Common non-seasonal viral infections after hematopoietic stem cell transplantation

Abstract
We are celebrating one millionth transplant in year 2013! With continued improvement in hematopoietic stem cell transplant (HCT) outcome, the indications for HCT continue to grow. Furthermore, the sources of stem cells and the number of suitable matches are expanding. At the same time, modified transplantation regimens have facilitated safer procedures despite increase in patient’s age and comorbidities. Viral infections are common in HCT recipients and continue to be a significant cause of morbidity and mortality. The viral infection risk is reported to be high among cord blood, mismatched, unrelated donor HCT and more high risk patients will receive HCT every year. The purpose of this paper is to review common non-seasonal viruses affecting HCT recipients and summarize their clinical presentation, prevention, monitoring, and treatment, with the goal of reducing preventable morbidity and mortality associated with viral infections after allo-HCT.

Key words: viral infections, viral reactivations, allogeneic hematopoietic stem cell transplantation, complications

Résumé
Nous célébrons en 2013 la millionième greffe de cellules souches hématopoïétiques (HCT). Avec l’amélioration continue des résultats, les indications à la greffe continuent de croître. En outre, les sources de cellules souches et le nombre de donneurs potentiels pour un même malade sont en expansion. Dans le même temps, la modification des régimes de conditionnement avant la greffe a permis la mise au point de procédures plus sûres, malgré l’augmentation de l’âge des patients et leurs comorbidités. Cependant, malgré ces progrès, les infections virales restent fréquentes chez les receveurs d’HCT et continuent d’être une cause importante de morbidité et de mortalité. Le risque d’infection virale est probablement le plus élevé parmi les receveurs de greffe de sang de cordon, ou en cas de donneur-receveur dit « mismatch » et non-apparenté. L’objectif de cette revue est de faire le point sur les virus non saisonniers courants qui affectent les receveurs d’HCT et synthétiser leur présentation clinique, les moyens de prévention, la surveillance à appliquer et les traitements permettant de réduire la morbidité évitable et la mortalité associées aux infections virales après HCT.

Mots clés : infections virales, réactivations virales, allogreffe de cellules souches hématopoïétiques, complications

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Viral infections after HCT

Over 50,000 patients worldwide each year undergo hematopoietic stem cell transplant (HCT) for curative intent of hematologic malignancies, solid tumors and other nonmalignant but potentially devastating medical conditions such as aplastic anemia [1]. Infections comprised of 8-16% of the cause of death in post-HCT recipients in 2008-09 [2]. Viral infections play a major role in the post-transplant recipients [3], and constitute up to 43% of all infections [4]. This article reviews major non-seasonal DNA viruses confronted by HCT recipients and briefly summarizes their prevention, monitoring, diagnosis, and treatment.

Varicella

Varicella zoster virus (VZV) is one of the most common viral diseases in post-HCT recipients with an estimated incidence between 17 to 50% [5-8]. While most VZV infections present as reactivation of the latent virus either as localized or less commonly disseminated herpes zoster, primary infection in the form of chickenpox also occurs. It is more common in children and usually occurs within the first 24 months after transplant [9]. Disease is mostly confined to the skin but cutaneous and visceral dissemination occurs occasionally with significant increase of mortality [10, 11]. Less common presentations include pneumonia or encephalitis. In one study, the mortality was around 2.5%; up to 54% of patients experienced significant complications such as post-herpetic neuralgia, motor weakness, scarring and bacterial superinfection [9]. In addition to VZV seropositivity or VZV infection prior to HCT, other factors associated with a higher incidence of VZV reactivation include age greater than or equal to 10 years, pretransplantation radiation with total body irradiation (TBI) or total lymphoid irradiation (TLI), graft-versus-host disease (GVHD), use of post-transplantation antithymocyte globulin, an underlying diagnosis other than chronic myelogenous leukemia and the use of cord blood [9, 12].

