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GUIDELINES

Viral disease prevention after hematopoietic cell transplantation

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Recommendations regarding CMV

Preventing exposure

Hematopoietic cell transplant (HCT) candidates should be tested for the presence of serum anti-CMV IgG Abs before transplantation to determine their risk for primary CMV infection and reactivation after HCT (AII). CMV is shed intermittently from the oropharynx and from the genitourinary tract of both immunocompetent and immunosuppressed subjects. There are no data showing that avoiding these body fluids is feasible or effective in preventing the acquisition of CMV in CMV-seronegative HCT recipients. As CMV-seronegative pregnant healthcare workers (HCWs) may be at risk for contracting CMV from these and other patients, standard universal precautions should be used in these situations.

With proper management, CMV-seronegative patients have a low risk for contracting CMV infection. To reduce the risk of CMV transmission, blood products from CMV-seronegative donors or leukocyte-depleted blood products should be used in CMV-seronegative allogeneic HCT recipients (AI).[209–211] The benefit of using either of these products in autologous HCT recipients to prevent CMV transmission is less clear. However, as many autologous HCT recipients have received previous T-cell-suppressive therapy, such as fludarabine or alemtuzumab, the use of CMV-safe blood products is recommended (BII). In many centers, and even in several countries, leukocyte filtration of blood products is mandatory. No controlled study has examined the potential benefit of the combination of seronegative blood products and filtered blood products. Leukocyte filtration should be performed at the blood bank and the established quality standard of $<5 \times 10^6$ residual leukocytes per unit should be followed (AII).[212,213]

Preventing disease and disease recurrence

Hematopoietic cell transplant recipients at risk for post transplant CMV disease (that is, all CMV-seropositive HCT recipients, and all CMV-seronegative recipients with a CMV-seropositive donor) should be placed on a CMV disease prevention program from the time of engraftment until at least 100 days after HCT (that is, phase II) (AI). Physicians should use either prophylaxis or preemptive treatment for allogeneic recipients (AI). In selecting a CMV disease prevention strategy, physicians should assess the risks and benefits of each strategy, the needs and condition of the patient and the hospital's virology laboratory support capability.

A prophylaxis strategy against early CMV replication (that is, <100 days after HCT) for allogeneic recipients involves administering prophylaxis to all allogeneic recipients at risk throughout the period from engraftment to 100 days after HCT (Appendix 1) (AI). Ganciclovir, high-dose acyclovir and valacyclovir have all shown efficacy in randomized studies in reducing the risk for CMV infection after HCT.[214–216] If ganciclovir is used, the induction course is usually started at engraftment (AI),[214,217,218] although a brief prophylactic course can be added during pretransplant conditioning (CIII). If acyclovir or valacyclovir is used, the patient must also undergo viral monitoring and receive preemptive antiviral therapy if evidence of CMV replication is found (AI).[215,216] For CMV disease prophylaxis, i.v. Ig is not recommended among HCT recipients (EIII).

In patients with CMV disease documented before transplantation, transplantation should be delayed until the disease is adequately treated (BII), and use of secondary anti-CMV prophylaxis during HCT should be considered

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(BIII).[219] Such patients should be closely monitored during the HCT procedure, including during the preengraftment phase if the transplant center usually starts monitoring for CMV reactivation after engraftment, and a low threshold for preemptive treatment should be used (BIII).[219]

The preemptive strategy targets antiviral treatment to those patients who have evidence of CMV replication after HCT (Appendix 1). It requires the use of sensitive and specific laboratory tests to rapidly diagnose CMV replication after HCT and to enable the immediate administration of effective antiviral therapy after CMV replication has been detected. Allogeneic recipients at risk should be screened for the presence of CMV in blood samples approximately once a week from 10 days to at least 100 days after HCT (that is, phase II) (AIII). CMV-seropositive cord blood transplant recipients are at increased risk of CMV reactivation and disease.[220,221] Thus, some researchers use acyclovir or valacyclovir prophylaxis[215,216] in combination with preemptive therapy in these patients (CIII). A preemptive strategy against early CMV replication (that is, <100 days after HCT) for allogeneic recipients is preferred over prophylaxis for CMV-seronegative HCT recipients of seropositive donor cells (that is, D positive and R negative) because of the low attack rate of CMV replication if screened or filtered blood product support is used (BII).

Diagnostic tests to determine the need for preemptive treatment include the detection of CMV pp65 Ag in leukocytes (antigenemia),[217,222] detection of CMV DNA by quantitative PCR[223–225] or the detection of CMV RNA.[226] HCT centers performing allogeneic transplants should have the capacity to perform one of these tests (AIII). Viral cultures of urine, saliva, blood or bronchoalveolar washings by rapid shell-vial culture[227] or routine culture[228,229] are today rarely used, as these techniques are less sensitive than CMV-DNA PCR or CMV pp65 antigenemia tests. However, it should be recognized that CMV pp65 antigenemia tests may be falsely negative in patients with neutropenia.

Ganciclovir is often used as a first-line drug for preemptive therapy. Although foscarnet is as effective as ganciclovir,[230] it is currently more commonly used as a second-line drug because of practical reasons (for example, requirement for prehydration and electrolyte monitoring). Allogeneic recipients who are $\leqslant 100$ days after HCT should begin preemptive treatment if CMV viremia, antigenemia or DNA is detected (AI). Preemptive therapy should be given for a minimum of 2 weeks (A1).[217] If CMV is still detected after 2 weeks of therapy, maintenance therapy can be given until CMV is undetectable,[230] or it can be continued up to day 100 (AI).[217] After discontinuation of preemptive therapy, routine weekly screening is necessary up to at least day 100 because recurrent episodes of CMV viremia commonly occur (BII).

At present, only the i.v. formulation of ganciclovir has been approved for use in CMV prophylactic or preemptive strategies (AI). Valganciclovir, a prodrug of ganciclovir, has been increasingly used in preemptive therapy,[231–234] and an interim analysis of a randomized, controlled study has shown comparable results in patients treated with i.v. ganciclovir or valganciclovir.[235] Dose adjustment for renal insufficiency is necessary with either drug to avoid hematological toxicity. Patients who are ganciclovir intolerant should be treated with foscarnet (AI).[236] HCT recipients receiving ganciclovir should have ANCs checked more than twice a week (BIII). Experts report managing ganciclovir-associated neutropenia by adding G-CSF[237] or temporarily stopping ganciclovir for ≈ 2 days if the patient's ANC is <1000 (CIII). Ganciclovir can be restarted when the patient's ANC is ≈ 1000 for two consecutive days. Alternatively, foscarnet can be substituted for ganciclovir if CMV can still be detected in blood. As neutropenia accompanying ganciclovir administration is usually brief, such patients do not require antifungal or antibacterial prophylaxis (DIII).

