically monitored weekly for the first 12–14 weeks posttransplant. There are no evidence-based recommendations regarding the viral load cutoff for initiating antivirals and the optimal duration of preemptive therapy. It may be preferable to initiate preemptive therapy in any high-risk

patients with a positive viral load at any level. In lower-risk patients, it is possible to establish local cutoff points and eventually delay therapy, consider reducing the levels of immunosuppressive therapy, and repeat a second viral load after a short interval, since small blips may resolve spontaneously. Treatment should be administered for a minimum of 2 weeks. Monitoring of CMV viral load should direct the duration of treatment. At least one negative viral load determination (or viral load below a specific threshold) in plasma specimens is required in order to withdraw treatment. Relapse of CMV infection is frequent after a therapy course, although it is generally resolved after a new course of treatment or even spontaneously.

There is no available data supporting the use of a combined preemptive therapy strategy after prophylaxis in low-risk transplant recipients. Nevertheless, this strategy, which is known as a "hybrid strategy," is commonly used in certain high-risk transplant recipients (D+/R−, lung, pancreas, and small bowel recipients and/or those receiving lymphocyte-depleting treatments). The duration of a preemptive approach post-prophylaxis has not been determined.

Taking into account the low risk of CMV disease reported in the subgroup of D−/R− recipients, the use of prophylaxis or preemptive therapy have not been recommended. Other measures, such as the use of leuko-depleted or CMV-seronegative blood products, directed at preventing CMV infection acquisition, are recommended.

Hypogammaglobulinemia (IgG <500 mg/dL) has been proposed as being a risk factor for CMV disease after SOT transplantation. In heart transplant recipients, the administration of non-specific intravenous immunoglobulins (IVIGs) with the goal of maintaining normal IgG levels was associated with a lower risk of CMV infection. In heart, lung, and intestinal transplant recipients at high risk for CMV disease (D+R−), some centers add specific anti-CMV IVIG to prevent CMV infection. The best dosing regimen has not been established.

A recommendation regarding the use of CMV vaccine in SOT recipients cannot be made as no vaccine has been approved for use in a clinical setting.

### 6.1.6 Treatment

Intravenous ganciclovir and oral valganciclovir are the antiviral drugs of choice for treating CMV infection and disease. Intravenous ganciclovir (5 mg/kg/12 h) should be used in patients with severe CMV disease or when valganciclovir is poorly tolerated or not well absorbed. It is important to administer the appropriate doses of intravenous ganciclovir or oral valganciclovir adjusted for renal function, as inadequate dosing can cause clinical failure or viral resistance. Oral valganciclovir (900 mg/12 h) is effective in patients with mild to moderate CMV disease. It can also be used in sequential therapy in patients treated with intravenous ganciclovir, once clinical improvement is documented.

The optimal duration of treatment should be guided by weekly virological monitoring (treat until viral load negative or below a certain threshold) and clinical response. The minimum duration of treatment is 2 weeks. Following initial treatment secondary prophylaxis is commonly used for a period of 1–3 months although

evidence for this is lacking and it is currently not recommended. The treatment of a recurrence should generally be the same used during the first episode.

The evidence to support the use of specific anti-CMV immunoglobulins in cases of life-threatening CMV disease, particularly severe pneumonitis, is lacking, although it is often used.

Resistance to antiviral drugs should be suspected in the presence of progressive or stable viral loads or if clinical symptoms persist despite adequate antiviral treatment for 2 weeks, particularly in case of risk factors (D+/R− serostatus, lung transplantation, serious invasive disease and/or high viral load, intermittent low-level viral replication during therapy or suboptimal drug levels, and prolonged antiviral drug exposure). If genotypic tests demonstrate the existence of a high-level resistance mutation in the UL97 gene or the UL54 gene (Table 6.1), foscarnet is indicated. Increasing the dose of ganciclovir up to 10 mg/kg/12 h might be useful for other mutations in the UL97 gene and can be considered for patients with non-severe CMV disease or in those whom the use of foscarnet should be avoided (nephrotoxicity).