While the diagnosis of VZV remains mostly a clinical diagnosis, polymerase chain reaction (PCR) of skin lesions, direct fluorescent antibody of skin lesions, viral culture, serologic testing, and bronchoalveolar lavage, and CSF fluid can be used as confirmatory tests in atypical cases [13-15].

Currently, guidelines recommend that all HCT transplant candidates undergo testing for the presence of serum anti-varicella zoster virus (VZV) IgG antibodies [16]. If seropositive, acyclovir is routinely used for long term prophylaxis up to one year post-transplant as this regimen has been highly effective in reducing VZV reactivation [16-18]. The optimal length of time for prophylaxis beyond one year remains undefined. While some studies have found that the risk of VZV reactivation persists even with acyclovir use [19], others have argued that long-term prophylaxis of low dose acyclovir successfully prevented severe VZV-related symptoms and death and a significantly decreased incidence of VZV reactivation [20]. Varicella zoster immunoglobulin (VZIG) is administered to VZV seronegative post-HCT patients who are exposed to a close contact or household member with shingles or chickenpox [16]. Although there continues to be discussion about the length of prophylaxis in VZV-seropositive patients, intravenous acyclovir remains the mainstay of treatment in VZV infections and should be used for at least two days after all lesions have crusted [16]. Foscarnet has been used during the rare case of acyclovir resistance [19, 21]. High dose valacyclovir has also been used as an alternative to acyclovir in the treatment of VZV infections [22].

Herpes simplex virus

Herpes simplex 1 and 2 (HSV1 and 2) are two of the most common opportunistic viral infections following HCT with an incidence of 44% in adults and with the vast majority of cases being reactivation rather than primary infection. Prior to acyclovir prophylaxis, HSV reactivation occurred up 80% of seropositive adults and 30% of seropositive children following transplant [23, 24]. Risks for reactivation include age greater than 35 year, females, unrelated donor or cord blood grafts and GVHD [25]. Manifestations of HSV vary but localized mucocutaneous lesions in the orofacial or genital area are the most common presentation. Herpetic esophagitis occurs in 10% of patients [26]. Less common presentations include pneumonia (2-3%), hepatitis, meningitis, encephalitis and bone marrow suppression [26].

PCR remains the preferred test to diagnose HSV infections as it is the most sensitive and specific. Viral culture, immunofluorescence assay, Tzanck smear of skin scrapings, and serology are other methods of confirming HSV infection [26]. Routine surveillance of HSV reactivation via viral culture or PCR is not routinely recommended [26]. Patients are tested for serum anti-HSV IgG prior to transplant. To prevent reactivation, seropositive allogeneic patients are given prophylaxis with acyclovir until engraftment occurs or until mucositis resolves whichever is longer [16]. Longer courses are considered in patients with GVHD or a history of frequent reactivations before the transplantation [21]. Seronegative patients are usually not given acyclovir prophylaxis even when the donor is HSV positive [16]. Patients who are on cytomegalovirus (CMV) re-activation management do not need additional acyclovir prophylaxis given ganciclovir’s or foscarnet in vitro activity against HSV 1 and 2 [16]. Valacyclovir...
and famciclovir are two additional antiviral agents that have also been shown to provide adequate prophylaxis to HSV in the limited studies [26]. Intravenous acyclovir is the treatment of choice for severe mucocutaneous or visceral HSV infection with higher doses recommended for HSV pneumonia, meningitis, or encephalitis. Acyclovir is associated with shortened course of viral shedding and faster healing of lesions [27]. Oral acyclovir, famciclovir, or valacyclovir can be used for less serious HSV infections [26]. When HSV infections are unresponsive to therapy, resistance testing should be considered because 10% of HSV infections are acyclovir resistant [28]. Foscarnet and cidofovir are used for multidrug resistant HSV but these drugs must be administered with adequate hydration given their nephrotoxicity [26].