True CMV antiviral resistance is quite rare in HCT patients, especially in those who have never been previously treated with antiviral agents. Increasing antigenemia or CMV DNA load early after initiation of antiviral therapy is usually not a sign of treatment failure in patients who have not been previously treated with antiviral agents, and therefore does not necessitate a change of therapy.[238,239] However, if the patient develops signs of CMV disease or if the level of antigenemia or the CMV DNA load continues to rise after more than 2 weeks of therapy, resistant CMV should be suspected and a change of therapy considered (BIII). Development of CMV drug resistance early after HCT has been observed in children transplanted for immunodeficiency or in those who received T-cell-depleted grafts or anti-T-cell Abs.[240] Ganciclovir or foscarnet can be considered as an alternative drug for second-line preemptive therapy (AI).[230] Cidofovir, a nucleoside analog, can be considered for second-line preemptive therapy, but careful monitoring of renal function is required, and it should be noted that cross-resistance with ganciclovir can occur (BII).[241–243] If possible, samples should be sent to a laboratory capable of documenting antiviral resistance (CIII).[244]

Certain CMV-seropositive autologous recipients are at increased risk for symptomatic CMV replication or disease.[245] These include patients undergoing conditioning regimens including TBI; patients receiving grafts manipulated to remove T cells; and patients who have recently (for example, within 6 months before HCT) received alemtuzumab, fludarabine or 2-chlorodeoxyadenosine. Such patients may benefit from the use of a preemptive strategy that includes monitoring for CMV reactivation until 60 days after HCT (CII). Patients transplanted with CD34+-selected grafts should be treated at any level of antigenemia[245] (BII). Other autologous recipients at high risk who experience moderately high levels of CMV antigenemia (that is, blood levels of $\geqslant 5$ positive cells per slide) or CMV DNA should receive 2 weeks of preemptive treatment with ganciclovir or foscarnet (CIII).[222] A prophylactic approach to CMV disease prevention is not recommended for CMV-seropositive autologous recipients (DII).[246]

As HCT recipients might develop two or more reactivations, patients considered to be at increased risk for late CMV disease should be routinely screened for evidence of CMV reactivation as long as substantial immunocompromise persists (BII)[247] (Appendix 1). Risk factors for late CMV disease include allogeneic HCT accompanied by chronic GVHD; steroid use; low CD4

counts (<50 cells per mm^3); use of grafts from CMV-seronegative donors in CMV-seropositive recipients; and use of unrelated, haploidentical, cord blood or T-cell-depleted HCTs.[248–251] The indication for antiviral therapy if CMV is detected after day 100 has to be determined on an individual basis depending on the patient's risk factors for developing late CMV disease (BIII). The choice and duration of antiviral therapy are similar to those for CMV infection that occurs during the first 100 days post transplant.

Strategies for preventing late CMV disease in high-risk patients include the use of continued surveillance and preemptive antiviral therapy,[247] as well as prophylaxis with antiviral drugs and cellular immunotherapy for patients with deficient or absent CMV-specific immune system function. Several small phase I/II studies have been published using adoptive transfer of CMV-specific CD4+ and/or CD8+ T cells, especially in patients developing repeated episodes of CMV disease.[252–255] However, none of these adoptive T-cell transfer techniques are in routine clinical practice and therefore cannot be recommended.

Recommendations regarding EBV

Preventing exposure

Hematopoietic cell transplant donors and candidates should be tested for the presence of serum anti-EBV IgG Abs before transplantation to determine the risk for primary EBV after HCT. The recommendation is stronger in pediatric patients (AII) than in adults (BII). Although fever and mononucleosis can occur in primary EBV infection, the most significant clinical syndrome associated with EBV replication in HCT recipients, particularly after primary infection, is post transplant lymphoproliferative disease (PTLD).[256] This disorder occurs principally in recipients with profound T-cell cytopenia (for example, after T-cell depletion, use of anti-T-cell Abs, umbilical cord blood transplants and haploidentical transplants).[257–259] Assessment of blood EBV DNA loads with quantitative PCR testing can identify those at risk for PTLD.[260–262]

In HCT recipients, EBV disease typically results from reactivation of endogenous infection or transmission of EBV from the graft.[258] Nevertheless, all transplant candidates, particularly those who are EBV seronegative, should be advised of behaviors that decrease the likelihood of EBV exposure (AII) (see Strategies for Safe Living after HCT).

Preventing disease

For prevention of EBV-related PTLD (Appendix 1), it is important to monitor high-risk (for example, after T-cell depletion, use of anti-T-cell Abs, umbilical cord blood transplants and haploidentical transplants) patients for EBV DNA load using a blood EBV PCR assay (BII). EBV DNA loads have been shown to rise as early as 3 weeks before disease onset. Monitoring for blood EBV DNA loads allows preemptive reduction in immunosuppression, if possible, as the first part of patient management. Owing to the variability of PCR techniques and the difference in risk for EBV-related PTLD depending on the degree of T-cell lymphopenia, no firm recommendation on the threshold for initiation of preemptive therapy can be made. If there is no response to reduction in immunosuppression, preemptive treatment with rituximab can prevent PTLD (BII).[263] Infusion of donor-derived, EBV-specific CTL has shown promise in the prophylaxis of EBV lymphoma among recipients of T-cell-depleted unrelated or mismatched allogeneic recipients (CII).[264,265] In addition, expanded donor-derived EBV-specific T cells have been used to control blood EBV DNA loads in this setting, but this procedure remains experimental (CII).[266,267] Use of B-cell depletion to minimize the risk of EBV PTLD has also been proposed (CII).[268] Finally, prophylaxis or preemptive therapy with currently available antiviral agents is not recommended because of lack of efficacy (DII).[257–259]

Recommendations regarding HSV

Preventing exposure

Hematopoietic cell transplant candidates should be tested for serum anti-HSV IgG before transplant (AII); however, type-specific anti-HSV IgG serology testing is not necessary. All HCT candidates, particularly those who are HSV seronegative, should be informed of the importance of avoiding HSV infection while immunocompromised and should be advised of behaviors that will decrease the likelihood of HSV exposure (AII) (see Strategies for Safe Living after HCT). Any person with disseminated, primary or severe mucocutaneous HSV disease should be placed under contact precautions for the duration of illness (AII)[144] to prevent transmission of HSV to HCT recipients.

