



Review

# Management of Herpesvirus Infections in Hematopoietic Cell Transplant Recipients

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**Abstract:** Following primary infection, herpesviruses establish latency in infected individuals in the host cells and may reactivate upon external stimuli and during periods of immunosuppression. The objective of this paper was to present current strategies on preventive and therapeutic management of infections with herpesviruses in recipients of hematopoietic cell transplantation. Strategies of antiviral management include prophylaxis, pre-emptive treatment and targeted treatment. Empirical therapy is not used in antiviral strategies. Prophylaxis can be done at universal (preventive strategy) and specific level. Universal prophylaxis includes non-pharmacologic methods of prevention of infection or reactivation. Risk-adapted specific prophylaxis includes use of specific antivirals or cellular therapy or other specific methods in order to prevent specific infection, in high-risk groups. Pre-emptive therapy means use of therapeutic approaches in asymptomatic infection, detected by a screening assay. Targeted therapy is used in established specific viral end-organ infections. The following sections of the paper refer to prophylaxis and treatment strategies, respectively, against CMV, EBV, HSV, VZV, HHV-6, HHV-7, and HHV-8 after allogeneic hematopoietic cell transplantation.

**Keywords:** hematopoietic cell transplantation; CMV; EBV; VZV; HHV-6; HHV-7; HHV-8



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## 1. Introduction

Infections are a major threat for morbidity and mortality for patients undergoing hematopoietic stem cell transplantation (HCT). Infections create a main obstacle to the success of HCT, along with relapsed malignancy and graft-versus-host disease (GVHD) and finally might compromise the benefit of transplantation. However, the continuous progress in development of preventive strategies and regimens were introduced and became available [1]. Major etiological cause of infections are bacteria, fungi, viruses, and parasites. Viral infections are most frequently diagnosed in patients after allo-HCT, both in children and adults [2–4].

Viruses causing infection after allo-HCT can be divided as typically latent (mainly herpesviruses) or sporadic (mainly respiratory viruses) in nature [5]. The third group include hepatotropic viruses. Following primary infection, herpesviruses establish latency in infected individuals in the host cells and may reactivate upon external stimuli and during periods of immunosuppression. The sporadic or episodic infections are typically acquired after exposure rather than as being a result of a reactivation event [1]. The viral pathogenesis has a significant impact on the type of preventive antiviral strategy.

This paper is aimed to present current strategies on preventive and therapeutic management of infections with herpesviruses in recipients of hematopoietic cell transplantation.

## 2. ECIL Guidelines

This review is based on European Conference on Infections in Leukemia (ECIL) recommendations, which were developed between ECIL2 (2007) and ECIL8 (2019) editions. The ECIL is a common initiative of the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation (EBMT), the Infectious Diseases Group of

the European Organization for Research and Treatment in Cancer (EORTC), the Supportive Care group of the European LeukemiaNet, and the Immunocompromised Host Society (ICHS). Objectives of ECIL are: to elaborate European guidelines on prophylaxis, and treatment of infectious complications in leukemic patients; to obtain information about what are current management strategies in Europe; to favor communication between groups; and to define new areas of clinical research. The first edition of ECIL was held in 2005, and then it became biannual meeting, dedicated to selected topics. ECIL uses CDC-based grading system of recommendations, slightly modified during subsequent editions. To unify these differences, in this paper the simplified system of recommendations was adopted (Table 1).

**Table 1.** Grading system of recommendations.

STRENGTH OF A RECOMMENDATION
<ul style="list-style-type: none"> <li>• Grade A: ECIL strongly supports the recommendation for use</li> <li>• Grade B: ECIL moderately supports the recommendation for use</li> <li>• Grade C: ECIL marginally supports the recommendation for use</li> <li>• Grade D: ECIL is against the use of the recommendation</li> </ul>
QUALITY OF EVIDENCE
<ul style="list-style-type: none"> <li>• Level I: evidence from at least one properly designed randomized, controlled trial</li> <li>• Level II: evidence from at least one well designed clinical trial, without randomization; from cohort or case-controlled analytical studies (preferably from more than one center); from multiple time series; or from dramatic results of uncontrolled experiments</li> <li>• Level III: evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees</li> </ul>

### 3. Principles of Antiviral Management after HCT

Preventative and therapeutic antiviral strategies for the most threatening viruses in HCT setting are discussed in the following sections of this review. The basic concepts of dealing with viral infections include: pre-transplant risk assessment, universal and specific antiviral prophylaxis, monitoring viral infections after transplant with possibility of pre-emptive treatment, and therapy of established viral infections. Screening for reactivation and its monitoring with option of using preemptive treatment and/or application of specific antiviral prophylaxis in seropositive recipients plays a role in preventing infection and/or disease caused by latent herpesviruses such as cytomegalovirus (CMV), Epstein–Barr Virus (EBV), Human Herpes Virus 6 (HHV-6), and varicella zoster virus (VZV).

Assessment of pre-transplant risk can be considered for many viral infections. The risk can be assessed both in donors and recipients. There is a possible risk of transfer of some viral infections from donor. The risk of viral infections that might be transmitted with the graft from the donor is well-known in case of herpesviruses CMV, EBV, and HHV-6; hepatotropic viruses HBV and HCV; as well as in case of HIV, HTLV-1/2, and West Nile virus. Other viruses that give viremia include influenza, adenovirus, and parvovirus B19. Assessment of pre-transplant risk is an important tool that can be used for management decisions pre-, peri-, and post-transplant. It can either be used for diagnosis of antibodies (e.g., CMV, EBV, VZV), or the virus (e.g., community acquired respiratory viruses; CARV), or both (e.g., HBV).