**Epstein-Barr virus**

Epstein-Barr virus (EBV) is a gamma herpes virus affecting over 90% of the world’s population, with the potential to cause uncontrollable B cell proliferation in humans [29]. It can manifest itself in post-HCT patients as primary infection or reactivation. Primary infections occur mainly in children in the form of mononucleosis, chronic active EBV infection, X-linked lymphoproliferative syndrome, and hemophagocytic lymphohistiocytosis (HLH). EBV reactivation is often subclinical, requiring no treatment, but can present in a multitude of clinical syndromes including encephalitis/myelitis, pneumonia, hepatitis, and post-transplant lymphoproliferative disorder (PTLD). The incidence of EBV-related PTLD is less than 2% but may be as high as 20% in patients with risk factors such as HLA-mismatch or unrelated donor, T cell depletion, severe GVHD, use of anti-T cell antibodies, umbilical cord transplants, haplo identical transplants, and the use of an EBV positive donor to an EBV negative recipient [30-34]. Mortality of untreated PTLD can be as high as 84% [35]. Testing for the presence of serum anti-EBV IgG antibodies in both HCT donors and candidates can help determine the risk of primary EBV infection [16]. Recent guidelines from the European Conference in Infections in Leukemia recommend patients at high risk for PTLD who are EBV-PCR negative undergo weekly screening for EBV DNA from the day of transplant to at least 3 months afterwards [26]. Longer monitoring is recommended for patients who have undergone mismatched, unrelated, T-depleted or haplo-HCT, and who experienced early EBV reactivation, or have GVHD [36]. A surveillance strategy for EBV reactivation by viral load monitoring is recommended for high-risk HCT recipients [26, 37]. Even though there is no defined viral load to define the diagnosis of PTLD or EBV reactivation, a rapid rise of viral load has been associated with the development of PTLD [38, 39]. Definitive diagnosis of PTLD requires the examination of biopsied tissue with immunohistochemistry or in situ hybridization in the appropriate clinical setting [39].

The initiation of preemptive therapy, defined as treatment given to an asymptomatic patient with EBV viremia, used to be a point of debate. Preemptive treatment generally reserved for high risk patients, such as those with X-linked lymphoproliferative disease, Wiskott-Aldrich syndrome, or undergoing treatment for rejection or GVHD [40]. The 4th European Conference in Infections in Leukemia (ECIL 4) recommends preemptive treatment with rituximab. Reduction of immunosuppressive agents, infusion of donor EBV-specific cytotoxic T-cell lymphocytes (CTL), and administration of cytotoxic T cell therapy are other options for preemptive therapy.

There is limited data regarding EBV prophylaxis. Antivirals such as ganciclovir, foscarnet and cidofovir have no effect on the prevention of PTLD. Immunoglobulin is not effective as a single agent in patients for prevention of EBV reactivation or infection [26]. First line treatment for PTLD is rituximab and reduction of immunosuppressive therapy although the latter is not always possible. The response rate to rituximab therapy is about 63% [41]. Rituximab has also been shown to prevent PTLD when used as preemptive therapy [41]. Infusions with EBV specific CTL have also been used for the prophylaxis and treatment of PTLD with good efficacy. However, there is a theoretical higher risk of GVHD following the therapy and the process of generating CTLs takes 8-10 weeks [42]. Response to treatment is defined as decrease in EBV-DNA load of at least 1 log of magnitude in the first week of treatment. Chemotherapy and hydroxyurea are considered second line therapy for PTLD [26].

**Human herpes virus 6**

Human herpes virus 6 (HHV-6) reactivation is common among pediatric and adult HCT recipients and 40-60% of all patients experience reactivation 2-4 weeks following transplant [43]. Clinical manifestations of HHV-6 reactivation include hepatitis, fever, rash, pneumonitis, gastrointestinal, myelosuppression and delayed engraftment, and encephalitis. While encephalitis is uncommon, occurring at 1-8% [44-46], it can be associated with high HHV-6 viral loads, poor neurologic outcomes and increased mortality [45, 47] and is considered the most significant clinical manifestation of HHV-6 disease. Risk factors for reactivation include allogeneic HCT, sex mismatch between donor and recipient, younger age, treatment with corticosteroids, advanced hematologic malignancy, myeloablative conditioning regimen, and use of cord blood [43, 47-51].
Diagnosis of HHV-6 infection is detection of virus by quantitative PCR in the plasma or CSF [47]. However, the virus can be chromosomally integrated and resulting in high viral load in the blood and sera without disease manifestations and produce false positives [52]. There are currently no guidelines for routine surveillance of viremia or prophylaxis [16].