Maribavir has been successfully used in salvage therapy in patients with refractory/resistant CMV infection and is currently in phase 3 trial for this indication. Brincidofovir and letermovir are also promising drugs that need clinical development in this indication. Switching immunosuppression from calcineurin inhibitors to an mTOR inhibitor-based regimen has been proposed as an adjunctive therapy, although most data on the effect of mTOR inhibitors on resistant CMV are provided from uncontrolled studies. There is no enough evidence to recommend leflunomide as a therapeutic agent for treating antiviral-resistant CMV infection.

Adoptive immunotherapy can be useful for the rescue of case refractory to conventional treatment and who do not develop a satisfactory immune response. However, clinical experience in the solid organ transplant setting is very limited.

**General Approach** The key recommendations for the management of CMV infection are provided in Table 6.3.

## 6.2 Prevention and Treatment of Other Herpes Viruses

### 6.2.1 Description of the Pathogens

Herpes simplex virus (HSV), varicella-zoster virus (VZV), and human herpesvirus 6 (HHV-6) and human herpesvirus 8 (HHV-8) belong to the *Herpesviridae* family and have the capacity to produce primary infection or reactivation in the recipients of a solid organ transplant. Clinical manifestations of VZV and HSV include mucocutaneous disease, although a higher rate of disseminated disease (gastrointestinal disease, CNS infection, respiratory tract infection) is seen in SOT recipients. Epstein-Barr virus is reviewed in a specific chapter. Human herpesvirus 7 is generally not of significant clinical impact. HHV-8 is associated with Kaposi's sarcoma (with cutaneous and disseminated manifestations), multicentric Castleman disease, and primary effusion lymphoma.

**Table 6.3** Key recommendations for the management of cytomegalovirus infection after solid organ transplantation

| Area of interest | Recommendations |
|---|---|
| Diagnosis | Methods based on quantitative CMV DNA amplification are the methods of choice<br>Genotypic testing has become the usual means for detecting drug resistance |
| Immunological monitoring | Testing for anti-CMV IgG antibodies should be performed before transplantation in donors and recipients<br>Pretransplant CMV-specific cell-mediated immunity may be used together with serological testing to stratify the risk of CMV infection after transplantation<br>Posttransplant monitoring of CMV-specific cell-mediated immunity can be useful in:<br>– High-risk patients (D+/R−, prior use of T-cell-depleting antibodies) on antiviral prophylaxis can be used to predict the risk of late CMV infection<br>– R+ patients under preemptive therapy to predict the occurrence of CMV infection or the spontaneous clearance of viremia without the need of antiviral prophylaxis<br>– Lack of response to antiviral therapy |
| Prevention (strategy) | For D+/R− kidney and liver recipients, universal prophylaxis is preferable to preemptive therapy<br>For D+/R− heart and lung recipients, the use of prophylaxis is preferable to preemptive therapy<br>Prophylaxis is preferable to preemptive therapy in lung, pancreas, and intestinal transplantation until more data are available<br>For seropositive recipients after kidney, liver, and heart transplantation, either strategy is acceptable<br>Prophylaxis is preferred in other high-risk patients (lymphocyte-depleting therapy, potent immunosuppression, and HIV infection) |
| Prevention (drug of choice) | Oral valganciclovir is the preferred antiviral<br>In patients with severe leukopenia, oral acyclovir or valacyclovir is an alternative to valganciclovir in kidney transplant recipients |
| Prevention (duration) | Six months is recommended for D+/R− kidney, heart, and pancreas transplant recipients<br>For D+/R− liver transplant recipients, the duration of prophylaxis should generally be between 3 and 6 months<br>When a prophylaxis strategy is used for the prevention of CMV in R+ patients (with either D+ or D−), 3 months of antiviral medication should be used for kidney, pancreas, liver, and heart transplant recipients<br>Between 6 and 12 months of prophylaxis is recommended for lung and intestinal transplant recipients |
| Prevention (preemptive therapy) | Preemptive therapy must be initiated with any viral replication in high-risk patients (D+/R−, lymphocyte-depleting treatments)<br>Preemptive therapy in R+ recipients must be initiated in base of a cutoff viral load established in each center or increasing kinetics<br>Maintain therapy for at least 2 weeks and/or at least one negative viral load determination |
| Prevention (hybrid strategy) | Preemptive therapy after finishing CMV prophylaxis can be recommended in high-risk transplant recipients, including D+/R−, lung, pancreas, and small bowel recipients, and/or those receiving lymphocyte-depleting treatments (the duration has not been determined) |

