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REVIEW

Human herpesvirus-6 infections in kidney, liver, lung, and heart transplantation: review

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Summary

Human herpesvirus-6 (HHV-6), which comprises of HHV-6A and HHV-6B, is a common infection after solid organ transplantation. The rate of HHV-6 reactivation is high, although clinical disease is not common. Only 1% of transplant recipients will develop clinical illness associated with HHV-6 infection, and most are ascribable to HHV-6B. Fever, myelosuppression, and end-organ disease, including hepatitis and encephalitis, have been reported. HHV-6 has also been associated with various indirect effects, including a higher rate of CMV disease, acute and chronic graft rejection, and opportunistic infection such as invasive fungal disease. All-cause mortality is increased in solid organ transplant recipients with HHV-6 infection. HHV-6 is somewhat unique among human viruses because of its ability to integrate into the host chromosome. The clinical significance of chromosomally integrated HHV-6 is not yet defined, although a higher rate of bacterial infection and allograft rejection has been suggested. The diagnosis of HHV-6 is now commonly made using nucleic acid testing for HHV-6 DNA in clinical samples, but this can be difficult to interpret owing to the common nature of asymptomatic viral reactivation. Treatment of HHV-6 is indicated in established end-organ disease such as encephalitis. Foscarnet, ganciclovir, and cidofovir have been used for treatment.

Introduction

Human herpesvirus-6 (HHV-6) was first isolated from the peripheral blood lymphocytes of immunocompromised patients in 1986 [1]. HHV-6 belongs to the β-herpes subfamily, and it is closely related to human cytomegalovirus (HCMV) and human herpesvirus-7 (HHV-7). All these β-herpesviruses are ubiquitous and they infect the majority of humans. HHV-6 is a member of the Roseola viruses and is the causal agent of roseola infantum (also known as exantema subitum), which is a febrile illness associated with skin rash during early childhood [2].

Human herpesvirus-6 is a large DNA virus measuring 200 nm in diameter, and consists of a linear double-stranded DNA of approximately 160–162 kb inside an icosahedral nucleocapsid [3]. There are two variants of HHV-6, variant A (HHV-6A) and B (HHV-6B) [4]. The HHV-6B genome contains 119 open reading frames (ORFs), nine of which are absent in HHV-6A [5]. The overall nucleotide sequence homology between HHV-6A and HHV-6B reaches as high as 90%, but there is increasing evidence that they are virologically and epidemiologically distinct and they should be considered two separate viruses [6]. These viruses have genetic homology as high as 67% with CMV, and 21% with the non-β herpesviruses [7,8].

Of the two viruses, HHV-6B is more commonly implicated in human diseases. HHV-6B causes the majority of reported symptomatic primary infections including roseola infantum [4]. The clinical symptoms of HHV-6 infections

are usually mild and self-limited, but complications such as seizures, otitis, respiratory or gastrointestinal symptoms, and rarely encephalitis and hepatitis have been described [9,10]. HHV-6 seroconversion mostly occurs before the age of 2 years, and the seroprevalence in the adult populations reaches as much as 95% [8,11].

Human herpesvirus-6 is a lymphotropic virus that replicates in CD4+ T-lymphocytes, and it uses the CD46 molecule as its cellular receptor [12]. The virus may also infect other cell types, such as monocytes and macrophages, astrocytes, fibroblasts, and cells of endothelial or epithelial origin [6]. HHV-6 infects various tissues including the brain, salivary glands, tonsils, lungs, kidneys, and liver. The tropism of the variants A and B is somewhat distinct, with HHV-6A being considered more neurotropic. Hence, HHV-6A has been associated with some chronic neurological disorders such as multiple sclerosis [13].