World-wide using strategies both by donor registries, and transplant centers require pre-transplant risk assessment and screening patient for: HIV, HBV, HCV, CMV, EBV, VZV, HSV (most of them are also legally required); and screening donor for: HIV, HBV, HCV, CMV, EBV, HTLV-1, and HTLV-2. Many centers additionally, just before admitting the patient to the ward screen patients for: respiratory viruses including COVID-19, CMV, adenovirus, and norovirus in stool in children.

Strategies of antiviral management include prophylaxis, pre-emptive treatment, and targeted treatment (Table 2). Empirical therapy is not used in antiviral strategies. Prophylaxis can be done at universal (preventive strategy) and specific level. Universal prophylaxis includes non-pharmacologic methods of prevention of infection or reactivation. Risk-adapted specific prophylaxis includes use of specific antivirals or cellular therapy or other specific methods in order to prevent specific infection, in high-risk groups. Pre-emptive therapy means use of therapeutic approaches in asymptomatic infection, detected by a screening assay. Finally, targeted therapy is used in established specific viral end-organ infections. While universal prophylaxis is designed for all patients, for each subsequent strategy the number of patients needed treatment is lower and lower.

**Table 2.** Strategies for managing viral infection following hematopoietic cell transplantation.

Strategy	Management
General prophylaxis	To prevent viral infection/ reactivation
Risk-adapted prophylaxis	To prevent viral infection/ reactivation in high-risk subgroups
Pre-emptive treatment	Treatment of (a)symptomatic viral infection detected by a screening assay in order to prevent viral disease
Targeted treatment	Treatment of end-organ viral disease

#### 4. Cytomegalovirus (CMV)

Cytomegalovirus (CMV), classified as the beta human herpesvirus type 5 (HHV-5), is a major cause of serious complications in recipients of allo-HCT [6]. While primary CMV infection in overall healthy individuals is usually asymptomatic, or it manifests as mononucleosis-like syndrome or a self-limited febrile sickness, its reactivation in allo-HCT recipients might be life-threatening [7].

CMV infection directly or indirectly adversely affect transplant outcomes [8]. Direct end-organ toxicity is the harmful effect of the virus itself; indirect CMV toxicity is caused by development of side effects of antiviral therapy and virus-related suppression of the immune system [9]. CMV replication after allo-HCT has been associated with increased non-relapse mortality [10]. Recipient pre-transplant CMV-seropositivity, recipient and donor status, post-transplant CMV reactivation or infection, and CMV disease lead to decrease survival after HCT [10–12].

##### 4.1. Prevention of Cytomegalovirus Reactivation and Disease

**Donor and recipient cytomegalovirus serological status.** In order to prevent primary CMV infection in CMV-seronegative recipient of allo-HCT, donor CMV-match selection, transfusion policy (i.e., tested safe blood products, including leukodepleted and filtered red cell and platelet concentrates) [7]. In pre-transplant phase it is mandatory that all patients and donors are tested for CMV IgG antibodies (AII) [6]. It is recommended to select CMV-seronegative donor for a CMV-seronegative recipient (AI; except haploidentical-HCT: AIII), and CMV-seropositive donor for CMV-seropositive recipient, if possible (BII) [6]. Any strategies permissive for any CMV reactivation with the aim of reducing leukemic relapse are discouraged, since any CMV replication after HCT increases the risk of overall mortality [10].

**Cytomegalovirus monitoring.** Patients after allo-HCT should be monitored for CMV DNA-emia in plasma or whole blood (AII) by qPCR assays which are more sensitive than detecting viral antigen pp65 (BII) [13], thus being the primary choice for most of transplant centers for monitoring viral load in everyday clinical practice. On the other hand, in case of suspected tissue involvement, the presence of tissue CMV should be documented by histopathology, immunohistochemistry, rapid culture, virus isolation, or DNA hybridization techniques and supported by the absence of other documented causes of pathology. It should be underlined that for a given patient, CMV monitoring should be done with the same method of DNA extraction, the same specimen type and PCR assay.

Monitoring should be done at least once weekly for the first 100 days after HCT (AII). Longer monitoring is usually recommended in patients with chronic GVHD, in case of previous CMV reactivation, in patients after mismatched, cord blood, or haploidentical HCT (without post-transplant cyclophosphamide); also in those being on long-term effective prophylaxis, or displaying persistent immunodeficiency (AIII). In spite of progress in PCT standardization, still the threshold of CMV-DNA to start pre-emptive therapy has not been well enough defined in order to be sure to involve all possible clinical situations. CMV DNA threshold values for pre-emptive therapy should be adapted locally according to the monitoring technique used, PCR standardization, and the transplant method (AIII). Immunological monitoring of allogeneic HCT recipients is recommended, at the minimal level of lymphocyte subpopulations, and preferentially with sequential monitoring of interferon- $\gamma$ -producing cytomegalovirus-specific T cells (BII) [6].