Preventing disease and disease recurrence

Acyclovir. Acyclovir prophylaxis should be offered to all HSV-seropositive allogeneic recipients to prevent HSV reactivation during the early post transplant period (AI).[269–273] The standard approach is to begin acyclovir prophylaxis at the start of conditioning therapy and continue until engraftment occurs or until mucositis resolves, whichever is longer, or $\approx$30 days after HCT (AI)[272] (Appendix 1). The continued use of acyclovir seems to prevent HSV reactivation disease in patients who received it for VZV or CMV prophylaxis (CII).[274] Routine acyclovir prophylaxis is not indicated for HSV-seronegative HCT recipients, even if the donor is HSV seropositive (DIII). Use of ganciclovir prophylaxis for CMV in HCT recipients is sufficient for the prevention of HSV because of this drug's *in vitro* activity against HSV-1 and HSV-2 (AII),[214,275] although ganciclovir has not been approved for use against HSV.

Acyclovir-resistant HSV infection occurs mainly in the setting of low-dose prophylaxis, intermittent treatment or with HSV-seronegative donors.[274,276,277] Foscarnet is the treatment of choice for resistant disease (BI); cidofovir may serve as an alternative (CIII). If post-engraftment acyclovir prophylaxis is given, experts recommend a sufficiently high dose to prevent the emergence of resistance (Appendix 1).[274]

Valacyclovir. Although valacyclovir is not approved for use in preventing HSV disease among HCT recipients,

comparative studies have shown that valacyclovir and acyclovir are equally effective in suppression of HSV after autologous HCT[278,279] in patients who can tolerate oral medications (CIII). Regarding safety, valacyclovir has been used for 1 year in HCT recipients for suppression of VZV without toxicity.[280] Physicians wishing to use valacyclovir in recipients with renal impairment should exercise caution and decrease the dose as needed.

Foscarnet. Owing to its substantial renal and infusion-related toxicity, foscarnet is not recommended for routine HSV prophylaxis in HCT recipients (DIII). However, patients who receive foscarnet for other reasons (for example, CMV prophylaxis) do not require additional acyclovir prophylaxis (DIII).

Famciclovir. At present, data regarding safety and efficacy of famciclovir among HCT recipients are limited; therefore, no recommendations for HSV prophylaxis with famciclovir can be made.

Other recommendations

HSV prophylaxis lasting >30 days after HCT might be considered for persons with frequent recurrences of HSV infection (BIII) (Appendix 1). Acyclovir or valacyclovir can be used during phase I (preengraftment) for administration to HSV-seropositive autologous recipients who are likely to experience substantial mucositis from the conditioning regimen (CIII). Acyclovir prophylaxis doses should be modified for use among children (Appendix 1). Owing to limited published data regarding valacyclovir safety and efficacy among children, no recommendations for the pediatric population can be made.[281]

Recommendations regarding VZV

Preventing exposure

Hematopoietic cell transplant candidates should be tested for the presence of serum anti-VZV IgG Abs (AII). However, these tests are not 100% reliable, particularly among severely immunosuppressed patients. All HCT candidates and recipients, particularly those who are VZV seronegative, should be informed of the potential seriousness of VZV disease among immunocompromised persons and advised of strategies to decrease their risk for VZV exposure (AII).[282]

Although the majority of VZV disease after HCT is caused by reactivation of endogenous VZV, HCT candidates and recipients who are VZV seronegative, or VZV seropositive and immunocompromised, should avoid exposure to persons with active VZV infections (AII).[283] HCWs, family members, household contacts and visitors who are healthy and who do not have a reported history of varicella infection or who are VZV seronegative should receive VZV vaccination before being allowed to visit or have direct contact with an HCT recipient (AIII). Ideally, VZV-susceptible family members, household contacts and potential visitors of immunocompromised HCT recipients should be vaccinated as soon as the decision is made to perform HCT and the vaccination schedule should be completed $\approx$4–6 weeks before HCT is performed (BIII). To date, no serious disease has been reported among immunocompromised patients from transmission of VZV vaccine virus, and the VZV vaccine strain is susceptible to acyclovir. However, HCT recipients undergoing conditioning therapy should avoid contact with any VZV vaccine recipient who experiences a rash after vaccination (BIII). Rash after vaccination can be due to wild-type VZV (median: 8 days; range: 1–20 days) or the VZV vaccine strain (median: 21 days; range: 5–42 days).[284,285]

All HCT recipients with multidermatomal VZV disease should be placed under airborne and contact precautions (AII)[144] to prevent transmission to other HCT recipients. Dermatomal zoster requires contact precautions until all skin lesions are crusted (AII), and some researchers also recommend airborne precautions because in immunocompromised patients, there is a high risk for dissemination of the zoster rash (CII). Airborne precautions should be instituted 8 days after exposure to VZV and continued until 21 days after last exposure (AII) or 28 days after exposure if the patient received varicella-zoster Ig (VZIG) (BII),[144] because a person infected with VZV can be infectious before the rash appears. The VZIG product currently available in the United States is VariZIG (Cangene Corporation, Winnipeg, Canada).[286]

Preventing disease

Antiviral drugs. Long-term acyclovir prophylaxis to prevent recurrent VZV infection is routinely recommended for the first year after HCT for VZV-seropositive allogeneic (BI)[280,287] and autologous (CII) HCT recipients (Appendix 1). The 1-year regimen of acyclovir is highly effective in reducing the risk of VZV disease during the year of acyclovir administration (BI).[280,287] Acyclovir prophylaxis may be continued beyond 1 year in allogeneic HCT recipients who have chronic GVHD or who require systemic immunosuppression (BII).[280,288] The optimal duration of prophylaxis is poorly defined in patients with chronic GVHD, as there seems to be a persistent risk of VZV reactivation disease even if acyclovir is continued until all systemic immunosuppressive drugs are discontinued and the CD4+ count exceeds 200 cells per μl.[288] Some clinicians advocate continuing acyclovir prophylaxis until 6 months after discontinuing all systemic immunosuppressive agents (CIII).

Valacyclovir is a prodrug of acyclovir and may be used as an alternative to acyclovir at any time that oral medications are used. Valacyclovir may provide higher drug levels in severely immunosuppressed patients than does acyclovir (BII). Although valacyclovir is not licensed in the United States for use in HCT recipients, a large randomized trial in HCT recipients found no safety issues with valacyclovir, even when used at very high doses.[216] No data on famciclovir in HCT recipients were found; consequently, no recommendations can be made regarding its use in place of acyclovir or valacyclovir.