(continued)

**Table 6.3** (continued)

| Area of interest | Recommendations |
|---|---|
| Prevention (D−/R− patients) | The routine use of prophylaxis or preemptive therapy against CMV is not recommended<br>Use leuko-depleted or CMV-seronegative blood products |
| Prevention (IgG deficit) | Non-specific or anti-CMV-specific IVIG is indicated in heart transplant recipients with IgG level <500 mg/dL |
| Treatment | CMV disease should be treated with oral valganciclovir (900 mg/12 h, for mild-moderate disease) or intravenous ganciclovir (5 mg/kg/12 h, for severe disease) corrected by renal function<br>Intravenous ganciclovir can be followed by oral valganciclovir when clinical and virological improvement has been achieved (sequential therapy)<br>Maintain treatment until resolution of symptoms and viral replication in plasma<br>Combined use of immunoglobulins can be considered in patients with hypogammaglobulinemia of life-threatening CMV disease (pneumonitis) |
| Treatment (resistance) | This is a complicated situation that should be managed by an expert transplant ID<br>CMV resistance must be suspected in cases of progressive or stable viral replication or persistence of symptoms despite adequate antiviral treatment for 2 weeks<br>A genotypic analysis of the UL97 and UL54 genes must be performed<br>Foscarnet is the alternative treatment of choice<br>High-dose ganciclovir (up to 10 mg/kg/12 h with normal renal function) can be used in non-severe patients without neutropenia, for whom the use of foscarnet should be avoided<br>An mTOR inhibitor-based regimen of immunosuppression should be used<br>The experience of salvage therapy with alternative regimens is limited (maribavir, leflunomide, artesunate, letermovir, or brincidofovir) |

## 6.2.2 Herpes Simplex Virus

### 6.2.2.1 Diagnosis

Although pretransplant IgG serostatus of recipients may be helpful for post-transplant risk stratification, serology is not useful for diagnosing acute disease. Transplant patients can have atypical mucocutaneous lesions and visceral or disseminated disease; therefore laboratory confirmation may be necessary. PCR testing of mucocutaneous lesions, and other clinical samples (plasma, cerebrospinal fluid, bronchoalveolar lavage), is the diagnostic test of choice. The clinical significance of finding HSV DNA in the blood of patients without disseminated disease has not been well established and therefore is not recommended to be tested routinely. Also, a positive PCR in the BAL may be either due to mucocutaneous contamination during sampling or due to HSV pneumonitis. Tissue histopathology with immunohistochemistry for HSV can be helpful in diagnosing invasive HSV disease.

#### 6.2.2.2 Prevention

HSV prophylaxis is generally indicated for HSV-1- or HSV-2-seropositive recipients not receiving CMV prophylaxis ((val)ganciclovir prevents HSV replication). Some experts also recommend prophylaxis in HSV seronegative to prevent the infection transmitted from organs or blood transfusions; however, this is a rare occurrence. A low-dose acyclovir regimen (< 1gr/day) is effective (200 mg three or four times a day, 400 mg two times a day) for prophylaxis. Valacyclovir (two times a day) or famciclovir can also be used.

Antiviral prophylaxis should continue for at least 1 month. Resumption of prophylaxis may be considered for CMV-seronegative patients being treated with T-cell-depleting agents. In patients with severe clinical recurrences (≥2), suppressive antiviral therapy may be indicated and may occasionally be required for very prolonged durations.

All recipients (not only seronegative) should avoid contact with persons with active lesions. Condoms do not completely protect against HSV transmission. HSV-2-seronegative transplant recipients should consider having their partner tested for HSV-2. In serodiscordant couples, daily antiviral therapy taken by the seropositive partner can prevent HSV-2 transmission to the seronegative partner. The efficacy of postexposure prophylaxis is unknown.