Prevention of cytomegalovirus replication by systemic antiviral chemoprophylaxis is aimed to prevent CMV reactivation in CMV-seropositive patients. Current pharmacological management strategies to prevent CMV infection (primary or reactivation) or CMV disease in recipient of allo-HCT include prophylaxis or pre-emptive therapy. Prophylaxis is defined as a strategy that antiviral agents is given to a patient either to prevent a primary, reactivated or recurrent CMV infection. Pre-emptive therapy is a strategy where antiviral agents are given for an asymptomatic CMV infection detected by a specific screening assay [6,14].

#### 4.2. Prophylaxis of CMV Infection

**Primary prophylaxis.** Prophylaxis of CMV infection was usually not preferred option in allo-HCT recipients, because of toxicity of (val)ganciclovir and foscarnet, or low effectiveness of (val)acyclovir (Table 3). The use of letermovir (LMV), a new antiviral drug, has shown improved option of anti-CMV prophylaxis, and probably has changed the landscape of anti-CMV management in HCT setting. LMV is a CMV terminase inhibitor, which was used in a 14-week prophylactic regimen in CMV-seropositive HCT recipients [15]. LMV has reduced clinically significant CMV infection (csCMVi) at 24 weeks without major toxic effects [6]. All-cause mortality has been reduced in patients treated with LMV at 24 and 48 weeks [10,15,16]. The positive effects of antiviral prophylaxis in allo-HCT recipients was confirmed in over 800 patients in real-world analysis [7]. Currently, there might be a rationale for a universal prophylaxis with LMV in all CMV+ recipients (R), since all the categories of patients (low risk, high risk) benefit from the prophylactic effect of LMV including a tendency to lower mortality. Another rationale is that patients might develop severe complications from CMV infections despite not being regarded as high risk.

**Secondary CMV prophylaxis.** There is also a rationale for secondary prophylaxis, and for delayed targeted strategy. While we are aware of the good effect of pre-emptive therapy in most standard or low risk patients, still half of the patients who develop one CMV episode will have at least one recurrence. While the first episode of a CMV reactivation is frequently easily managed at least in standard risk patients, it becomes more difficult in clinically resistant cases. Thus, the secondary prophylaxis in patients who have experienced one episode can be considered. It has already been shown that secondary anti-CMV prophylaxis with LMV is a safe and effective approach in a large proportion of patients, targeted at high-risk patients for additional CMV recurrence [17]. However, no prospective controlled trial was performed so far. When primary prophylaxis for CMV+ recipients is the standard, a secondary prophylaxis would have restricted indications: the use after treatment of primary infection (including D+/R-); CMV infection/disease occurring after the end of primary prophylaxis; and patient who did not receive primary prophylaxis with LMV upfront.

**Table 3.** Recommendations for antiviral pre-emptive treatment for cytomegalovirus (CMV) viremia.

Intervention	Prophylaxis	Pre-Emptive Treatment	
		First Line	Second Line
LETERMOVIR	AI		
GANCICLOVIR 10 mg/kg/day divided in two doses; maintenance dose 5 mg/kg/day for 7–14 days, until PCR negativity.	CI	AI	AII (if not used in first line therapy)
FOSCARNET 180 mg/kg/day in 2–3 doses	DII	AI	AII (if not used in first line therapy)
VALGANCICLOVIR	CII	AII	
COMBINATION THERAPY (GANCICLOVIR+ FOSCARNET)		DIII	CII
CIDOFOVIR 5 mg/kg, administered weekly. Hyperhydration oral probenecid is mandatory due to risk of acute kidney injury.		-	BII
REDUCTION OF IMMUNOSUPPRESSION		-	BIII
ACYCLOVIR	CI		
LEFLUNOMIDE/ARTESUNATE			CIII
Intravenous immunoglobulins (IVIG)	DI		DIII

#### 4.3. Preemptive Therapy against CMV Disease

In the year 2019, preemptive therapy is regarded to be the standard strategy for CMV prevention after allogeneic HCT [6,14,18,19]. In preemptive strategy, patients are monitored for CMV reactivation usually by PCR. Detection of asymptomatic CMV reactivation above a “viral load threshold” leads to the introduction of preemptive treatment, in order to prevent CMV disease. Current ECIL7 recommendations for first- and second-line preemptive therapy for allo-HCT recipients are shown in Table 3 [6].

The pitfall of preemptive therapy is that the strategy of viremia-guided preemptive therapy still allows for CMV reactivation. Although preemptive treatment of asymptomatic CMV reactivation is efficacious in reducing tissue invasive CMV disease, emerging data suggest a negative long-term effect of CMV replication [10]. The duration of anti-CMV treatment should be at least 2 weeks, aiming for at least one negative test for presence of CMV. Increasing CMV-DNA-emia within the first 2 weeks of antiviral therapy does not indicate a need of changing the therapy. If CMV is still detected after 2 weeks of therapy, additional maintenance therapy with an antiviral compound given once daily can be considered. Repeated courses of additional pre-emptive therapy or a prolonged initial pre-emptive therapy might be necessary in patients showing slow or delayed decrease in viral load [6].

#### 4.4. Treatment of Cytomegalovirus Disease

Antiviral therapy with intravenous ganciclovir is recommended by ECIL-7 for CMV disease as the first-line option (AII) [6]. Addition of G-CSF can be considered in case of neutropenia to allow prolonged ganciclovir therapy. Foscarnet can be used instead of ganciclovir in case of toxic effects or evidence of antiviral resistance (AIII). No positive effect of standard or CMV-specific immunoglobulins on outcome of CMV infection was shown in any studies, thus its use is rather controversial. There are, however, evidences that addition of IVIG or hyperimmunized CMV-Ig to antiviral therapy can be justified for the treatment of CMV pneumonia (CIII). Intravitreal injections of ganciclovir or foscarnet can be recommended for the treatment of CMV retinitis, usually combined with systemic therapy (BII). Oral valganciclovir can be used alternatively in place of intravenous ganciclovir or

foscarnet, with exception of patients with severe gastrointestinal GVHD (BIII). Cidofovir (CDV) or the combination of intravenous ganciclovir and foscarnet are other second- or third-line therapies for CMV disease (BII).