Resistance to acyclovir has been rarely documented to date in HCT recipients;[289] however, when clinically suspected or virologically documented, acyclovir resistance occurs among patients, HCT physicians should use foscarnet for preemptive treatment of VZV disease (BIII).[289,290]

Any HCT recipient or candidate undergoing conditioning therapy who experiences a VZV-like rash (whether after exposure to a person with wild-type varicella or shingles or exposure to a VZV vaccinee with a rash) should receive preemptive i.v. acyclovir until $\approx$2 days after all lesions have crusted (BII). Treatment may be completed with oral valacyclovir if the patient can tolerate oral medication.

Passive immunization and VZV-seronegative HCT recipients

Owing to the high morbidity of VZV-associated disease among severely immunocompromised HCT recipients and until further data are published, there are situation-specific indications for the administration of VZIG or VariZIG, where available, for VZV-seronegative HCT recipients. Immunocompromised HCT recipients (that is, an allogeneic patient $<$24 months after HCT; $\geqslant$24 months after HCT and on immunosuppressive therapy; or having chronic GVHD) should receive VZIG or VariZIG as soon as possible, and no later than 96 h after close or household contact with a person having either chickenpox or shingles (AII). Post-exposure acyclovir or valacyclovir (Appendix 1) may be used as an alternative if VZIG or VariZIG is not available (CII).[291,292] VZIG or VariZIG, acyclovir or valacyclovir should also be administered to all VZV-seronegative HCT recipients undergoing conditioning therapy who are exposed to a VZV vaccinee having a varicella-like rash (BIII). If VZV-seronegative HCT recipients undergoing conditioning therapy are closely exposed to varicella $>$3 weeks after receiving VZIG or VariZIG, they should receive another dose of VZIG or VariZIG, or another course of valacyclovir if VZIG or VariZIG is not available (BIII).[282]

Passive immunization and VZV-seropositive HCT recipients

Varicella-zoster Ig or VariZIG, acyclovir, or valacyclovir can be used after VZV exposure, including exposure to a VZV vaccinee having a varicella-like rash, for HCT recipients who were VZV seropositive before HCT and are highly immunosuppressed (that is, because of high-dose steroid therapy or T-cell depletion) (CIII).[292] These recommendations are made because the vaccinee might be unknowingly incubating wild-type varicella, particularly during the first 14 days after varicella vaccination, and because vaccine-strain VZV has been rarely transmitted by VZV vaccinees with post-vaccination vesicular rashes.[282] Furthermore, varicella vaccination is only $\approx$85% effective. Thus, vaccine recipients may still become infected with wild-type virus years after vaccination[293] and may thus be a source of transmission to immunocompromised patients.

VZV vaccines. Use of VZV vaccines (Varivax and Zostavax, Merck, Whitehouse Station, NJ, USA) is discussed in the HCT Recipient Vaccination section. A vaccine-associated rash occurs in $\approx$1–5 and 0.5% of recipients of the varicella and zoster vaccine, respectively.[294,295] This rash is a potential source of transmission of the vaccine virus strain to HCT recipients. As the risk of vaccine virus transmission is low, particularly in the absence of a vaccine-associated rash, household members should receive varicella vaccine to protect HCT recipients from potential exposure to wild-type disease (AIII). Individuals who experience a vaccine-associated rash should avoid close contact with HCT recipients in the home setting (BIII). If contact occurs, the HCT recipient should be considered for post-exposure prophylaxis with valacyclovir, as outlined above (CIII).

An inactivated VZV vaccine has been used investigationally among HCT recipients.[296] Studies are ongoing to further define its utility and no recommendation regarding its use can be made at this time.

Other recommendations

Recommendations for VZV prevention are the same for allogeneic or autologous recipients. Recommendations are also the same for allograft recipients with different-intensity conditioning regimens. Recommendations for preventing VZV disease among pediatric or adult HCT recipients are the same, except that appropriate dose adjustments for acyclovir derivatives and VZIG should be made for pediatric HCT recipients (AIII) (Appendix 1).

Recommendations regarding community-acquired respiratory viral infections: influenza, respiratory syncytial virus, human metapneumovirus and parainfluenza virus

Preventing exposure

Preventing community-acquired respiratory viral (CRV) exposure is critical in preventing CRV disease.[297,298] Measures for preventing nosocomial CRV transmission are presented in the Infection Prevention and Control in Healthcare Facilities: Recommendations Regarding CRV Infections section. Use of PCR testing in donors with respiratory infections remains investigational (CIII). Viral cultures of asymptomatic HCT candidates are unlikely to be useful. Whether multiplex PCR testing can identify asymptomatic shedders before HCT is presently being studied. PCR-based routine surveillance of asymptomatic patients after HCT remains investigational.

Hematopoietic cell transplant recipients with symptoms of an upper respiratory infection (URI) or lower respiratory infection should be placed under contact precautions to avoid transmitting infection to other HCT candidates and recipients, HCWs and visitors until the etiology of illness are identified (BIII).[144] Optimal isolation precautions should be modified as needed after etiology is identified (BIII). HCT recipients and candidates, their family members and visitors, as well as all HCWs, should be informed regarding CRV infection-control measures and the potential severity of CRV infections among HCT recipients (BIII).[297–299]

Preventing disease

Hematopoietic cell transplant physicians should determine the etiology of a URI in an HCT recipient, if possible, because respiratory syncytial virus (RSV), influenza, parainfluenza and adenovirus URIs can progress to more serious lower respiratory infection, and certain CRVs can

be treated (BIII). Appropriate diagnostic samples include nasopharyngeal washes, swabs or aspirates; throat swabs (in combination with nasal samples); and bronchoalveolar lavage fluid. HCT candidates with URI symptoms at the time that conditioning therapy is scheduled to start should postpone their conditioning regimen until URIs resolve, if possible, because certain URIs might progress to lower respiratory infection during immunosuppression (BIII).[298,300–302] The clinical relevance of recently discovered viruses (for example, human bocavirus, non-severe acute respiratory syndrome coronaviruses, human rhinoviruses, human metapneumovirus) that are detectable by molecular methods is currently undefined and no recommendations can be made for the routine screening of these viruses (CIII).