#### 6.2.2.3 Treatment

Disseminated, visceral, or extensive mucocutaneous HSV disease should be treated with intravenous acyclovir at a dose of 5–10 mg/kg every 8 h for a minimum of 2 weeks (3 weeks in case of encephalitis). Non-severe mucocutaneous disease can be treated with oral acyclovir, valacyclovir, or famciclovir for a minimum of 1 week. Overall treatment durations are determined by clinical response. HSV keratitis can be treated with systemic or topical agents (trifluridine solution, vidarabine ointment, or topical ganciclovir gel).

Resistance must be considered in patients whose lesions are not responding clinically to appropriate doses of systemic therapy. Genotypic testing for known resistance mutations is available in some settings. Intravenous foscarnet or cidofovir are recommended, but both are associated with significant renal toxicity. Topical agents (imiquimod, cidofovir, trifluridine) can be used for resistant anogenital disease.

**General Approach** The main recommendations for the management of HSV infection are provided in Table 6.4.

### 6.2.3 Varicella-Zoster Virus

#### 6.2.3.1 Diagnosis

All transplant candidates should undergo serologic testing for VZV to determine the need for vaccination in case of seronegativity and to assess posttransplant risk. In general, both primary varicella and herpes zoster have typical clinical presentations

**Table 6.4** Key recommendations for the management of herpes simplex virus infection after solid organ transplantation

| Area of interest | Recommendations |
|---|---|
| Diagnosis | Pretransplant IgG serostatus of donor and recipient is necessary to determine preventive strategies<br>Polymerase chain reaction is the diagnostic test of choice<br>Tissue histopathology with immunocytochemistry can be helpful |
| Prevention | Prophylaxis is indicated only for seropositive recipients not receiving CMV prophylaxis<br>Low-dose acyclovir (< 1gr/day) is indicated (200 mg three or four times a day, 400 mg two times a day)<br>Valacyclovir (500 mg two times a day) or famciclovir can also be used<br>Antiviral prophylaxis should continue for at least a month<br>Suppressive antiviral therapy can be indicated even during years or lifelong in cases of frequent severe recurrences<br>Avoid contact with persons with active lesions<br>Condoms do not completely protect against HSV transmission<br>Seronegative HSV-2 recipients: consider having their partner tested for HSV-2<br>Serodiscordant couples: daily antiviral therapy taken by the seropositive partner can be considered in individual basis |
| Treatment | Disseminated, visceral, or extensive mucocutaneous disease: intravenous acyclovir (5–10 mg/kg every 8 h during a minimum of 2–3 weeks)<br>Not severe mucocutaneous disease: oral treatment during a minimum of 1 week (acyclovir, valacyclovir, or famciclovir)<br>Keratitis: systemic or topical agents (trifluridine solution, vidarabine ointment, or topical ganciclovir gel) |
| Resistance | Genotypic testing can be available<br>Intravenous foscarnet or cidofovir (renal toxicity) is indicated<br>Topical agents (imiquimod, cidofovir, trifluridine) can be used for resistant anogenital disease |

that allow for a presumptive clinical diagnosis. Nevertheless, transplant recipients can have atypical presentations or multi-organ involvement with delayed or absent rash. Also, in some instances, VZV Infection may be difficult to differentiate from HSV infection. Therefore a definitive laboratory testing is indicated for atypical cases and visceral disease. PCR is the method of choice (vesicle fluid, serum, spinal fluid, and other tissues).

#### 6.2.3.2 Prevention

***Antiviral Therapy*** Antiviral prophylaxis for VZV is not needed during periods of CMV prophylaxis with valganciclovir. In CMV-seronegative patients followed by a preemptive approach, (val)acyclovir is efficacious for preventing both HSV and VZV during the early posttransplant period.

***Pretransplant Vaccination*** Seronegative potential transplant patients should receive varicella vaccination with the live attenuated vaccine at least 4 weeks before transplant.

***Posttransplant Vaccination*** The live vaccine poses a risk of disseminated infection in immunosuppressed patients and therefore is contraindicated for posttransplant recipients. Recently, an inactivated zoster vaccine has become available for prevention of singles, but there are limited published data on its use in transplant patients.