**CMV pneumonia.** The risk for CMV pneumonia increases with increasing CMV-DNA load; however, a definite threshold value for CMV-DNA load for introduction of beginning treatment of any diagnosis of organ involvement cannot be established. Performing bronchoscopy with broncho-alveolar lavage (BAL) is largely desired diagnostic approach in case of suspicion of CMV pneumonia. A negative CMV-DNA test in the BAL fluid has a high negative predictive value close to 100% and practically excludes the possibility of CMV pneumonia. The cut-off value for blood/plasma CMV-DNA-emia might be differentiated between transplant centers, different patients and specificity of performing the BAL procedure and the CMV-DNA quantitation assay used. Severity of CMV pneumonia can obviously influence on CMV-DNA levels, what may impact the clinical decisions. A CMV-DNA viral load >200 IU/mL in BAL fluid has already a good positive predictive value in diagnosing pneumonia in allo-HCT recipients, while lower levels in BAL might indicate pulmonary shedding. Recommendation for antiviral therapy of CMV pneumonia are presented in Table 4. There is no strictly recommended time of therapy of CMV disease. In case of CMV pneumonia, it is usually 21–28 days of induction therapy, followed by at least 7–14 days of maintenance treatment [6].

**Table 4.** Treatment of CMV pneumonia.

Intervention	Dosage as in Pre-Emptive Treatment
FIRST LINE OF THERAPY	
Ganciclovir iv (AII)	Therapy of choice for at least 21 days. Dosage: 10 mg/kg/day divided in two doses; maintenance dose 5 mg/kg/day for 7–14 days, until PCR negativity.
Foscarnet iv (AIII)	180 mg/kg/day in 2–3 doses.
CMV-IVIG (CIII)	500 mg/kg every 48 h; 7–10 doses, followed by weekly administration for 2–4 weeks
SECOND/THIRD LINE OF THERAPY	
Cidofovir	Typical dose 5 mg/kg, administered weekly. Hyperhydration oral probenecid is mandatory due to risk of acute kidney injury.
Foscarnet + Ganciclovir (BII)	
Adoptive immunotherapy (BII)	Cytotoxic T-lymphocytes CMV-CTL (VST: viral specific T-cells)

Maribavir was shown to be effective for resistant or refractory CMV disease both in a phase 2 [20] and phase 3 study [21]. No data exist so far to support the use of letermovir or brincidofovir as treatments for CMV disease, and thus no recommendations can be given for these drugs.

**Management of CMV infection and disease after auto-HCT.** The risk of CMV infection in auto-HCT recipients is 30–50% in seropositive individuals, but in comparison to allo-HCT recipients, the risk of CMV disease incidence and frequency is <1%. The risk of CMV reactivation can be increased in case of CD34-selected patients and in patients receiving anti-thymocyte globulin (ATG) for the treatment of autoimmune disease. Nevertheless, for patients undergoing auto-HCT, routine monitoring and pre-emptive anti-CMV therapy is not recommended (DII). Still, high-risk recipients of auto-HCT, such as patients with autoimmune disease with CD34 selection or those receiving ATG, monitoring and the use of pre-emptive therapy might be beneficial (CII) [6].

## 5. Epstein-Barr Virus (EBV)

EBV infection may be associated with a heterogeneous group of diseases, including non-neoplastic and neoplastic diseases, such as infectious mononucleosis (IM), various types of lymphomas, or nasopharyngeal carcinoma. Primary EBV infection or reactivation usually induces an asymptomatic infection or IM in immunocompetent people. If the

balance between EBV-infected cells and the immune system is disrupted, EBV may result in a wide spectrum of diseases, ranging from fever to lymphoproliferative diseases in immunocompromised people. In recipients of allogeneic HCT, the spectrum of diseases includes asymptomatic EBV DNA-emia, fever, post-transplant lymphoproliferative disorder (PTLD), and end-organ diseases (pneumonia, encephalitis/myelitis, and hepatitis) (Table 5). Additionally, EBV contributes to development of acute and chronic GVHD [22–24].

**Table 5.** Manifestations of Epstein–Barr (EBV)-related diseases after transplantation.

EBV-Related Diseases after Allo-HCT
<ul style="list-style-type: none"> <li>• Asymptomatic infection with/without fever</li> <li>• EBV hepatitis</li> <li>• Meningoencephalitis</li> <li>• Lymphocytic interstitial pneumonitis</li> <li>• Hemophagocytic lymphohistiocytosis (HLH)</li> <li>• Oral hairy leukoplakia</li> <li>• Post-transplant lymphoproliferative disease (PTLD): plasmacytic hyperplasia, infectious mononucleosis, florid follicular hyperplasia, polymorphic, monomorphic (B-cell and T-/NK-cell types), and classical Hodgkin lymphoma.</li> </ul>

The most severe form of EBV-related complications after HCT is PTLD. It occurs in about 3% of patients, with differences dependent on type of transplantation. The following risk factors for PTLD are recognized: unrelated or HLA-mismatched transplant, the use of thymoglobulin, in vitro or in vivo T-cell depletion, cord blood transplant, serological EBV incompatibility between donor and recipient, and splenectomy.