While viremia can often resolve without treatment, foscarnet and gancyclovir, either alone or in combination, are recommended by International Herpes Management Forum as first line therapy for HHV-6 encephalitis given its associated high morbidity and mortality [53, 54]. Cidofovir can also be used but is considered second line therapy [54]. In general, treatments with gancyclovir, cidofovir, and foscarnet have been shown to be effective in most studies [51, 55, 56]. Antiviral treatment response was observed in 89% of the patients and was shown to shorten the duration of HHV-6 reactivation in one trial [51]. Only one study showed no significant change in survival; however, the study may have been underpowered to detect a clinical significance [46].

### Adenovirus

Adenovirus can occur in HCT recipients as primary infection or reactivation of latent virus. It is more common in the pediatric population with an incidence rate of 31-47%. The frequency ranges from 3-29% in adult population [57-62]. In healthy individuals, adenovirus causes mild respiratory and gastrointestinal illness. However, in immunocompromised HCT recipients, infection by adenovirus can lead to severe respiratory disease such as pneumonia, hepatitis, colitis, hemorrhagic cystitis and enteritis, nephritis, encephalitis, keratoconjunctivitis, and disseminated disease involving multiple organ failure [63]. Disseminated disease is associated with a mortality of 8-26% [63]. Patients considered highest risk are those who have refractory GVHD, umbilical cord blood transplantation, haploidentical transplantation, stem cell graft T-cell depletion of greater than 2-3 log_{10}, and use of anti-T cell antibodies such as antithymocyte globulin (ATG) or alemtuzumab [64, 65].

PCR of adenooviral load in peripheral blood is the preferred diagnostic test as it is the fastest and most sensitive test compared to viral culture and direct fluorescence assay [66, 67]. Adenovirus can also be detected in stool and nasal washings via PCR and the presence of virus in local sites often precedes invasive viremia by up to 11 days [68]. It is recommended to consider ophthalmology consult to screen for keratoconjunctivitis as well as gastroenterology consult for endoscopy with biopsies for diarrhea [63]. Weekly PCR monitoring for the first 6 months following HCT or the duration of severe immunsuppression can be considered for high-risk patients [63]. There is some controversy regarding the timing of initiation of treatment. Lindemans, et al [63], suggests starting preemptive treatment for high risk patient with a viral load of greater than 100cp/ml. This may be based on studies which demonstrate increased morbidity and mortality with high viral loads of adenovirus [69].

Treatment of adenovirus ranges from antiviral therapy to immunotherapy. Cidofovir is the most efficacious agent [63]. It is co-administered with probenecid and generous hydration to decrease nephrotoxicity. Ribavirin is also used but with varying effect as in-vitro adenovirus activity differs widely between subtypes [63]. Most recently, CMX001, a lipid-conjugate of the nucleotide analog, cidofovir, was shown to eradicate disseminated adenovirus infection in a HCT recipient [70]. While antivirals have some efficacy, viral clearance occurs when T cells reconstitute after HCT [63]. Adenovirus-specific cytotoxic T cells have also been shown to be effective but their use is limited to certain centers [63].