After primary infection, HHV-6 persists in the state of latency in the host. Latent HHV-6 may reactivate later in life, especially during periods of immunosuppression. During latency, the HHV-6 genome is harbored as circular DNA in various cells, although mainly in those of monocyte and macrophage origin [14]. In the minority of individuals, the viral genome is integrated into the host chromosome, a condition known as chromosomally integrated HHV-6 (CIHHV-6) [15–17]. The incidence of CIHHV-6 is reported to be between 0.2% and 1% based on a study of blood donors from United Kingdom [18]. Because of chromosomal integration, CIHHV-6 can be inherited. Both HHV-6A and HHV-6B can be chromosomally integrated, although the majority of reported cases have been ascribable to CIHHV-6B. The clinical significance of CIHHV-6 is still not defined, but it has caused difficulties in the interpretation of nucleic acid testing for diagnosis [17]. Because CIHHV-6 is present in every cell, individuals with CIHHV-6 have exceedingly high levels (most likely over a million copies per ml of blood) of the HHV-6 genome in their blood samples. Reactivation of CIHHV-6 has been demonstrated in experimental settings, and this poses a theoretical concern during periods of immunosuppression such as after transplantation when reactivation of latent viruses are common and may cause clinical disease [19]. To date, however, reactivation of CIHHV-6 in the clinical setting has not been demonstrated.

HHV-6 infections after solid organ transplantation

Epidemiology

Human herpesvirus-6 infection is frequently detected in immunosuppressed transplant patients [20]. HHV-6 infection may be transmitted through organ transplantation, but considering the high seroprevalence rate in the population, infection is most likely to result from reactivation of recipient's endogenous virus [8,11]. HHV-6 infections in transplant recipients are mostly attributable to asymptomatic reactivations of the virus. In adult patient populations, primary HHV-6 infections are rare. In one study, a high HHV-6 seroprevalence (96.4%) among adult solid organ transplant patients was reported, and only one patient developed symptomatic primary HHV-6 infection [21]. In another series of adult living related liver transplant recipients where the seroprevalence reported was 97%, none of the few HHV-6 seronegative patients demonstrated seroconversion after transplantation [22]. The incidence of HHV-6 reactivation peaks at 2–4 weeks after transplantation [23–26], but late infections that occur months or years after transplantation may occur [27].

The overall incidence of HHV-6 infection varies widely, depending on the study and method of testing, from as low as 0 to as high as 82% of solid organ transplant recipients [8,28]. Most HHV-6 infections have been reported in liver and kidney transplant recipients, and the incidence is estimated to be 22–54% and 23–55%, respectively [24,25,29–36]. HHV-6 infections have also been reported after kidney-pancreas [37] and intestinal transplantation [38,39]. After heart and lung transplantation, the reported incidence of HHV-6 infection is as high as 66–91%, causing mostly asymptomatic infections or occasionally clinical symptoms [40–43].

Clinical presentations

Human herpesvirus-6 infection in solid organ transplant patients is usually asymptomatic, although complications have also occasionally been reported. Among the reported HHV-6 associated diseases are fever and other clinical symptoms, such as neurological disorders, encephalitis, rash, graft dysfunction, pneumonitis, gastrointestinal infection, and hepatitis [20,23,26,27,32,44–48]. A recent study of living donor liver transplant recipients demonstrated a significantly higher rate of mortality among those with HHV-6 reactivation compared to those without viral reactivation [22].

Human herpesvirus-6 may infect the transplanted allograft and cause dysfunction [27,49,50], although no direct loss of a transplanted allograft owing to HHV-6 has been reported. In liver transplantation, pre-transplant HHV-6 infection of patients with acute liver failure was found to be a risk factor for post-transplant HHV-6 infection of the liver [51,52]. However, the recurrent hepatic HHV-6 infection had no impact on either allograft or patient survival [52].

Human herpesvirus-6B is the most commonly detected variant among transplant patients with asymptomatic

reactivation as well as in those cases with symptomatic infection. However, HHV-6A has also been reported to occasionally cause giant cell hepatitis or fever with liver dysfunction and renal allograft rejection [53–55].