#### 5.1. Diagnosis of EBV-PTLD after Allo-HCT

The diagnosis of PTLD includes: (A) a physical examination; (B) imaging, including PET or CT scan of the thorax or abdomen. In case of gastro-intestinal symptoms, endoscopy is recommended; (C) biopsy with histologic confirmation by EBV-encoded RNA (EBER) and molecular studies; (D) EBV-DNA viral load tested using PCR. Any lesions suspected for PTLD should undergo imaging and biopsy followed by a histological evaluation.

#### 5.2. Treatment of EBV-PTLD

The following treatment of PTLD is recommended (Table 6) [25]: (A) anti-proliferative therapy with anti-CD20 monoclonal antibodies (rituximab); (B) reduction of immunosuppression (RIS); (C) immunotherapy with EBV-specific cytotoxic T-cells; alternatively an infusion of donor lymphocytes (DLI) can be considered, in order to restore T-cell reactivity. Other therapies, including chemotherapy, antiviral agents, interferon, surgery, or intravenous immunoglobulins (IVIG), are not recommended. The use of rituximab is a therapy of choice for EBV-PTLD after allo-HCT. Reduction or withdrawal of immunosuppression when applied in addition to rituximab improves the outcome of EBV-PTLD.

*Treatment of EBV-negative PTLD or T-lineage PTLD.* EBV-negative B-lineage PTLD, which usually present lately (>5 years) after HCT, should be regarded as malignant lymphoma and treated with appropriate chemotherapy protocols. T-lineage PTLD are extremely rare after HCT; these cases also should be treated according to appropriate chemotherapy protocols for malignant lymphomas.

**Table 6.** Anti-EBV-post-transplant lymphoproliferative disorder (PTLD) prophylaxis and therapy.

Treatment Strategy	Prophylaxis	Preemptive Therapy	Therapy of PTLD		
			First Line	Second Line	CNS Involvement
Rituximab	CII	BII	AII	AII	BIII
RIS		BII	AII		
Rituximab + RIS		AII	AII	AII	
CTL	CII	CII	CII	BIII	CIII
DLI				BIII	
Chemotherapywith rituximab				CII	BII
Radiotherapy					CIII
Antivirals	DII	DII	DII	DIII	DII
IVIG	DIII			DIII	
Surgery				DIII	

RIS—reduction of immunosuppression; CDV—cidofovir; DLI—donor lymphocyte infusion; CTL—cytotoxic T-lymphocytes.

## 6. Herpes Simplex Virus (HSV)

HSV types 1 and 2 commonly cause typical mucocutaneous lesions. Most of adult and large proportion of pediatric patients are HSV seropositive. Most of HSV symptoms in patients after HCT result from reactivation of latent herpesvirus. Majority of these lesions occur during the first month after HCT. Prophylaxis with antiviral drug is recommended to be given to HSV-seropositive patients, with the aim to shorten the duration of HSV disease, as well as the prevention of the HSV dissemination to the form of visceral disease which might be the life-threatening condition.

The diagnosis of mucocutaneous HSV disease is made on clinical basis. Its presence can be confirmed by PCR (BIII), but this is done rarely. Serological tests are used for identification of the seropositive patients before HCT (BII), while are not useful in the diagnosis of HSV reactivation in post-transplant phase. Routine screening for HSV reactivation by PCR assay after HCT is not recommended. On the other hand, diagnosis of visceral HSV disease is difficult and this suspicion should be confirmed by PCR method (BIII). In case of HSV meningitis and/or encephalitis, PCR assay for HSV-DNA in cerebro-spinal fluid (CSF) is necessary (AII) [26,27].

### 6.1. Prevention of HSV Disease

**HSV seronegative patients.** Prophylaxis with antiviral drug in HSV-seronegative patients after HCT or during chemotherapy is thus not recommended (DIII), since primary HSV infections in these patients are unusual.

**HSV seropositive patients.** HSV-seropositive patients undergoing allo-HCT should receive antiviral drug prophylaxis (AI), and HSV-seropositive patients treated for acute leukemia by chemotherapy should also be considered for antiviral prophylaxis (BIII). In HCT patients, prophylaxis is recommended with oral acyclovir  $3 \times 200$  mg/d to  $2 \times 800$  mg/d po (AI), intravenous acyclovir 250 mg/m<sup>2</sup> or 5 mg/kg q12h iv (AI), oral valaciclovir  $2 \times 500$  mg/d (AII), or oral famciclovir  $2 \times 500$  mg/d (BIII) for 3–5 weeks after HCT or after the start of chemotherapy. Even longer periods of prophylaxis is recommended in children treated for acute leukemia (BIII) or in patients with graft-versus-host disease (GVHD) or receive immunosuppressive treatment including steroids (BII). The intravenous administration is recommended in patients who develop severe mucositis during chemotherapy or radiotherapy (CIII) [26,27].