***Postexposure Prophylaxis*** Options for postexposure prophylaxis include passive immunoprophylaxis and/or antiviral therapy. VZV immunoglobulins are recommended in susceptible (seronegative) patients exposed to VZV and should be given as soon as possible but within at least 10 days of exposure. Antiviral therapy should be considered as adjunctive therapy or in patients who were unable to receive immunoprophylaxis before 10 days after their exposure. Acyclovir or valacyclovir or famciclovir can be used for a 7–14-day course.

#### 6.2.3.3 Treatment

***Varicella*** Patients should be treated with acyclovir, initiated early, especially within 24 h of rash onset.

***Herpes Zoster*** Patients with disseminated or organ invasive disease should be treated with IV acyclovir. Localized non-severe HZ can be treated with oral valacyclovir or famciclovir, with the exception of herpes zoster ophthalmicus or herpes zoster oticus, for which intravenous administration is recommended.

**General Approach** The main recommendations for the management of HZV infection are provided in Table 6.5.

**Table 6.5** Key recommendations for the management of herpes zoster virus infection after solid organ transplantation

| Area of interest | Recommendations |
|---|---|
| Diagnosis | Pretransplant IgG serostatus of donor and recipient is necessary<br>Polymerase chain reaction is the diagnostic test of choice |
| Prevention | Prophylaxis is not indicated for seropositive recipients receiving CMV or HSV prophylaxis<br>Transplant candidates should receive varicella vaccination at least 4 weeks before transplant Posttransplant vaccination with the live VZV vaccine (Zostavax®) is contraindicated. Experience with the new inactivated vaccine (Shingrix®) is lacking but can be a very effective strategy to prevent zoster in transplant recipients<br>Options for postexposure prophylaxis include passive immunoprophylaxis and/or antiviral therapy (as soon as possible but within at least 10 days of exposure) |
| Treatment | Patients with varicella or invasive disease should be treated with intravenous acyclovir<br>Localized non-severe herpes zoster can be treated with oral drugs (with exception for herpes zoster ophthalmicus or oticus) |

### 6.2.4 Human Herpesvirus 6

#### 6.2.4.1 Diagnosis

Routine monitoring for HHV-6 is not recommended based on the current evidence or low rate of disease and subclinical infections. Diagnostic testing should be limited to symptomatic HHV-6 disease, in order to guide treatment.

Quantitative real-time PCR is preferred for the detection of HHV-6 viremia. It can distinguish between HHV-6A and HHV-6B, but they may not always differentiate active from latent infection depending on the sample type or assay used. HHV-6 has the characteristic of being capable of integrating into the human genome (ciHHV-6), specifically in the telomeric area of all chromosomes. ciHHV-6 is characterized by persistent HHV-6 viral loads typically of over a million copies per mL of whole blood, which may be misinterpreted as active infection leading to unnecessary treatment. It is not known whether patients with ciHHV-6 may develop active infection. Qualitative or quantitative HHV-6 PCR of the cerebrospinal fluid is useful to diagnose HHV-6 encephalitis in patients with the appropriate clinical signs. Immunohistochemistry to detect viral antigens in biopsy specimens is appropriate in cases of organ disease, although it can be detected in the absence of symptoms.

#### 6.2.4.2 Prevention

Specific antiviral prophylaxis or preemptive therapy for HHV-6 infection is not recommended. Antiviral prophylaxis for CMV does appear to reduce the incidence of HHV-6 viremia.

#### 6.2.4.3 Treatment

Treatment of asymptomatic viral reactivation is not recommended. Ganciclovir, foscarnet, and cidofovir can be active against HHV-6. Ganciclovir is the drug of choice although some experts prefer to give foscarnet in case of CNS infection. HHV6-A can be resistant to ganciclovir though mutations in U69 and U28 genes. Foscarnet can be used in resistant HHV-6. Reduction in immunosuppression is important for severe disease.