HHV-6 infections after kidney transplantation

Human herpesvirus-6 has been recognized as a cause of infection in kidney transplant recipients for more than 20 years now [29,30,56]. HHV-6 infections after kidney transplantation were usually asymptomatic, and the findings were mainly based on serological analysis or isolation of the virus from blood specimens [31,32]. Frequent detection of HHV-6 DNA in peripheral blood mononuclear cells from asymptomatic kidney transplant patients has also reported [57]. However, the presence of HHV-6 specific antigens by immunohistochemistry in kidney biopsy material has been associated with pathological conditions, such as acute and chronic rejection or cyclosporine-related nephropathy [30,49]. HHV-6 antigens have been found in the distal tubular epithelial cells and in a few infiltrating lymphocytes, although immunoreactivity has also been detected in the glomeruli and vascular endothelia [49]. Interestingly, HHV-6 has also been isolated from a few renal tissues obtained during transplant surgery without concurrent viremia [30]. HHV-6 antigens have been detected in the tubular epithelium of five of nine patients with acute rejection. HHV-6 antigens have also been found in some intra-operative biopsies [49,58] and that kidney transplant recipients receiving an allograft from the same donor had the same HHV-6 isolate [31]. This suggests that HHV-6 may be transmitted with the donor kidney allograft and that reactivation after transplantation could be attributable to the HHV-6 strain of either the recipient or donor origin. HHV-6 may persist in kidney allografts [59]. In an analysis of 22 kidney transplant biopsies of patients with previous CMV infection, HHV-6 antigens were detected in seven patients, and in one patient, both HHV-6 and CMV antigens were detected in the graft. However, the significance of the persistent HHV-6 regarding transplant outcome remains uncertain.

Although HHV-6 infection in kidney transplant recipients is mostly subclinical, symptomatic or even fatal HHV-6 infections have been described. The symptoms of HHV-6 disease are usually nonspecific, including fever or gastrointestinal symptoms, whereas rash or hepatitis are less common. HHV-6 has been associated with a higher risk of CMV disease, and concomitant or recent CMV infection may induce the clinical symptoms [60,61]. Pure HHV-6 infections are limited to small series and case reports describing fever, elevated creatinine levels, liver dysfunction, and colitis [54,62,63]. The few fatal cases of HHV-6 disease, all incidentally caused by HHV-6A, were characterized by hemophagocytic syndrome, pancytopenia, encephalitis, severe hepatitis, or colitis [64,65]. Additional studies with adequate diagnostic methods, including quantitative nucleic acid testing and demonstration of the virus specific antigens in the kidney biopsy material, should be performed to obtain more information about HHV-6 infection in kidney transplantation. The recent availability of quantitative nucleic acid testing of peripheral blood has resulted in the low frequency of *in situ* hybridization analysis and antigen detection of biopsy material of kidney allografts. Quantification of HHV-6 DNA from biopsy specimens may bring some information as high viral loads in renal tissue have been correlated with significant illness owing to HHV-6 infection of pediatric kidney transplant patients [66].

Nucleic acid testing has allowed for initial characterization of CIHHV-6 in kidney transplant recipients. In a cohort study of 47 kidney transplant recipients, CIHHV-6 was detected in one patient, giving a calculated prevalence of 2.1%. The patient with CIHHV-6 developed neurological illness and thrombosis after kidney transplantation, and died from pulseless electrical activity. It was unclear if this was related to CIHHV-6 reactivation and disease [67].

HHV-6 infections after liver transplantation

The information concerning HHV-6 in solid organ transplantation is based mainly on studies conducted in liver transplant patients. Most reviews on ''HHV-6 in SOT'' which describe evidence of pathogenicity and clinical significance, also mainly deal with liver transplantation. Recent reviews on HHV-6 in liver transplantation describe the hepatic involvement of HHV-6 in more detail [68,69]. The first reports on symptomatic HHV-6 disease, including febrile dermatosis with thrombocytopenia and encephalopathy were published in the 1990s [23,32,45]. Although asymptomatic HHV-6 reactivations after liver transplantation were the most common clinical presentation [33], several studies have suggested the potential clinical significance of HHV-6 as a potential pathogen in liver recipients [24,26,27,70]. In one study of 200 liver transplant recipients, HHV-6 was found to be a causative agent of febrile disease in 1% of cases, when other pathogens had been excluded [26].