Recommendations regarding influenza

Lifelong seasonal influenza vaccination with the trivalent inactivated vaccine is recommended for all HCT candidates and recipients (see Vaccination section) (AII). In addition, influenza vaccination of family members and close or household contacts is strongly recommended during each influenza season (for example, October–May in the Northern hemisphere), starting from the season before HCT and continuing $\approx$24 months after HCT (AII)[303] to prevent influenza. All family members and close or household contacts of HCT recipients should continue to be vaccinated annually as long as the HCT recipient's immunocompromise persists, even if beyond 24 months after HCT (AII).[303] Seasonal influenza vaccination is strongly recommended for all HCWs of HCT recipients (AI).[304]

If HCWs, family members or other close contacts of HCT recipients receive influenza vaccination during an influenza outbreak, they should receive chemoprophylaxis, if feasible, for 2 weeks after influenza vaccination (BI) while the immunological response to the vaccine develops. However, if an outbreak occurs with an influenza strain that is not contained in the available influenza vaccine, all healthy family members, close and household contacts, as well as HCWs of HCT recipients and candidates, should receive influenza chemoprophylaxis with an active agent against the current circulating strain of influenza until the end of the outbreak (BIII).[303] Zanamivir may be given for the prevention of influenza A and B, including influenza from strains resistant to oseltamivir. The duration of prophylaxis depends on the type of exposure. Zanamivir can be administered to persons 5 years of age or older for prevention of influenza and 7 years or older for treatment of influenza. Oseltamivir can be administered to persons $\approx$1 year of age or older. Patients with influenza should be placed under droplet and standard precautions (AIII) to prevent transmission of influenza to HCT recipients. HCWs with influenza should be excused from patient care until they are no longer infectious (AIII).

Hematopoietic cell transplant recipients $<$6 months after HCT should receive chemoprophylaxis with neuraminidase inhibitors during community influenza outbreaks that lead to nosocomial outbreaks (AII). During community outbreaks, all HCT recipients who have not yet received a current influenza vaccination should be vaccinated against influenza immediately if they are more than 4 months after HCT (BIII). In addition, to allow sufficient time for the patient to experience an immunological response to influenza vaccine, chemoprophylaxis can be used for these HCT recipients for 2 weeks after vaccination during a nosocomial or community influenza outbreak (CIII). Influenza chemoprophylaxis has been recommended for all influenza-exposed HCT recipients who are $<$24 months after HCT or who are $>$24 months after HCT and substantially immunocompromised regardless of vaccination history, because of their likely suboptimal immunological response to influenza vaccine (BII).[305,306] Drug resistance patterns of circulating influenza strains should guide the choice of prophylactic agent.

Healthy children who receive influenza vaccination for the first time might not generate protective Abs until 2 weeks after receipt of the second dose of influenza vaccine. Therefore, during an influenza A outbreak, pediatric recipients who are $<$9 years old, are $\leqslant$6 months after HCT and receiving their first influenza vaccination should be given $\approx$6 weeks of influenza A chemoprophylaxis after the first dose of influenza vaccine (BIII) (Appendix 1).[307,308] To prevent severe disease, HCT patients with influenza URI should receive early preemptive therapy with drugs shown to be susceptible to the circulating strain. (AII).[309,310]

Recommendations regarding RSV

Respiratory secretions of any hospitalized HCT candidate or recipient who experiences signs or symptoms of CRV infection should be tested promptly by viral culture and rapid diagnostic tests for RSV (BIII). If two diagnostic samples taken $\approx$2 days apart do not identify a respiratory pathogen despite the persistence of lower respiratory symptoms, bronchoalveolar lavage and further testing are advised (BIII). This testing is critical because of the high morbidity and case fatality of RSV disease and the frequent presence of significant co-pathogens among HCT recipients when it occurs during the peritransplant period.[311,312] HCT recipients, particularly those who are preengraftment and lymphopenic or those who have preexisting obstructive airway disease, are at highest risk for severe RSV pneumonia. These patients should have their illness diagnosed early (that is, during RSV URI) and receive aggressive treatment to prevent fatal RSV disease (BIII).

On the basis of retrospective studies, as well as a prospective trial with inadequate accrual, some researchers recommend preemptive aerosolized ribavirin for patients with RSV URI, especially those with lymphopenia (during the first 3 months after HCT) and preexisting obstructive lung disease (late after HCT) (CIII).[310,313] Although a definitive, uniformly effective preemptive therapy for RSV infection among HCT recipients has not been identified, certain other strategies have been proposed, including systemic ribavirin,[314–316] RSV Abs (that is, passive immunization with high-RSV-titer i.v. Ig and RSV Ig) in combination with aerosolized ribavirin[301,317] and RSV MoAb.[314,318] No randomized trial has been completed to test the efficacy of these strategies. No specific recommendation regarding any of these strategies can be given at this time. To prevent RSV disease, some centers provide monthly palivizumab prophylaxis during RSV season (for

example, November–April in the Northern hemisphere) for pediatric recipients at risk for primary RSV disease (that is, children <4 years old) (CIII). Routine i.v. Ig therapy would still be required if indicated[319] (that is, for those with hypogammaglobulinemia) (Appendix 1).

Recommendations regarding parainfluenza virus
Immunoprophylaxis, withdrawal of immunosuppression to prevent progression and preemptive treatment for parainfluenza virus infections among HCT recipients have been proposed.[320] However, no recommendation can be made in these guidelines because of insufficient data. No commercially licensed drugs or vaccines against parainfluenza viruses are currently available.

Recommendations regarding human metapneumovirus
Human metapneumovirus can cause pneumonia in HCT recipients.[321] Ribavirin has *in vitro* and animal model activity against human metapneumovirus.[322,323] However, no recommendations can be made in these guidelines because of lack of treatment data.

Other disease prevention recommendations
The recommendations for preventing CRV infections and their recurrence are the same for allogeneic or autologous recipients. Generally, these recommendations apply to children[308,319,324,325] and adults, but with appropriate adjustments in antiviral drug and influenza vaccine doses for children (Appendix 1). Progression to lower tract disease seems to be less common in HCT recipients with nonmyeloablative conditioning, but no specific recommendations for these patients can be made at this time.

Recommendations regarding adenoviruses

Preventing exposure
Adenovirus infections after HCT can result from reactivation or *de novo* acquisition. As many different serotypes exist and knowledge about cross-reactive immunity is limited, pretransplant serological testing of either the patient or the donor is not likely to be helpful. As cellular immune responses are cross-reactive across various serotypes and are likely to provide long-term protection against adenovirus reactivation, serious adenovirus infections in adults are uncommon.[326,327] HCT recipients should follow similar preventive measures as those for other respiratory or enteric viruses (see recommendations regarding CRV, CMV and enteric viruses) with regard to contact and nosocomial spread (see Infection Prevention and Control in Healthcare Facilities and Safe Living after HCT).