### Hepatitis B

Hepatitis B virus (HBV) reactivation can occur in 14-50% of patients undergoing allogeneic HCT [71-73]. Clinical manifestation of reactivated HBV ranges from asymptomatic patients with rising ALT and HBV DNA levels to hepatitis leading to fulminant liver failure. Mortality of HBV reactivation ranges from 4 to 41% [71]. The following groups of people are at risk for developing severe hepatitis B infection: 1) HBV naïve patients exposed to HBV via infected donor, blood products, or sexual contact; 2) HCT recipients with chronic HBV infection, 3) HCT recipients undergoing prolonged immune suppression who have serologic evidence of resolved or occult HBV. Additional risk factors include allogeneic HCT from unrelated donor, steroids, and GVHD [71].

Thus, current guidelines recommend that all HCT recipients and donors undergoing testing for past or active HBV infection with HBV surface antigen (HBSAg), antibodies to HBV core antigen (anti-HBc), and antibodies to HBV surface antigen (anti-HBs). Donors and recipients who test positive for HBSAg and anti-HBc are tested for HBV DNA [16]. Antiviral treatment is recommended for recipients with a positive HBV DNA. Prophylactic treatment is offered to recipients with positive anti-HBc and HBSAg. Duration of treatment has not be studied but continuing treatment 6 months after cessation of immunosuppressive therapy is commonly practiced. Quarterly monitoring of anti-HBs levels is recommended. HBV DNA testing should follow if anti-HBs titers are reduced. Patients who lose anti-HBs responses with undetectable HBV DNA can receive active immunization; patients with detectable HBV DNA receive antiviral therapy [16].
Ideally, all HBV naïve recipients undergo vaccination with HBV prior to transplant. If post-vaccination anti-HBs titer <10 IU/L or if recipients are unable to undergo vaccination prior to transplant, HBIG can be administered but not routinely recommend prior to stem cell infusion. All HCT recipients who remain uninfected post-HCT and fail to respond to pretransplant vaccination are revaccinated after immune recovery [16]. Although viral transmission is not universal, an HBV naïve recipient preferably should not receive HCT from a donor with past or active HBV infection (depending on availability of alternative stem cell source). Donors with a detectable HBV DNA load should receive antiviral treatment for at least 4 weeks or until viral load is undetectable. Another acceptable option is that the harvest should be reduced to the smallest allowable volume, tested for HBV DNA, and recipients are managed based on donor’s HBV-DNA status. If the donor and harvest are HBV DNA-negative, monthly ALT level is monitored in the first 6 months, and HBV DNA or HBsAg levels are tested if the ALT rises. Antiviral treatment is indicated in recipients with a detectable HBV DNA load or positive HBsAg. If donor or harvest product is positive for HBV DNA, the recipient receives prophylaxis with lamivudine from time of transplant to 6 months following cessation of immunosuppressive drugs and administering Hepatitis B immunoglobin (HBIG) 4 weeks post transplant. ALT and HBV DNA are monitored monthly with modifications in treatment if HBV DNA is detectable while on lamivudine prophylaxis [16]. Lamivudine remains the first line therapy for HBV reactivation and HCT patients with chronic hepatitis B. Length of treatment is usually at least 6 months following transplant in autologous recipients, at least 6 months after cessation of immunosuppressive therapy in allogeneic HCT recipients, and much longer for those receiving treatment for GVHD [16]. Lamivudine is most effective when HBV DNA levels are just starting to rise. Therefore, frequent monitoring of HBV levels is recommended to prevent the high mortality associated with reactivated HBV [74]. Entecavir and tenofovir have also been used with success in a case report for treatment of reactivated hepatitis B [75].