## 6.2. Therapy of HSV Disease

Intravenous acyclovir 250 mg/m<sup>2</sup> or 5 mg/kg every 8 h for 7–10 days is the therapy of choice for severe mucocutaneous or visceral HSV disease (AI). For HSV pneumonia or HSV meningitis and encephalitis, a higher dose of intravenous acyclovir 500 mg/m<sup>2</sup> or 10 mg/kg every 8 h for 14–21 days, is recommended (CIII). For less serious manifestations of HSV disease, oral acyclovir, from 5 × 200 mg/d to 5 × 400 mg/d for 10 days (AI), valacyclovir 2 × 500 mg/d for 10 days (BIII), or famciclovir 2 × 500 mg/d for 10 days (BIII) may be considered as alternatives [26,27].

In case of clinical resistance and unresponsiveness to antiviral therapy given at appropriate dose, resistance testing should be performed (CIII). This happens rarely, and in this case intravenous foscarnet 60 mg/kg every 12 h or 40 mg/kg every 8 h for 7–21 days or until complete healing is recommended (BIII). Cidofovir 5 mg/kg intravenously once a week for 2 weeks, then once every 2 weeks with simultaneous administration of probenecid and high hydration is also recommended if resistance occurs (BIII). Topical treatment with trifluridine 5% ophthalmic solution every 8 h or topical 0.3% or 1% cidofovir gel once daily (CIII) [26,27].

## 7. Varicella-Zoster Virus (VZV)

Clinical manifestations of infection with VZV are varicella (chickenpox) and herpes zoster (shingles). Primary VZV infection causes varicella, a common childhood disease. After primary VZV infection, the virus establishes latency in the dorsal root ganglia. Reactivation results in herpes zoster appearing as painful vesicular lesions in the distribution of dermatomes in the immunocompetent host. Visceral dissemination of VZV can manifest as encephalitis, hepatitis, or pneumonia and may include abdominal pain (which may precede the rash), nausea, vomiting and diarrhea, moderately or profoundly elevated liver and pancreatic enzymes. Hemorrhagic varicella may sometimes occur. Seronegative HCT recipients are at risk of developing varicella after being exposed to an individual with VZV infection. In immunocompromised patients, varicella can manifest as a very severe disease. The risk of varicella is at its highest in the first 24 months after HCT, or even beyond this time if patient is still on immunosuppressive treatment and/or having chronic GVHD.

Diagnosis of VZV is based on clinical symptoms. In case of unclear situation or suspicion of visceral disease, PCR for VZV DNA is considered the best diagnostic tool. Samples from vesicles, crusts, throat swabs tissue of infected viscera, CSF in case of VZV encephalitis can be used. PCR of blood samples (serum/plasma) can document VZV DNA viremia in HCT recipients with zoster. PCR can also distinguish vaccine strain from wild-type VZV in clinical specimens.

### 7.1. Management after Exposure to VZV

The medical staff should advise on anti-VZV precautionary measures to patients and their guardians (AII). HCT recipients should avoid exposure to people with chickenpox or zoster (AII), and vaccine recipients experiencing a rash after varicella vaccine (BIII). Such rash might develop in up to 5% of children and 10% of adults within one month after vaccination. Family members, and household contacts known to be VZV-seronegative or children with no history of VZV infection preferentially should be given varicella vaccine at least 4 weeks before start of conditioning (BIII). Patients with varicella or disseminated herpes zoster should be placed under airborne and contact isolation. This isolation should continue until the rash remains vesicular and all zoster lesions are crusted (BIII) [26,27].

VZV is transmitted by inhalation of respiratory secretion or by direct contact with an individual with VZV disease. VZV transmission by marrow or stem cell products has not been documented. Varicella develops in approximately 90% of susceptible immune competent household contacts to an individual with varicella. The incubation period is 10–21 days after initial contact, but may be prolonged for up to 28 days in immunocompromised patients, who have received varicella-zoster immune globulin VZIG for prophylaxis.

**VZV seronegative patients.** In case of contact with varicella or zoster, airborne precautions should be instituted no later than 7 days after the first contact and continued at least until 21 days post-exposure or 28 days after the last exposure if the patient received passive immunization against VZV (AIII) [26]. Exposure for immunocompromised patient which necessitates intervention in case of varicella is defined as face to face contact of at least 5 min or intimate contact (touching or hugging) with a person with varicella or with disseminated herpes zoster. Patients residing in the same household with a contagious person or in the same room in hospital are also at risk.

Passive immunization with VZIG after the exposure is rarely used nowadays. If this is the case, VZIG at a dose of 0.2–1 mL/kg intravenously or intramuscularly, or IVIG at dose 300–500 mg/kg should be given within 96 h after the exposure. This refers to patients within the first 2 years after HCT, those who have chronic GVHD, and are receive immunosuppressive treatment (AII). After exposure to VZV, seronegative HCT patients should receive antiviral prophylaxis if they were exposed to a VZV vaccinee presenting with varicella-like rash, since it may be contagious (BIII) [26].

Antiviral post-exposure prophylaxis should be: acyclovir ( $4 \times 800$  mg;  $4 \times 600$  mg/m<sup>2</sup> for children), or valaciclovir ( $3 \times 1000$  mg;  $3 \times 500$  mg if body weight <40 kg), or famciclovir ( $3 \times 500$  mg). Treatment duration should be 3–21 days after exposure (AIII). In case of another exposure occurring >21 days after a passive immunization or antiviral prophylaxis was administered, it is recommended that another prophylaxis should be applied (CIII) [26,27].

**VZV seropositive patients.** There is no rationale for antiviral prophylaxis in VZV-seropositive patients after exposure. This is particularly important due to scarcity and cost of VZIG, as well as lack of evidences on its efficacy. Nowadays, antiviral prophylaxis in VZV-seropositive HCT recipients is optional (CIII) [26].