Post-transplant hepatitis [44] and intrahepatic HHV-6 infections associated with liver dysfunction have been described [27]. In a retrospective analysis of 121 liver recipients, HHV-6 was thought to be an etiological agent in eight cases (6.7%) and HHV-6 was demonstrated in six available liver biopsies [27]. The hepatic pathogenicity of HHV-6 was further demonstrated in a prospective series of 51 adult liver transplant recipients, where eight of

11 patients with HHV-6 antigenemia demonstrated significant graft dysfunction, and three of these had HHV-6 antigens in the liver biopsy specimens (5.9%) [25]. All cases of HHV-6 antigenemia were attributable to HHV-6B. However, infection with HHV-6A can also be possible, as others have reported a case of giant cell hepatitis caused by HHV-6A [55]. Pre-transplant HHV-6 infection with acute liver failure was reported to be a risk factor for the development of post-transplant HHV-6 infection of the liver allograft [52], although the intragraft HHV-6 infection had no appreciable long-term impact on the transplant outcome.

In addition to the infection of the liver allograft, gastrointestinal HHV-6 infections may occur during the post-transplant period [48]. In 90 liver transplant recipients undergoing gastroscopic examination for dyspeptic symptoms, HHV-6 antigen positive cells were found in the biopsy specimens of 21 (23%) of patients [48]. Most patients had concomitant HHV-6 antigenemia. Histopathological findings were, however, mild and nonspecific.

Encephalitis is the most prominent finding of HHV-6 infection in hematologic transplant recipients, but this entity seems to be rare after liver transplantation. Some reports describe neurological complications [36,71], although no HHV-6 associated neurological symptoms were recorded in the large series of liver transplant patients [26]. Likewise, only a single case of HHV-6 pneumonia has been described [45].

The clinical significance of CIHHV-6 has been investigated in a recent study of liver transplant recipients. In a large cohort of 548 liver transplant recipients, CIHHV-6 was detected in seven patients and the prevalence was calculated at 1.3%. Notably, bacterial infections were significantly more common in the CIHHV-6 group compared to the group without HHV-6 (71.4% vs. 31.4%; $P = 0.04$). A higher rate of allograft rejection was observed in the CIHHV-6 group compared to the group of patients with low-level HHV-6 DNA load (71.4% vs. 37.1%; $P = 0.12$) and those without HHV-6 DNA infection (71.4% vs. 42.9%; $P = 0.25$), although these differences did not reach statistical significance. These data suggest that patients with CIHHV-6 may be at increased risk of indirect HHV-6 effects after transplantation, although this clinically relevant observation warrants confirmation using a larger cohort of transplant recipients [72].

HHV-6 infections after lung and heart transplantation

Human herpesvirus-6 has frequently been detected in blood and bronchoalveolar lavage (BAL) specimens of lung transplant patients [42,43,73]. The overall frequency of HHV-6 DNA detection in BAL was about 20%, and it was usually detected together with the other opportunistic herpesviruses CMV, HHV-7 and EBV [74–76]. However, the clinical significance of HHV-6 finding in BAL has remained unclear, probably also ascribable to the concomitance of other viral infections. In a recent report of 27 lung transplant recipients who received universal antiviral prophylaxis and underwent BAL examinations with transbronchial biopsy (TBB) [76], HHV-6 was found in 21% of BAL specimens and in 1 TBB specimen. In organizing pneumonia, HHV-6 was detected in four of four specimens, suggesting its potential role in the pathogenesis [76]. In addition to possible infection of the lung allograft, HHV-6 has been associated with encephalitis and colitis in a few cases [43,77].