**General Approach** The main recommendations for the management of HHV-6 infection are provided in Table 6.6.

### 6.2.5 Human Herpesvirus 8

#### 6.2.5.1 Diagnosis

Pretransplant serological screening is not routinely indicated due to a low specificity for screening, although it may be considered in geographic regions with high rates of infection. Quantitative PCR is the method of choice to detect viremia, which is associated with the development of Kaposi's sarcoma. PCR may be an option

**Table 6.6** Key recommendations for the management of human herpesvirus 6 infection after solid organ transplantation

| Area of interest | Recommendations |
|---|---|
| Diagnosis | Pretransplant IgG serostatus of donor and recipient is not recommended<br>Polymerase chain reaction is the diagnostic test of choice. In case of persistent high viral loads (>$10^6$), chromosomal integrated HHV-6 should be suspected<br>Routine monitoring for HHV-6 is not recommended<br>Diagnostic testing should be limited to symptomatic HHV-6 disease, in order to indicate treatment<br>PCR of the cerebrospinal fluid is useful to diagnose HHV-6 encephalitis |
| Prevention | Specific antiviral prophylaxis or preemptive therapy for HHV-6 infection is not recommended |
| Treatment | Treatment of asymptomatic viral reactivation is not recommended<br>Ganciclovir is the drug of choice<br>HHV6-A can be resistant to ganciclovir<br>Foscarnet can be used in resistant HHV-6 |

to monitor for risk of disease as a part of a preemptive strategy in selected high-risk individuals. In addition, HHV-8 viral load measurements can be used to assess response to therapy. Testing for the presence of HHV-8 in biopsy or fluid samples using immunohistochemistry, in situ hybridization, or PCR is also valuable.

#### 6.2.5.2 Prevention

The efficacy of antiviral prophylaxis in HHV-8-seropositive recipients or in patients receiving an organ from a seropositive donor is unknown. Avoidance of over-immunosuppression in high-risk individuals and in those with detectable HHV-8 viremia is advisable. Use of immunosuppression regimens containing sirolimus rather than calcineurin inhibitors may be indicated.

In high-risk patients, monitoring of HHV-8 viral load after transplantation may be a useful to determine the risk of disease. However, the frequency and duration of monitoring or the level of clinically relevant HHV-8 replication has yet to be determined. Moreover, once HHV-8 is detected, current data are insufficient to define a beneficial preemptive strategy with antivirals (ganciclovir, foscarnet, cidofovir),

#### 6.2.5.3 Treatment

An individualized reduction or cessation of immunosuppression (kidney transplant) is the first-line therapy for the treatment of Kaposi's sarcoma. Patients receiving a calcineurin inhibitor-based regimen should be switched to an mTOR inhibitor-based regimen. Sirolimus has antitumor properties and can block HHV-8 replication. Patients whose tumor lesions do not regress may require intralesional chemotherapy, surgical excision or radiation therapy or other local treatment for isolated lesions, or systemic chemotherapy for visceral or severe disease, using liposomal doxorubicin, paclitaxel, or other agents. The benefits of antiviral therapy with (ganciclovir, foscarnet, cidofovir) have been suggested but are unproven.

**Table 6.7** Key recommendations for the management of human herpesvirus 8 infection after solid organ transplantation

| Area of interest | Recommendations |
|---|---|
| Diagnosis | Pretransplant IgG serostatus of donor and recipient can be necessary in geographic areas with high rate of infection<br>Polymerase chain reaction is the diagnostic test of choice<br>Routine monitoring for HHV-8 is recommended in high-risk patients (seropositive donor or recipient) |
| Prevention | Antiviral prophylaxis with ganciclovir can be indicated in high-risk patient with an undetermined duration<br>Preemptive therapy can be indicated in high-risk patients |
| Treatment | First line:<br>– Reduction or cessation of immunosuppression (kidney transplant)<br>– Conversion to an mTOR inhibitor-based regimen of immunosuppression<br>Second line:<br>– Intralesional chemotherapy<br>– Surgical excision<br>– Radiation therapy or other local treatment for isolated lesions<br>– Systemic chemotherapy for visceral or severe disease (liposomal doxorubicin, paclitaxel, or other agents)<br>The benefits of antiviral therapy with ganciclovir, foscarnet, and cidofovir have been suggested |

**General Approach** The main recommendations for the management of HHV-8 infection are provided in Table 6.7.

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## Suggested Reading

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