**BK virus**

Human polyomavirus type I, or more commonly known as the BK virus, can reactivate and cause organ dysfunction in HCT recipients. Urinary shedding of BK occurs in 60-80% of recipients but BK associated hemorrhagic cystitis is observed at a frequency of 5-15% three to six weeks following transplant [76-80]. Besides hemorrhagic cystitis, BK can also induce nephropathy which can lead to chronic kidney disease or end stage renal disease requiring dialysis. Pneumonitis, upper respiratory infections, hepatitis and encephalitis are less common presentations of BK viral infection [81]. Reported predisposing factors include GVHD and patients with positive PCR prior to transplant and recipients of unrelated or haploidentical or cord blood rafts have higher risks of developing hemorrhagic cystitis [82]. Urine analysis is often used in the initial diagnosis of hemorrhagic cystitis. A basic metabolic panel and urine analysis can be used in the diagnosis of nephropathy. PCR in the urine and blood is often used to confirm that hemorrhagic cystitis or nephropathy is induced by BK virus. A recent study showed that patients with higher BK plasma viral loads had a worse clinical course, significant renal dysfunction, and increased mortality [83]. However, there are no guidelines regarding routine monitoring or frequency of PCR measurements once the diagnosis of BK-induced hemorrhagic cystitis or nephropathy is made [16]. Currently, the treatment for hemorrhagic cystitis is largely supportive with pain control, intravenous fluids, bladder irrigation, and transfusion support as needed. Cidofovir has been used to treat BK induced hemorrhagic cystitis but there have been no clinical trials to demonstrate its efficacy [84]. BK induced nephritis/nephropathy is also treated with supportive care with intravenous fluids and renal replacement therapy [16].