Frequent asymptomatic HHV-6 reactivations have also been described in heart and heart-lung transplant recipients. HHV-6 is mostly found in association with CMV (and HHV-7), and the clinical symptoms have been concluded to be due mainly owing to CMV infection [40,43]. On the other hand, higher mortality rate was recorded in the patients with HHV-6 infections compared to those without HHV-6 [42]. Cases of giant cell hepatitis and encephalitis after heart transplantation have been reported [47,53]. Immunohistochemical studies of lung and heart transplant biopsy material would possibly reveal more information about the role of HHV-6 in pathologies of cardiothoracic organ transplants.

Indirect effects of HHV-6

In addition to the direct effects of HHV-6, numerous indirect effects that have also been reported or suggested. HHV-6 is considered to be an immunomodulatory virus that may facilitate superinfections with fungal or other opportunistic infections [23,36,78–80]. HHV-6 reactivations are often related with CMV and HHV-7 infections and recurrent hepatitis C, and interactions between these viruses have been suggested [34,60,81–86]. Concurrent intragaft infection of HHV-6 and CMV have been found both in liver and kidney transplants [27,59].

Human herpesvirus-6 has also been associated with liver allograft rejection and chronic allograft nephropathy [24,27,34,54,87–89]. In liver transplantation, intragraft HHV-6 infection has been associated with portal lymphocyte infiltration and increase of vascular adhesion molecules, such as ICAM-1 and VCAM-1, known to be important in leukocyte extravasation and lymphocyte activation [87]. Recently, it has been reported that both HHV-6 and HHV-7 infections are associated with the development of chronic allograft nephropathy [89]. Demonstration of HHV-6 in BAL has also been suggested as a risk factor for bronchiolitis obliterans syndrome, which is a form of chronic rejection in lung transplant recipients

Table 1. Direct and indirect effects of human herpesvirus 6 infections in kidney, liver, heart, and lung transplant recipients.

Transplant type	HHV-6 effects	References
Kidney transplant recipients	Asymptomatic HHV-6 reactivation in the majority of patients; clinical disease only in an estimated 1% of patients	
	Direct effects: fever, rash, renal dysfunction such as a rise in serum creatinine, hepatitis and liver dysfunction, gastrointestinal symptoms including colitis, hemophagocytosis syndrome, and encephalitis	[54,62,63,64,65,66]
	Indirect effects: Acute and chronic rejection including chronic allograft nephropathy, higher rates of CMV disease	[27,30,49,89]
Liver transplant recipients	Asymptomatic HHV-6 reactivation in the majority of patients; clinical disease occurs in an estimated 1% of patients	
	Direct effects: fever, rash, thrombocytopenia, neurologic abnormality including encephalopathy, hepatitis including giant cell hepatitis, gastrointestinal illness such as dyspepsia, pneumonia	[23,26,27,32,36,45,48,52,55,71]
	Indirect effects: Higher rates of CMV disease, accelerated HCV recurrence, higher rates of invasive fungal diseases	[34,60,62,81–86]
Heart and lung transplant recipients	Incidence is not fully defined, but reactivation is presumed to be mostly asymptomatic	
	Direct effects: Pneumonia, encephalitis, colitis, giant cell hepatitis	[43,47,53,76,77]
	Indirect effects: bronchiolitis obliterans syndrome, higher all-cause mortality	[42,73]

Notes: HHV-6, human herpesvirus 6; CMV, cytomegalovirus; HCV, hepatitis C virus.

[73]. However, no association between beta-herpesviruses, including HHV-6 and bronchiolitis obliterans syndrome have been demonstrated in the era of antiviral prophylaxis [75]. The HHV-6 associated direct and indirect effects in kidney, liver, lung and heart transplantation are summarized in Table 1.

