Human herpesvirus 6 (HHV-6) frequently reactivates after allogeneic stem cell transplantation (SCT). Most patients are asymptomatic and viremia often resolves without therapy; however, transplant-related complications may be associated with reactivation. Multiple presentations have been attributed to HHV-6 reactivation after SCT including encephalitis. Several strategies have been trialed to reduce such risks or complications. Challenges exist with prospective monitoring strategies, and established thresholds of high-level reactivation may be limited. Three published guidelines and extensive trials focusing on preemptive and prophylactic strategies are reviewed. Future areas of investigation and high-risk populations are described. Existing trials and testing platforms have significant limitations, and to date no clear benefit for a preemptive or prophylactic intervention has been demonstrated.

**Keywords.** encephalitis; human herpesvirus-6; stem cell transplantation.
encephalitis [7, 9, 11, 16, 17]. Pneumonitis, hepatitis, myelitis, fever, rash, and myelosuppression have been attributed to HHV-6 reactivation after SCT or cellular therapy, but often alternative etiologies are present and should be ruled out [8, 9, 18–20]. The most feared and defined syndrome is a posttransplant limbic encephalitis comprised of anterograde amnesia, temporal lobe seizures, and/or enhancement of the uncus, amygdala, or hippocampus on magnetic resonance imaging [9, 21, 22]. Radiographic or clinical evidence of limbic system involvement is not required, though, and not seen in many patients with HHV-6B encephalitis.

HIGH-LEVEL HHV-6 REACTIVATION

Previous studies correlated high levels of plasma HHV-6 DNA with CNS disease or increased mortality with a proposed cutoff of $\geq 10^4$ copies/mL as high-level reactivation [8, 9, 11, 12, 14, 15]. This is limited by a lack of validation of such a threshold or standardization among commercially available assays. Compounding the issue, testing platforms may produce discordant results even in at-risk patients presenting with compatible syndromes [23]. Later studies show that HHV-6B encephalitis occurs even absent of high-level plasma DNA reactivation [23–25]. Detection of HHV-6 DNA in cerebrospinal fluid (CSF) may occur in a substantial portion of SCT patients without CNS dysfunction or with dysfunction due to an alternative etiology [25]. Treatment of such patients did not significantly change outcomes. Detection of HHV-6 DNA in plasma or CSF alone is insufficient for diagnosis of HHV-6 disease given how commonly reactivation occurs following allogeneic SCT, and alternative etiologies should be evaluated and ruled out prior to diagnosing HHV-6–related disease. High levels or persistently detectable HHV-6 DNA can suggest ciHHV-6 and should be evaluated if the diagnosis is unclear to avoid unnecessary or potentially harmful treatments [5, 26]. In prospectively monitored high-risk CBT, high-level reactivation has not been shown to be associated with poor outcomes including engraftment time, day 100 grade II–IV aGVHD, transplant-related mortality, or 1-year disease-free survival, and treatment of such patients did not alter outcomes [13]. Treatment when undertaken must be carefully considered, particularly if a benefit is unclear.

CURRENT CLINICAL PRACTICE GUIDELINES AND THERAPIES

Two clinical practice guidelines, from the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and the European Conference on Infections in Leukaemia (ECIL), are published regarding HHV-6 disease in SCT. While the JSHCT guideline focuses primarily on HHV-6B encephalitis, the ECIL guideline notes that associations with disease states outside of encephalitis or fever with rash are only based on moderate or weak evidence [7, 26]. With rash alone, alternative etiologies are often more likely. In a study of transplant recipients with rash and HHV-6 reactivation, every single patient was diagnosed with aGVHD on histopathology and no HHV-6 antigen was detectable by immunostaining on samples on which it was performed [8]. An additional guideline published by the American Society for Transplantation and Cellular Therapy includes recommendations for HHV-6B specifically after CBT [27]. First-line therapies include ganciclovir and foscarnet. While these agents and cidofovir all have in vitro and in vivo activity against the virus, cidofovir is considered second line due to poor CNS penetration [7, 26, 28]. When initiated for treatment, maximum dosing should be given due to improved outcomes compared to reduced dosing regimens [26, 29]. In patients with HHV-6B encephalitis, a retrospective analysis demonstrated a reduction in 30-day all-cause mortality in patients receiving foscarnet, either alone or in combination; however, no clear significant difference was noted in patients treated with monotherapy ganciclovir compared to monotherapy foscarnet [29]. In the JSHCT guideline, foscarnet is therefore recommended (weak recommendation) as first-line therapy [26]. In vitro studies of human astrogliaoma cells demonstrated a reduced antiviral activity of ganciclovir in HHV-6A–infected cells not seen in HHV-6B–infected cells [30]. The clinical significance is unclear; as noted nearly all cases of HHV-6 reactivation after SCT are due to HHV-6B, and HHV-6A has not been causally linked to disease in this population [5–7]. Combination therapy with foscarnet and ganciclovir may be associated with reduced long-term neurologic sequelae, but no mortality benefit has been demonstrated, and guidelines only recommend consideration in severe cases [26, 31]. No randomized clinical trials exist for treatment of HHV-6B encephalitis. The duration of treatment is unclear. Guidelines recommend at least 3 weeks, and an extension of therapy until either HHV-6 DNA is undetectable in plasma and CSF and symptoms have improved [7, 26]. Refractory cases occur despite combination therapy and cidofovir may be trialed; however, there are no specific evidence or guideline recommendations in such situations. A comprehensive review for alternative etiologies should be undertaken. Even with appropriate therapy, outcomes may be poor and long-term neurologic sequelae common [10, 11, 26, 29, 31]. Comparisons of the 3 guidelines are available in Table 1. Where available, strength of recommendation is made based on the European Society of Clinical Microbiology and Infectious Diseases grading system for the ECIL guideline and the Grading of Recommendations Assessment, Development and Evaluation methodology for the JSHCT guideline.