**Cytomegalovirus**

Cytomegalovirus (CMV) is a significant pathogenic disease causing primary infection and reactivation of latent disease in 50-80% of HCT recipients [85, 86]. Prior to antiviral therapy, 25% of at-risk recipients died from CMV disease within one year after transplant [87]. Clinical manifestations of CMV disease can vary significantly, including pneumonia, hepatitis, mononucleosis, gastritis, retinitis, encephalitis, esophagitis, colitis, retinitis and myelosuppression [88]. Among them, CMV pneumonia is considered the most serious manifestation as it is associated with a high mortality rate of greater than 50% [89]. The risk factors for CMV reactivation and primary infection include all CMV-seropositive recipients, CMV-seronegative recipients receiving seropositive donor cells [16], use of alemtuzumab during conditioning, high dose corticosteroids, T-cell depletion, reduced-intensity conditioning transplant, GVHD, and use of mismatched or unrelated donors [85, 90]. Current guidelines recommend that all transplant candidates undergo testing for the presence of anti-CMV IgG antibodies prior to transplant to determine their risk of primary CMV infection and reactivation [16]. To decrease the risk of transmission, CMV-seronegative recipients are provided CMV-negative or leukocyte depleted blood.
<table>
<thead>
<tr>
<th><strong>Rate</strong></th>
<th><strong>Diagnosis</strong></th>
<th><strong>Risk Factors</strong></th>
<th><strong>Clinical Manifestations</strong></th>
<th><strong>Monitoring</strong></th>
<th><strong>Prophylaxis</strong></th>
<th><strong>Treatment</strong></th>
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<tbody>
<tr>
<td><strong>Varicella</strong></td>
<td>17 to 50% Usually clinical. Confirmed by PCR, direct fluorescent antibody, viral culture, and serologic testing</td>
<td>age ≥ 10 years, pretreatment radiation with total body irradiation (TBI) or total lymphoid irradiation (TLI), graft-versus-host disease (GVHD), use of post-transplantation antithymocyte globulin, underlying diagnosis other than chronic myelogenous leukemia, use of cord blood</td>
<td>Vesicular rash, visceral dissemination, pneumonia, encephalitis</td>
<td>none</td>
<td>Acyclovir for seropositive recipients</td>
<td>Acyclovir, valacyclovir, foscarnet</td>
</tr>
<tr>
<td><strong>Herpes Simplex Virus (HSV)</strong></td>
<td>40-50% Up to 80% reactivation in adults and 30% reactivation in children</td>
<td>Age ≥ 35, females, unrelated donor grafts and GVHD</td>
<td>mucocutaneous lesions in the orofacial or genital area, herpetic esophagitis, pneumonitis, hepatitis, meningitis, encephalitis and bone marrow suppression</td>
<td>None</td>
<td>Acyclovir, valacyclovir, famciclovir for seropositive recipients</td>
<td>Acyclovir, valacyclovir, famciclovir, foscarnet, cidofovir</td>
</tr>
<tr>
<td><strong>Epstein-Barr Virus (EBV)</strong></td>
<td>&lt;2% PTLD, but up to 20% in patients with risk factors</td>
<td>HLA-mismatch or unrelated donor, T cell depletion, severe GVHD, use of anti-T cell antibodies, umbilical cord transplants, haploidentical transplants, and the use of an EBV positive donor to an EBV negative recipient</td>
<td>mononucleosis, chronic active EBV infection and X-linked lymphoproliferative syndrome, including encephalitis/myelitis, pneumonia, hepatitis, and post-transplant lymphoproliferative disorder (PTLD)</td>
<td>Weekly screening for EBV DNA in high risk patients</td>
<td>None</td>
<td>PTLD: reduction of immunosuppression, rituximab, EBV specific cytotoxic T cell lymphocytes</td>
</tr>
<tr>
<td><strong>Human Herpes Virus-6 (HHV-6)</strong></td>
<td>40-60% reactivation</td>
<td>PCR</td>
<td>allogeneic HCT, sex mismatch between donor and recipient, younger age, treatment with corticosteroids, advanced hematologic malignancy, and use of cord blood</td>
<td>hepatitis, fever, rash, pneumonitis, gastroduodenitis, myelosuppression and delayed engraftment, and encephalitis</td>
<td>None</td>
<td>gancyclovir, cidofovir, and foscarnet</td>
</tr>
<tr>
<td><strong>Adenovirus</strong></td>
<td>31-47% in children; 3-29% in adults</td>
<td>PCR, viral culture, direct fluorescent assay, biopsy</td>
<td>refractory GVHD, umbilical cord blood transplantation, haploidentical transplantation, stem cell graft T cell depletion of greater than 2-3 log&lt;sub&gt;10&lt;/sub&gt;, and use of anti-T cell antibodies such as antithymocyte globulin (ATG) or alemtuzumab</td>
<td>pneumonia, hepatitis, colitis, hemorrhagic cystitis and enteritis, nephritis, encephalitis, keratoconjunctivitis, disseminated disease</td>
<td>Weekly PCR in high risk patients</td>
<td>cidofovir, ribavirin, CMX001, adenovirus-specific cytotoxic T cells</td>
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<tr>
<td>Rate</td>
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<tr>
<td><strong>Hepatitis B</strong></td>
<td>14-50%</td>
<td>HBV naive patients exposed to HBV via infected donor, blood products, or sexual contacts, recipients with chronic HBV infection, recipients undergoing prolonged immune suppression who have serologic evidence of resolved or occult HBV, allogenic HCT from unrelated donor, steroids, and GVHD</td>
<td>Rising ALT levels, hepatitis, fulminant liver failure</td>
<td>Monthly monitoring of ALT followed by HBV DNA or HBsAg if ALT rises in high risk patients</td>
<td>Lamivudine in patients with chronic or past infection of HBV, or patients with HBV positive donors</td>
<td>Lamivudine, Entecavir, and tenofovir</td>
</tr>
<tr>
<td><strong>BK Virus</strong></td>
<td>5-15% for hemorrhagic cystitis</td>
<td>Urine analysis, basic metabolic panel, PCR</td>
<td>Hemorrhagic cystitis, nephropathy</td>
<td>None</td>
<td>None</td>
<td>pain control, intravenous fluids, bladder irrigation, transfusion support, renal replacement therapy</td>
</tr>
<tr>
<td><strong>Cytomegalovirus (CMV)</strong></td>
<td>50-80%</td>
<td>CMV pp65 antigen, CMV DNA by PCR, or CMV RNA, viral cultures, biopsy</td>
<td>CMV-seropositive recipients, CMV-seronegative recipients receiving seropositive donor cells (16), use of alemtuzumab during conditioning, high dose corticosteroids, T-cell depletion, reduced-intensity conditioning transplant, GVHD, and use of mismatched or unrelated donors</td>
<td>Weekly CMV PCR or antigen test</td>
<td>Ganciclovir, high dose acyclovir and high dose valacyclovir</td>
<td>Ganciclovir, foscarnet, cidofovir</td>
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products [91, 92]. Additionally, HCT transplant from a CMV-negative donor is preferred for seronegative recipients as primary CMV infection occurs in 30% of seronegative recipient from a seropositive donor [93, 94]. For the diagnosis and monitoring of CMV infection, preferred diagnostic tests include CMV pp65 antigen, CMV DNA by PCR, or CMV RNA via peripheral blood [95]. PCR is the most sensitive. The CMV pp65 antigen is a rapid and useful for predicting the development of invasive disease but can be falsely negative in patients with neutropenia [16, 96]. Viral cultures of bronchoalveolar lavage, urine, saliva, or blood are other modalities for diagnosis but they are less sensitive [16]. Detection of CMV can also be seen on biopsy specimens via histology or culture [97].