Preventing infection and disease
Hematopoietic cell transplant patients can be stratified according to their risk for adenoviral disease:

- Lowest risk—autologous HCT recipients[328–330]
- Intermediate risk—T-cell replete, related-donor allograft recipients without GVHD
- Higher risk—recipients of T-cell-depleted (2–3 $\log_{10}$), related- or unrelated-donor transplants;[331,332] HLA-mismatched transplant recipients other than allele DRB1 mismatch;[333] patients with GVHD who receive systemic steroids[328,334,335] and pediatric recipients.
- Highest risk—refractory GVHD, umbilical cord blood transplantation, haploidentical transplantation, stem cell graft T-cell depletion of >2–3 $\log_{10}$, use of anti-T-cell Abs (for example, ATG (antithymocyte globulin), alemtuzumab).[331,336]

For patients at highest risk, weekly monitoring for active adenovirus infection by PCR either for the first 6 months after HCT or for the duration of severe immunosuppression/lymphopenia could be considered (CII).[333,337] Quantitative PCR testing should be strongly considered for monitoring progression of adenovirus infection and response to treatment (BII). There are no definitive data on a critical value for viral load in peripheral blood to indicate initiation of intervention; thus, no recommendation can be made.

Clearance of adenovirus has been shown to be associated with recovery of adenovirus-specific T-cell immunity.[338,339] When possible, rapid tapering or withdrawal of immunosuppression constitutes the best way to prevent progression of adenovirus infection (AII).[331,332,340,341] However, this strategy might not always be feasible in severe GVHD or with severe lymphopenia because of the use of anti-T-cell Abs or T-cell depletion of the graft. Few antiviral agents have *in vivo* activity against adenoviruses, and no randomized, placebo-controlled study of antiviral drug therapy for adenoviral infection has been conducted. The available data suggest that cidofovir or ribavirin could be used as preemptive antiviral therapy of adenoviral disease in selected high-risk HCT patients (CII) (Appendix 1). A reduction of DNA load has been shown mainly with cidofovir[342,343], but the evidence of its efficacy in preventing mortality in HCT patients is inconsistent.[344] Differences in responses may be due to strain-specific susceptibilities.[345] The duration of preemptive therapy is subject to tolerance and clearance of viral load.

Current evidence strongly supports the role of adenovirus-specific T cells in controlling the progression of adenoviral disease.[346] However, this approach is at an early stage of development and should not be used outside the context of a clinical trial.

Recommendations regarding Polyomaviruses, BK and JC

Human polyomavirus type I, commonly called BK virus (BKV), and human polyomavirus type II, commonly called JC virus (JCV), infect 50–90% of humans worldwide before the age of 10 years, without known symptoms or signs.[347,348] Urinary shedding of BKV and/or JCV occurs in 5–20% of healthy immunocompetent blood donors.[349] BKV and JCV are nonenveloped virions found in urban sewage and fairly resistant to environmental inactivation.[350]

Polyomavirus disease in HCT patients most often corresponds to secondary BKV replication with impaired polyomavirus-specific cellular immunity. Urinary shedding of BKV occurs in 60–80% of HCT recipients.[347,348,351–353] The major disease linked to high-level polyomavirus

replication is BKV-associated hemorrhagic cystitis (PVHC), which affects 5%–15% of HCT recipients at 3–6 weeks after transplant.[352,354] PVHC occurs typically after engraftment and must be distinguished from hemorrhagic cystitis caused by other pathogens (for example, adenovirus or CMV) and from early-onset hemorrhagic cystitis, which arises before engraftment and has been linked to urotoxic conditioning regimens with CY, ifosfamide, BU and/or TBI.[352,354] BKV viruria reaching high viral loads of $>10^7$ genome equivalents per ml (geq/ml) is observed in 20–80% of HCT patients, but less than one-fifth of HCT recipients develop PVHC.[354] PVHC is diagnosed in HCT patients with post-engraftment cystitis who have pain and urinary urgency, together with hematuria of grade II (macrohematuria[352]) or higher, high-level BKV replication (that is, $\geqslant 10^7$ geq/ml) and exclusion of other pathogens. There are reports of sporadic cases of JCV-associated PVHC,[355] BKV- or JCV-associated polyomavirus nephropathy[347,356–359] and JCV- or BKV-mediated polyomavirus multifocal leukoencephalopathy.[360,361]

Preventing exposure

There is no evidence to support routine testing of HCT recipients or donors for the presence of BKV-specific or JCV-specific Abs (DIII). There are no commercially available, standardized or Food and Drug Administration-approved assays to measure BKV- or JCV-specific Abs. The role of primary infection, of donor–recipient mismatch and of BKV-specific Ab titers in HCT recipients is presently unknown.

There is no evidence to support specific infection-control measures for HCT patients with BKV viruria (DIII). In patients with disseminated BKV replication involving the respiratory and gastrointestinal tract, separation from other patients with significant immunodeficiency should be considered (CIII).

Preventing disease and disease recurrence

There is no evidence to support the use of quinolones or cidofovir as specific universal prophylaxis for PVHC or other polyomavirus-associated complications (DIII). There is insufficient evidence to support the use of quinolones for preemptive treatment of asymptomatic HCT patients who develop BKV viruria or viremia (DIII). Fluoroquinolones can inhibit BKV replication in tissue culture and have been reported to reduce BKV loads in HCT patients, but a significant reduction of PVHC has not been shown.[362] Ciprofloxacin and levofloxacin are frequently used, alone or in combination with other antibiotics, in patients undergoing HCT in antibacterial prophylaxis during neutropenia and in empiric or specific antibiotic therapy, and seemingly resistant BKV isolates have been reported.[362,363] There is no evidence to support the use of cidofovir for preemptive treatment of asymptomatic HCT patients who develop BKV viruria or viremia (DIII). Cidofovir has been administered i.v. in a low dose (that is, up to 1 mg/kg thrice weekly, without probenecid) or a high dose (that is, 5 mg/kg per week with probenecid) to HCT patients with PVHC, but no randomized trials are available proving its clinical efficacy (CIII).

Recommendations regarding Hepatitis A virus

The seroprevalence of hepatitis A virus (HAV) varies widely, with higher rates in resource-limited societies. Testing of HCT candidates or donors for HAV IgG Abs is generally not recommended, as its sole positivity in the absence of IgM indicates remote exposure and has no impact on HCT outcome (DIII). However, testing for IgM is indicated as a part of the workup of patients with signs of acute hepatitis (AII). If an HCT candidate tests positive for HAV IgM, transplantation should be delayed because of an increased risk of sinusoidal obstruction syndrome after liver-toxic myeloablative conditioning regimens (DII). If the HCT donor tests positive for HAV IgM, transplantation should be delayed because of a high risk of transmission and increased morbidity and mortality (EII). HAV vaccination recommendations for HCT recipients are provided in Table 6.