Diagnosis of HHV-6 infections

The diagnosis of clinically significant HHV-6 infection is not easy, as most infections are asymptomatic, its detection in the clinical specimen does not necessarily implicate the virus as the etiology of a specific illness, and the differentiation between latent and active infection is not always possible. Serology is of very limited diagnostic value owing to high seroprevalence rate (over 95%) in adult transplant patients. Viral culture of HHV-6 is possible in lymphoid cell lines, but the technique is laborious, not routinely used in diagnostic laboratories, and the turn-around time is too slow to be of use in guiding the management in real-time clinical practice. Recently, several virus detection methods have been developed, including some that can discriminate between HHV-6A and HHV-6B. Those tests include an HHV-6 antigenemia assay which detects the viral antigens in peripheral blood mononuclear cells (PBMC) by monoclonal antibodies and immunoperoxidase staining or immunofluorescence, although this method is qualitative rather than quantitative [6,25]. Quantitation of HHV-6 positive cells is, however, also possible [90]. On the other hand, demonstration of HHV-6 specific antigens in tissue or cellular specimens by immunostaining may be more informative regarding infected organ than the demonstration of viral DNA in the blood [27,45,49]. Other tests to demonstrate the presence of HHV-6 in the tissue specimens are based on DNA hybridization or PCR *in situ* techniques [68].

Currently, molecular assays are the most common laboratory methods for the detection of HHV-6 reactivation and replication in solid organ transplant patients [68,91]. Qualitative demonstration of viral DNA in the relatively acellular cerebrospinal fluid is suitable for the diagnosis of HHV-6 encephalitis, but quantitative methods are needed to diagnose an active systemic HHV-6 infection. Quantitative tests have been developed to monitor viral load either in plasma, whole blood or mononuclear cells, mostly by real-time PCR, and some PCR tests are even able to differentiate HHV-6A and HHV-6B [92–94]. As detection of viral DNA by PCR from leukocyte containing specimens may reflect either latent or active viral infection, the quantification of HHV-6 DNA is usually performed from plasma or serum samples. However, it has been recently demonstrated the HHV-6 DNA in plasma reflects the presence of infected blood cells rather than circulating viral particles, and quantification of viral DNA in whole blood has been found preferable in the diagnosis of active HHV-6 infection [95]. On the other hand, when various PCR assays were compared, three reliable quantitative

Table 2. Contemporary laboratory methods to diagnose HHV-6 infection.

Test	Method (sample)
Quantitative nucleic acid tests (QNAT)	PCR (plasma, serum, whole blood, CSF, BAL fluid)
Qualitative nucleic acid detection	PCR (CNS-fluid)
Antigenemia test (qualitative, quantitative)	Antigen detection in PBMC (blood)
Immunohistochemistry	Antigen detection in tissue (biopsy)

TaqMan-based real-time PCR assays for the detection of HHV-6 DNA in serum were reported and proposed for use with clinical samples [96]. The quantification of HHV-6 DNA, either in whole blood, plasma or serum, by means of real-time PCR, is currently the most common tool to diagnose an active HHV-6 infection, although the methods are not standardized and no clear cut-off levels exist to differentiate asymptomatic viral replication from symptomatic clinical disease. Also, methods for the detection of HHV-6 mRNA have been developed to distinguish between latent and active infection in transplant patients [97], although these tests are not in general use (Table 2).

The interpretation of active HHV-6 infection on the basis of nucleic acid testing that amplifies and detects HHV-6 DNA should also take into account the possibility that one may be detecting CIHHV-6. As discussed above, CIHHV-6 is inherited and the viral genome is present in every nucleated cell. Accordingly, PCR testing of cell-based samples will yield exceedingly high viral genome copies, and may be misinterpreted as an active infection in solid organ transplant patients [98,99]. In a cohort study of 548 liver transplant recipients, CIHHV-6 was detected in seven patients, and these were characterized by having HHV-6 loads of over a million copies per mL of whole blood [72]. Such exceedingly high viral copy numbers are even rarely seen in HHV-6 associated diseases, hence the very high level may provide an indication as to the diagnosis of CIHHV-6. Serial measurements (to document persistently elevated HHV-6 levels over time in the absence of symptoms), or measurements of siblings and relatives (because of the inherited nature of this condition), or cytogenetic testing and PCR assay of hair follicle samples, may be needed to confirm the diagnosis in some cases.