Because CMV-seropositive recipients and CMV-seronegative recipients with a seropositive donor are considered high risk for CMV infection and reactivation, prophylaxis or preemptive treatment is warranted in these patients from time of engraftment to at least 100 days after HCT [16]. Ganciclovir, high dose acyclovir and high dose valacyclovir can be used for the prophylaxis against CMV [98-100]. When high dose acyclovir or valacyclovir are used for prophylaxis, routine viral monitoring is recommended [85].

While valacyclovir is more effective than acyclovir in reducing CMV infection and the need for preemptive therapy, there is no effect on overall survival [100]. IVIG is currently not routinely recommended for prophylaxis because there was no advantage in terms of infection prevention or survival and there was increased risk of veno-occlusive disease [16, 101]. Preemptive therapy is defined as the initiation of antiviral therapy upon detection of CMV viremia and replication through routine monitoring. High risk recipients are recommended to undergo weekly screening up to at least 100 days following HCT [16]. Once CMV viremia is detected, ganciclovir remains first line for preemptive therapy [102]. Antiviral treatment should be given for a minimum of two weeks. Maintenance therapy is required if CMV is still detected two weeks following treatment and weekly monitoring for CMV viremia is recommended after discontinuation of preemptive therapy [16]. Valganciclovir, an oral prodrug of ganciclovir, has similar efficacy and safety compared to ganciclovir for preemptive treatment of CMV [103, 104]. Foscarnet and cidofovir are also effective for preemptive therapy if drug resistance occurs or if ganciclovir is not tolerated because of neutropenia [102]. Foscarnet and cidofovir are second line therapies because of associated nephrotoxicity.

The same antivirals used for preemptive therapy are also used for CMV disease. Ganciclovir or foscarnet in combination with IVIG are the mainstays of treatment of CMV pneumonia. For CMV colitis or esophagitis, IV ganciclovir or foscarnet are standard therapy choices. Systemic ganciclovir, foscarnet or cidofovir +/- intraocular ganciclovir injections/implants are used for CMV retinitis [85].

There are many new treatments in development for the treatment of CMV following HCT, including the ongoing trials of the effectiveness of the antiviral agent, maribavir, for the prophylaxis and treatment of CMV [105, 106]. More recently, a CMV DNA vaccine has shown promise in reducing the occurrence and recurrence of CMV viremia in a phase 2 trial [107].

In some cases, CMV drug resistance occurs and is characterized by increasing CMV viral loads or the development of CMV disease despite antiviral therapy. Genotype resistance studies are available to guide changes to antiviral therapy [95].

**Conclusion**

Viral reactivation continues be a major cause of significant morbidity and mortality in immunocompromised HCT recipients. While the management of certain viral infections is straightforward, the complex course of some diseases and the side effects of treatment preclude a “one size fits all” approach (See table 1). More research and development is needed in order to determine the proper monitoring, prophylaxis and treatment of viral infections following hematopoietic stem cell transplantation.

**Conflicts d’intérêt : Aucun.**

**Références**