Recommendations regarding Hepatitis B virus

Hepatitis B virus (HBV) can cause severe hepatitis after HCT. However, rates of HBV-associated cirrhosis and hepatocellular carcinoma do not seem higher in HCT patients compared with non-HCT patients.[364] Severe hepatitis B has been observed in HCT recipients in the following situations:

- HBV-naive HCT recipients exposed to HBV through an infected donor, infected blood products or through sexual contact;
- HCT recipients with chronic hepatitis B experiencing prolonged immune suppression;
- HCT recipients with serological evidence of resolved HBV infection who have reverse seroconversion after prolonged immune suppression;
- HCT patients—generally in countries with endemic HBV—with latent occult hepatitis B (all serological markers negative) that activates after prolonged immune suppression.[365]

Risk factors for reactivation and exacerbation of HBV replication in HCT recipients include treatment with high-dose steroids,[366,367] fludarabine/rituximab[368] or alemtuzumab.[366,367,369] Clinical hepatitis may become further exacerbated during immune recovery and discontinuation of immunosuppression.

Preventing exposure

Testing both recipients and potential donors for evidence of active or past HBV infection is critical for the prevention of HBV exposure and disease in HCT recipients. Appropriate assays include HBV surface Ag (HBsAg), Abs to HBsAg (anti-HBs) and Abs to HBV core Ag (anti-HBc) (AII). All anti-HBc-positive and HbsAg-positive donors and recipients should also be tested for HBV DNA (AIII). HBV-naive HCT candidates should not receive transplants from HBsAg-positive or HBV DNA-positive donors, if another equally suitable donor is available (AII). However, the use of a donor with active HBV replication is not absolutely

Table 6 Vaccinations considered optional or not recommended for both autologous and allogeneic HCT recipients

Vaccine	*Recommendations for use*	*Rating*
Optional		
Hepatitis A	Follow recommendations for general population in each country • Ig should be administered to hepatitis A-susceptible HCT recipients who anticipate hepatitis A exposure (for example, during travel to endemic areas) and for post-exposure prophylaxis.	CIII
Varicella (Varivax, live)	Limited data regarding safety and efficacy.	EIII (<24 months post-HCT, active GVHD or on immunosuppression) CIII (>24 months, without active GVHD or on immunosuppression)
Human papillomavirus	Follow recommendations for general population in each country No data exist regarding the time after HCT when vaccination can be expected to induce an immune response	CIII
Yellow fever (live)	Limited data regarding safety and efficacy. The risk–benefit balance may favor use of the vaccine in patients residing in or traveling to endemic areas.	EIII (<24 months, active GVHD or on immunosuppression) CIII (>24 months, without active GVHD or on immunosuppression)
Rabies	Appropriate for use in HCT recipients with potential occupational exposures to rabies[827] Preexposure rabies vaccination should probably be delayed until 12–24 months after HCT. Postexposure administration of rabies vaccine with human rabies Ig can be administered any time after HCT, as indicated[a] [827,828]	CIII
Tick-borne encephalitis (TBE)	According to local policy in endemic areas. No data exist regarding the time after HCT when vaccination can be expected to induce an immune response	CIII
Japanese B encephalitis	According to local policy when residing in or travelling to endemic areas. No data exist regarding the time after HCT when vaccination can be expected to induce an immune response	CIII
Not recommended		
Bacillus Calmette–Guérin (live)	Contraindicated for HCT recipients	EII
Oral poliovirus vaccine (live)	Should not be given to HCT recipients, as an effective, inactivated alternative exist	EIII
Intranasal influenza vaccine (live)	No data regarding safety and immunogenicity. Should not be given to HCT recipients, as an effective, inactivated alternative exist	EIII
Cholera	No data were found regarding safety and immunogenicity among HCT recipients	DIII
Typhoid, oral (live)	No data were found regarding safety and immunogenicity among HCT recipients.	EIII
Typhoid (i.m.)	No data were found regarding safety, immunogenicity, or efficacy among HCT recipients.	DIII
Rotavirus	Must be given before 12 weeks of age to be safe.	EIII
Zoster vaccine (Zostavax, live)	No data regarding safety among HCT recipients.	EIII

Abbreviation: HCT = hematopoietic cell transplant.
[a]Current Advisory Committee on Immunization Practices (ACIP) and American Academy of Pediatrics guidelines for post-exposure human rabies Ig and vaccine administration should be followed, which include administering five doses of rabies vaccine administered on days 0, 3, 7, 14 and 28 post-exposure.

contraindicated for an HBV-naive recipient, as viral transmission is not universal (BIII). The overriding concern must be HLA matching and other outcome-related issues.

Vaccination of all HBV-naive HCT candidates should be considered (AIII). An attempt should be made to provide hepatitis B immunization to HBV-seronegative HCT candidates with HBsAg-positive donors, preferably before chemotherapy for the initial two doses 3–4 weeks apart and for a third dose 6 months later, ideally before HCT (BIII). If this schedule cannot be met, the third dose should be

administered a few months after completion of chemotherapy. It is noteworthy that the response to vaccination is likely to be poor in patients undergoing chemotherapy. If the post-vaccination anti-HBs titer is <10 IU/l or the pretransplantation vaccination is impractical, HBIG (0.06 ml/kg) should be administered immediately before infusion of stem cells (AIII). HCT recipients who fail to respond to pretransplant vaccination, but remain uninfected after transplant (that is, negative for HBsAg, anti-HBc, anti-HBs and HBV DNA) should be revaccinated after immune recovery with 1–3 doses of hepatitis B vaccine (BII).

If the donor has a detectable HBV DNA load, the following measures are recommended (BIII):

- Administer antiviral treatment to the donor for at least 4 weeks, or until HBV DNA is undetectable (if time permits). Many experts prefer entecavir for this purpose (CIII).
- Reduce harvest volume to the minimum possible without compromising the planned CD34+ cell dose, and test an aliquot of the cell product for HBV DNA.
- If, at the time of harvest, both the donor and harvested cells are HBV DNA negative, monitor alanine aminotransferase (ALT) levels monthly in the recipient for the first 6 months. If the ALT level increases, test the recipient for HBV DNA (AIII). If HBV DNA testing is not available, testing for HBsAg is an acceptable alternative. If HBV DNA is detected or a positive HBsAg is identified, antiviral treatment is indicated (AIII).
- If the donor or cell product is positive for HBV DNA at the time of harvest, provide the HCT recipient prophylaxis with lamivudine from day zero through at least 6 months after discontinuation of immunosuppressive drugs. Consider the administration of a second dose of HBIG at 4 weeks after transplantation (AIII). Monitor ALT and HBV DNA monthly. If HBV DNA is positive during lamivudine prophylaxis, treatment may be modified as detailed below.