### 7.2. Prevention of VZV after HCT

Testing for VZV IgG serostatus before transplant should be done in all allo-HCT candidates (AIII). Antiviral prophylaxis with acyclovir/valaciclovir is still the primary and optimal mode of prevention in HCT recipients. It is an effective, cheap, and safe approach, and it should be given for at least one year after allo-HCT and for 3–6 months after auto-HCT. Prophylaxis with oral acyclovir ( $2 \times 800$  mg; for children:  $2 \times 20$  mg/kg) or valaciclovir ( $2 \times 500$  mg) is recommended for one year after HCT (AII), or even longer in case of GVHD with immunosuppressive therapy (BII) [26]. On the other hand, there is no rationale for prophylaxis in auto-HCT recipients.

### 7.3. Vaccination

According to ECIL-7 guidelines for VZV-vaccination after HCT, live attenuated varicella-vaccine has limited immunogenicity with response 13–64% after 1 dose given at 12–38 months. Risk of vaccine-related varicella is possible. Nevertheless, it can be considered in a carefully selected population after HCT for prevention of varicella. Live-attenuated VZV vaccine is not recommended in HCT-recipients (DIII). Live-attenuated VZV vaccine (LAVV) is contraindicated in HCT-recipients with active GVHD, relapse of the underlying disease, or ongoing immunosuppression (DIII). In adolescents >13 years and adults, one dose of LAVV (Varilrix) can be considered in a seronegative patient >24 months after transplant, in overall good clinical condition, without signs and symptoms of GVHD, without immunosuppressive therapy, without relapse of the underlying disease, and without immunoglobulins administration since at least 8 months (BII). The addition of a second dose after 6 weeks in adults may be considered in patients who were seronegative before HCT or had no history of VZV infection. Vaccination of individuals >12 months or recent (3 days) exposure to varicella with 2 doses (Varivax) at >1 month interval can be considered. Patients should be additionally informed about the risk of varicella-like rash occurring at a median of 21 days after vaccine shot, in order to receive early antiviral treatment if necessary. New inactivated zoster vaccine V212, not yet commercially available showed

safety in HCT recipients, promising data in auto-HCT, but it was poorly immunogenic in allo-HCT recipients [27–29].

#### 7.4. Treatment of VZV Disease

In HCT recipients and patients treated for leukemia who have a varicella-like rash treatment should be started immediately with intravenous acyclovir 500 mg/m<sup>2</sup> every 8 h (AI). Strict clinical assessment for the possibility of visceral VZV disease even without mucocutaneous manifestations (e.g., in cases of encephalitis, meningoencephalitis, pneumonitis or hepatitis) is necessary, and intravenous acyclovir 500 mg/m<sup>2</sup> every 8 h should be considered in such cases (AIII). Oral valacyclovir (3 × 1000 mg), famciclovir (3 × 500 mg), acyclovir (5 × 800 mg; pediatric dose: 4 × 20 mg/kg daily), or brivudin (125 mg once daily; pediatric dosage: 5 mg/kg/day in 3 divided doses), for 7 days, are other options for recipients with VZV stable localized disease (CII). Brivudin is contraindicated in patients receiving 5-fluoropyrimidines derivatives (DII). Therapy should be continued for at least 7 days and for at least 2 days after all lesions are crusted (AI). In case of a vesicular rash following exposure to varicella vaccine should be managed in the same way (BIII). If VZV acyclovir-resistant infection occurs, an intravenous foscarnet (2 × 60 mg/kg) or cidofovir (5 mg/kg weekly for 2 weeks, followed by one dose every 2 weeks combined with oral probenecid and intravenous hydration) is recommended (AIII) [26,27].

### 8. Human Herpes Virus 6 (HHV-6)

Two human herpesvirus-6 are known to be distinct species: HHV-6A and HHV-6B. So far it is not known if HHV-6A might cause any specific disease, while HHV-6A is an etiology of exanthema subitum in young children (usually during first 2 years of life), and might cause encephalitis after HCT. Additionally, chromosomally integrated HHV-6 (CIHHV-6) is of clinical significance. Both HHV-6 species, typical for herpesviruses, after primary infection establish latency and persist in different cells including monocytes, CD4-positive T-lymphocytes, epithelial, fibroblastic, and neuronal cells [14].

Chromosomally integrated HHV-6 occurs with 1% of prevalence in the general population and is inherited from the mother or father via vertical transmission. In such a case, HHV-6 is present in every nucleated cell, usually there is 1 copy of HHV-6 DNA per leukocyte, and HHV-6 DNA is detected in hair follicles and nails. CIHHV-6 has been shown to have disease association: with angina pectoris, with hemophagocytosis, encephalitis, and is associated with a GVHD and CMV reactivation, and increased all-cause mortality [30]. There is little data on any specific HHV-6-related diseases in patients after auto-HCT or with non-HCT hematologic malignancies.

**Definitions.** Primary HHV-6 infection means the detection of HHV-6 in a patient without evidence of previous HHV-6 exposure [31]. Reactivation of HHV-6 means detection of HHV-6 in a patient with evidence of previous HHV-6 exposure. In both cases CIHHV-6 must be excluded, including donor-derived CIHHV-6 in case of allo-HCT. Standardization for HHV-6B DNA is already available. CIHHV-6 is diagnosed when viral genome is integrated into a chromosome. CIHHV-6 reactivation is diagnosed when integrated virus is confirmed by virus culture plus sequencing the viral genome, confirming its identity with the integrated virus. HHV-6 DNA can be detected in latent form in every nucleated cell in the body. CIHHV-6 is determined by quantitative PCR in blood/serum, and by FISH in hair follicles or nails [14,31].