PREEMPTIVE STRATEGIES

Due to poor outcomes of HHV-6B encephalitis, preemptive and prophylactic strategies have been attempted without significant success. Preemptive monitoring of HHV-6 DNA has
several challenges. HHV-6 DNA rises rapidly and suddenly around the onset of symptoms in patients with HHV-6B encephalitis [8, 10, 32, 33]. Due to viral kinetics, the high incidence of asymptomatic HHV-6 reactivation after SCT, and the limitations with current testing platforms, there is no established role for HHV-6B preemptive monitoring to prevent HHV-6B encephalitis. In preemptive treatment studies, foscarnet is more frequently utilized, rather than ganciclovir, due to concerns of myelosuppression [33, 34]. Multiple prospective and multicenter studies have found no benefit from preemptive strategies, and the majority of patients developed some adverse event potentially attributable to foscarnet therapy [32, 33]. A lack of evidence supporting a specific threshold to initiate therapy further complicates preemptive strategies.

**PROPHYLACTIC STRATEGIES**

Prophylactic strategies have not fared better. In a small heterogeneous safety study of 20 patients, prophylactic foscarnet 90 mg/kg/day demonstrated non–statistically significant potential to reduce HHV-6B–related CNS dysfunction at a potential cost for a trend of increased side effects [35]. However, a larger prospective cohort analysis of 118 patients found no benefit of prophylactic foscarnet 50 mg/kg/day in preventing HHV-6 reactivation or HHV-6B encephalitis [36]. Specifically for high-risk double CBT, a retrospective secondary analysis found higher rates of HHV-6 reactivation in patients receiving sirolimus and mycophenolate mofetil compared to cyclosporine and mycophenolate mofetil [37]. Multivariate analysis showed that only HHV-6 reactivation before neutrophil recovery was associated with risk of graft failure. The study likely suffered from ascertainment bias as HHV-6 reactivation was not evaluated prospectively but only in response to symptoms, such as delayed engraftment, and a similar study of 125 double CBT patients with prospective monitoring found no such findings as well as a HHV-6 reactivation rate of 94% [13]. While the study suggests that sirolimus may be associated with HHV-6 reactivation, patients receiving sirolimus were

| Table 1. Comparison of Guideline Recommendations for Human Herpesvirus 6B DNA Monitoring and Therapy |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Population | ECIL, 2019 Allogeneic SCT | JSHCT, 2019 Allogeneic SCT | ASTCT, 2021 CBT |
| Accepted risk factors for HHV-6B encephalitis | CBT, T-cell depleted allografts, unrelated donor or mismatched donor, aGVHD grades II–IV, glucocorticoid therapy | CBT, male sex, unrelated donor or mismatched donor, corticosteroid therapy, pre-engraftment syndrome, engraftment syndrome, aGVHD | Not discussed |
| Potential risk factors for HHV-6B encephalitis | Haploidentical transplant, pre-engraftment syndrome | Haploidentical transplant | Not discussed |
| When to test for HHV-6B DNA | No indication for routine testing, consider if unclear | 1–10 x 10^6 copies/mL in whole blood or persistent DNA in plasma or serum (strong) | >10^6 copies/mL in whole blood or viremia unresponsive to therapy |
| Treatment | Foscarnet 90 mg/kg q12h OR ganciclovir 5 mg/kg q12h (AIIu) | Primary: foscarnet 60 mg/kg q8h or 90 mg/kg q12h (weak) Secondary: ganciclovir 5 mg/kg q12h (weak) Combination therapy in severe cases (weak) | Not discussed |
| Duration of therapy | At least 3 weeks with clearance of DNA from blood and, if possible, CSF (CIII) | At least 3 weeks with clearance of DNA from blood and, if possible, CSF (weak) | Not discussed |
| Notes | No indication for routine testing, consider if unclear | No indication for routine testing, consider if unclear | Can be considered, no evidence to support; alternatively, as clinically indicated |

Abbreviations: aGVHD, acute graft-vs-host disease; AIIu, Strongly supports a recommendation for use, based on evidence from at least one uncontrolled trial or from cohort- or case-control analytic studies; ASTCT, American Society for Transplantation and Cellular Therapy; CIII, Marginaly supports a recommendation for use, expert opinion; CBT, cord blood transplant; CI, HHV-6, chromosomally integrated human herpesvirus 6; CSF, cerebrospinal fluid; DIIu, Supports a recommendation against use, based on evidence from at least one uncontrolled trial or from cohort- or case-control analytic studies; ECIL, European Conference on Infections in Leukaemia; HHV-6B, human herpesvirus 6B; JSHCT, Japan Society for Hematopoietic Cell Transplantation; q8h, every 8 hours; q12h, every 12 hours; SCT, stem cell transplant.