Antiviral therapy

Based on *in vitro* studies, the current antiviral drugs with efficacy against CMV such as ganciclovir, foscarnet and cidofovir, also have antiviral activity against HHV-6 [8,100,101]. The activity of ganciclovir is highly superior to that of acyclovir. However, ganciclovir is more effective against CMV than both HHV-6B and HHV-6A. The most effective compounds against HHV-6 *in vitro* are cidofovir and foscarnet [8,100,101].

There are, as yet, no controlled studies on antiviral therapy of HHV-6 infection in solid organ transplant patients. The currently available antivirals have, however, been used for the treatment of encephalitis and other severe syndromes of HHV-6. Most case reports deal with stem cell transplantation indicating an *in vivo* efficacy of ganciclovir or foscarnet against viral replication and clinical symptoms [20]. In solid organ transplantation, ganciclovir or foscarnet have been occasionally used for treatment. Some indirect information on ganciclovir is provided by the multicenter CMV prophylaxis trials. Antiviral prophylaxis with ganciclovir or valganciclovir decreased the incidence and HHV-6 viremia in solid organ transplant patients [102]. Ganciclovir prophylaxis has also been reported to delay and shorten HHV-6 viremia in renal transplant recipients [103]. On the other hand, ganciclovir treatment of CMV disease in liver transplant patients demonstrated a decline in concurrent HHV-6 antigenemia, albeit at a slower rate compared with the decline in CMV levels [83]. In a recent large randomized trial comparing ganciclovir and valganciclovir in the treatment of CMV disease in solid organ recipients, the response to antiviral treatment of concomitant HHV-6 and HHV-7 infections was analyzed [104]. Ganciclovir and valganciclovir were both effective in the treatment of CMV disease, but had no clear effect on HHV-6 and HHV-7 viremia. The recent guidelines from the American Society of Transplantation Infectious Disease Community of Practice do not recommend specific antiviral prophylaxis or pre-emptive therapy for HHV-6 infection, but for established HHV-6 disease, especially with encephalitis, intravenous ganciclovir and foscarnet are considered to be first-line agents [105]. Viral load monitoring should be used as an adjunct to clinical assessments in guiding the duration of anti-HHV6 treatment as has also been emphasized in a recent review on acute HHV-6 infections [106].

Conclusions

In conclusion, HHV-6 is a common infection after kidney, liver, lung, and heart transplantation. Although the reactivation rate is high, clinical disease is estimated to occur in only 1% of patients. However, the clinical role of HHV-6 infection might be underestimated, as HHV-6 diagnostics is not routinely performed. Fever, myelosuppression, and end-organ disease including hepatitis, gastrointestinal disease, and encephalitis have been associated with HHV-6. In addition, HHV-6 has been associated with a higher rate of CMV disease after liver and kidney

transplantation, a higher rate of acute and chronic graft rejection, and a higher rate of opportunistic infections, such as invasive fungal disease. All-cause mortality is also increased in solid organ transplant recipients with HHV-6 infection. The vast majority of primary HHV-6 infections result in viral latency, but in 1% of cases this is in the form of HHV-6 integration into the host chromosome. The clinical significance of chromosomally integrated HHV-6 is not yet defined, although one study of liver transplant recipients indicated a tendency of higher rate of indirect effects, such as bacterial infections and allograft rejection. The diagnosis of HHV-6 is now commonly made using nucleic acid testing, which detects HHV-6 DNA in clinical samples, although this can be difficult to interpret owing to the common nature of asymptomatic viral reactivation. In addition, one should consider the detection of CIHHV-6 cases which are characterized by exceedingly high levels of HHV-6 that have been integrated into every nucleated cell. Antiviral prophylaxis and preemptive therapy are not recommended for HHV-6. Furthermore, HHV-6 surveillance after transplantation is not routinely performed in clinical practice. Treatment of HHV-6 is indicated in established end-organ disease such as encephalitis. For treatment, one may use foscarnet, ganciclovir, and cidofovir.

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