**Chromosomally integrated human herpesvirus 6 (CIHHV-6).** In case of donor CIHHV-6 presence, HHV-6 blood viremia will increase after HCT when leukocyte engraftment occurs. In this situation antivirals will not decrease quantity of integrated latent viral DNA. Opposite, in case of recipient CIHHV-6 presence, blood HHV-6 viremia will decrease after HCT, but HHV-6 DNA will be present in non-hematopoietic cells. Routine testing of HCT donors or recipients for CIHHV-6 is not recommended nowadays. If CIHHV-6 needs to be diagnosed for, negativity for blood/serum HHV-6 DNA performed before transplant in donor or recipient excludes CIHHV-6. Presence of CIHHV-6 can be confirmed by detection

of one copy of HHV-6 DNA per cellular genome or by presence of HHV-6 DNA in nails and hair follicles occurs only in patients with CIHHV-6 or by FISH testing showing integration of HHV-6 into a chromosome. Testing plasma/blood is not recommended. CIHHV-6 reactivation must be diagnosed by virus culture plus viral genome sequencing in order to confirm identity of integrated viral with the virus isolate [14,31].

**Risk factors** for HHV-6 encephalitis after allo-HCT include HHV-6 reactivation, with high viremia in blood or plasma, cord blood transplantation, acute GVHD grade II-IV and occurrence of pre-engraftment syndrome. Most of these risk factors are common for other viral infections, thus the co-infections of different viruses either simultaneously or sequentially is a common phenomenon [14].

**Diagnosis of HHV-6B encephalitis** should be based on clinical symptoms of encephalopathy (such as altered mental status, seizures, short-term memory loss) and presence of HHV-6 DNA in CSF. It requires exclusion of CIHHV-6 in donor and recipient, as well as other infectious and non-infectious causes. In case of detection of CIHHV-6, testing for evidence for CIHHV-6 reactivation in the CSF or brain tissue is required to confirm CIHHV-6 [14,31].

**Diagnosis of HHV-6B myelosuppression and graft failure**, require testing of blood or bone marrow for presence of HHV-6B DNA. Exclusion of CIHHV-6 in donor and recipient, as well as other infectious and non-infectious causes is necessary. Possibility of other HHV-6 end-organ diseases is low. In case of suspicion of pneumonia, a bronchoalveolar lavage samples should be tested for HHV-6 DNA, however, the clinical value of its presence is still not determined [14,31].

#### *Treatment Strategies for HHV-6 Infection*

**Prevention.** Routine blood screening for HHV-6 after allo-HCT is not recommended (DII). No effective prophylactic or pre-emptive strategies have been identified, and are not recommended (DII).

**Treatment of HHV-6 encephalitis.** In case of HHV-6-related encephalitis or any other HHV-6-related end-organ disease, ganciclovir or foscarnet are recommended (AII). The typical dose is  $2 \times 5$  mg/kg for ganciclovir, and  $2 \times 90$  mg/kg for foscarnet (AII). Treatment should be continued for at least 3 weeks and until negativity of HHV-6 DNA in blood and/or CSF (CIII). Combination therapy with ganciclovir and foscarnet can be considered (CIII). Reduction of immunosuppressive treatment is recommended, if possible (BIII) [14,31]. The data on the use of cidofovir against HHV-6 are insufficient to make any recommendations.

A new therapeutic approach is the adoptive immunotherapy with the use of virus-specific T (VST) cells (previously CTL: cytotoxic T-lymphocytes). This approach is a safe and effective method both in donor and third-party donor settings. The experience is however based on small and uncontrolled studies only, so no recommendations can be given so far.

### **9. Human Herpes Virus 7 (HHV-7)**

HHV-7 primary infection is a cause of *exanthema subitum (roseola)* in young children. Most children by the age of 5 years are infected with this virus. HHV-7 detection after HCT occurs in about 10% of patients, and it might be rarely associated with encephalitis or myelitis. Risk factors for HHV-7 infection include: allogeneic HCT, use of TBI, pediatric age, and CMV reactivation. Presence of HHV-7 DNA is diagnosed by qPCR. Specific prophylaxis against HHV-7 is not used, and infection with this virus does not require specific targeted treatment [14,27].

### **10. Human Herpes Virus 8 (HHV-8)**

HHV-8 (Kaposi's sarcoma-associated herpesvirus, KSHV) is the etiologic cause of Kaposi's sarcoma, primary effusion lymphoma and Castleman's disease. HHV-8 is very rare after HCT, and can manifest as fever, skin involvement (mainly in adults), bone mar-

row aplasia, plasmocytosis, visceral dissemination (mainly in children). The diagnosis of Kaposi sarcoma with skin lesions is clinically-based as a malignant tumor should be confirmed histopathologically [32]. HHV-8 DNA is diagnosed by qPCR. Due to its rarity, prophylaxis is not necessary. In cutaneous disease, surgical treatment or electrochemotherapy is preferable approach. In disseminated disease, interferon-alpha or chemotherapy is recommended. Antiviral treatment is not efficacious [14,27,33].

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