[3] Specific to HHV-6B encephalitis.
[4] Refers to ECIL guideline for preemptive therapy, which explicitly recommends against preemptive therapy.
older and had fewer comorbid conditions, and the change occurred due to a change in institutional practice in 2012 and prospective monitoring of HHV-6 DNA was not performed. Further case-controlled or prospective studies with prospective monitoring of HHV-6 DNA would be required to confirm this association. A subsequent retrospective analysis of 25 CBT patients receiving foscarnet prophylaxis of 45 mg/kg twice daily failed to demonstrate a reduction in cumulative rates of HHV-6 reactivation, but did suggest higher rates of neutrophil engraftment and 6-month overall survival [38]. Unfortunately, prospective monitoring was only performed in the foscarnet prophylaxis group of this study and compared to a control population, which in part as previously discussed, did not have prospective monitoring and likely suffered from ascertainment bias [37, 38]. Additionally, donor type of single vs double CBT, HLA matching, total nucleated cell dose, and CD34 dose were significantly different between groups, making comparisons difficult [38]. Single CBT alone was associated with improved neutrophil engraftment compared to double CBT [38]. A larger prospective multicenter trial evaluated 57 patients receiving foscarnet prophylaxis of 90 mg/kg daily and found no difference in rates of HHV-6B encephalitis; moreover, a non–statistically significant trend toward more encephalitis occurred in the foscarnet arm [24]. The primary endpoint of lower rates of high-level HHV-6 reactivation, defined as $\geq 10^4$ copies/mL of HHV-6 DNA in plasma, was significant in the foscarnet prophylaxis arm; however, this only occurred at the week 3 and week 4 timepoints during the study and no difference in rates of HHV-6B encephalitis, grade II–IV aGVHD, or grade III/IV aGVHD were found [24]. Most (5/7) patients receiving prophylaxis who developed encephalitis did not have high-level HHV-6 reactivation. Overall survival and rates of graft failure were not evaluated between groups. Notably, 13 of 57 (23%) of patients were unable to complete 21 days of foscarnet prophylaxis, and of 3 of 57 (5.2%) developed acute kidney injury limiting therapy entirely [24]. Dose adjustment was required in 18.5% of overall foscarnet administrations due to renal dysfunction.

**DISCUSSION AND FUTURE DIRECTIONS**

Due to these studies, all 3 published guidelines either expressly recommend against routine prospective testing of HHV-6 DNA after allogeneic SCT, or limit it to a consideration for a short period after transplantation in only the highest-risk patients such as after CBT [7, 26, 27]. In such populations, published guidelines note consideration of a limited monitoring period of 2–6 weeks or 60 days following CBT, but acknowledge there is no current evidence of a benefit for preemptive or prophylactic therapy in these patients [26, 27]. Haploidentical transplantation may present an additional population with higher risk of HHV-6B encephalitis for which prospective studies are needed [39–41]. HHV-6 reactivation remains challenging in the allogeneic SCT setting and may be associated with significant complications such as delayed platelet engraftment, high-grade aGVHD, and HHV-6B encephalitis. Reactivation is common, particularly after CBT, and studies to date have not been able to reliably predict which patients are at highest risk of progression to HHV-6B encephalitis and disease, in part due to viral kinetics and limitations of current testing platforms. While earlier studies proposed a risk threshold for high-level HHV-6 DNA reactivation in plasma, current evidence suggests that disease, including HHV-6B encephalitis, may occur even in the absence of high-level plasma reactivation [23–25]. The potential for distinct HHV-6 reactivation in patients with ciHHV-6 has been considered but remains clinically controversial [7]. Testing platforms suffer from a lack of standardization in measurement of HHV-6 DNA levels, and discordance among platforms has been noted [23]. Additional populations, such as patients following chimeric antigen receptor T-cell therapy, may carry increased risks and require further evaluation [20, 23]. In unclear scenarios, ciHHV-6 should be evaluated, but is not yet standard of care in most transplant centers. Prospective monitoring and preemptive, and prophylactic therapy trials have not demonstrated a clear benefit for patient outcomes and pose significant potential drug toxicities with therapy that should be carefully considered by providers and transplant centers caring for such patients in the absence of HHV-6 disease.

**Notes**

**Potential conflicts of interest.** The author: No reported conflicts.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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