If the donor is anti-HBc positive, but negative for both HBsAg and anti-HBs, the donor should be tested for HBV DNA (BIII). If the HBV DNA assay is positive, treat as described in the bullets above for a donor with a detectable HBV viral load (BIII). If HBV DNA testing is negative, repeat testing of the donor at the time of harvest should be considered. If HBV DNA remains negative, HCT is performed without further precaution (DIII). If the repeat test is positive, treat as described above (BIII).

HBV-naive HCT recipients who are in a monogamous relationship with a known HBsAg carrier, or who are sexually active and not in a long-term monogamous relationship, should always use latex condoms during sexual contact to reduce their risk of primary HBV infection (AIII).[370]

Preventing disease

For HCT candidates with evidence of past exposure to HBV (that is, who are anti-HBc positive), the specific recommendations depend on the pattern of test results. As the risk of post-HCT hepatitis is reduced because of the adoptive transfer of a donor's natural immunity, equally suitable donors showing natural immunity (anti-HBs positive, anti-HBc positive) are preferred over donors without natural immunity for recipients with evidence of previous HBV exposure.[364]

If the HCT recipient is anti-HBc positive and anti-HBs positive, the risk of HBV reactivation is considered low during chemotherapy/conditioning but higher after prolonged treatment with prednisone for GVHD. Serum ALT should be followed in such patients, and if the level increases, HBV DNA load should be assessed. Patients with a positive HBV DNA load should receive preemptive antiviral treatment as described below (AIII). Prophylactic antiviral treatment may be considered for anti-HBc-positive and anti-HBs-positive recipients before, and for 1–6 months after, HCT (CIII). In addition, anti-HBs levels should be monitored every 3 months. Reduction in anti-HBs titer should prompt HBV DNA testing (BIII).[371] Patients who lose anti-HBs responses but have no HBV DNA in serum should receive active immunization in an attempt to restore protective levels of anti-HBs (BIII). Patients with positive HBV DNA assays should receive antiviral therapy (AIII). The duration of antiviral treatment in this setting has not been studied, but a common practice is to continue therapy for at least 6 months after discontinuation of immune suppressive drugs (BIII).[372–374] Rebound HBV replication and clinical hepatitis may follow discontinuation of antiviral treatment and should be monitored by regular measurement of ALT and HBV DNA (for example, biweekly) (BIII).

Hematopoietic cell transplant candidates with evidence of active HBV replication (HBsAg positive and/or HBV DNA positive) should have a liver biopsy before HCT, because preexisting biopsy-proven cirrhosis and hepatic fibrosis can increase transplant-related morbidity and mortality (BIII). Antiviral therapy should be initiated before conditioning. If HCT is not urgent, antiviral treatment should be administered for 3–6 months before conditioning. In patients with persisting HBV DNA while on therapy with lamivudine, treatment may be modified as detailed below. Rebound HBV replication and fulminant hepatitis may occur after discontinuation of antiviral treatment. Therefore, discontinuation of antiviral therapy should be performed judiciously, with frequent monitoring of liver function and HBV DNA (BIII).

Hematopoietic cell transplant candidates who are positive for anti-HBc but negative for HBsAg and anti-Hbs should be tested for HBV DNA. If HBV DNA is undetectable, the patient should receive HBV vaccination as described above and proceed to HCT. Further management regarding monitoring and antiviral treatment should be performed as described for anti-HBc-positive and anti-HBs-positive HCT candidates (BIII). If HBV DNA is positive, proceed to HCT with preemptive antiviral therapy as described above.

Antiviral treatment. Therapy should be coordinated between the HCT physician and Infectious Disease and/or Hepatology specialist(s) with expertise in chronic viral hepatitis. Lamivudine (100 mg/day) is the first choice for antiviral therapy (AI). Antiviral therapy should be continued for at least 6 months after transplant in autologous

HCT patients, for 6 months after discontinuation of immune suppressive drugs in allogeneic HCT patients and longer in patients receiving immunosuppression for chronic GVHD (BIII). Extended use of lamivudine not only results in reduction of HBV reactivation and the resultant complications but also lowers HBV-associated mortality.[375,376]

Recommendations regarding Hepatitis C virus

Hematopoietic cell transplant from donors who are Hepatitis C virus (HCV)-RNA positive invariably transmits HCV to uninfected recipients, with development of viremia in the immediate post transplantation period.[377] Conversely, the risk of transmission is decreased if HCV-RNA is undetectable at the time of hematopoietic cell donation.[377] There is no evidence of adverse short-term effects of HCV infection in HCT recipients, and HCV-infected HCT patients have similar morbidity up to 10 years after transplant.[378] Subsequently, however, these patients are at risk for progression to cirrhosis, which may occur more rapidly than in non-HCT patients. The cumulative incidence of biopsy-proven cirrhosis is 11 and 24% at 15 and 20 years after transplant, respectively, with a median of 18 years compared with 40 years for non-HCT HCV-infected patients.[379] Extrahepatic manifestations and infection with HCV genotype 3 increase the risk of progression.

Preventing exposure
All HCT candidates should be assessed for risk of HCV infection with a careful history, physical examination and serum ALT testing (BIII), as well as by the measurement of anti-HCV Ab titers (AII). Even if anti-HCV titers are negative, nucleic acid testing for HCV-RNA should be undertaken in patients whose history indicates increased risk for HCV infection (for example, transfusion with blood not tested for HCV—reliable testing of blood supply began in 1992 in developed countries; i.v. or inhaled drug abuse; or tattoos) or who have an unexplained elevation of serum ALT (AII).[380]

Hepatitis C virus-infected patients requiring HCT and for whom there is no alternative donor can proceed with HCT from an HCV-positive donor, provided they have a full understanding of the long-term side effects (BIII).[378] The donor should be assessed for chronic liver disease and other extrahepatic manifestations of HCV, which might contraindicate donation (EIII).

Similar to recipients, all donors should be screened for anti-HCV Abs, and those found to be anti-HCV positive or at a high risk for HCV infection should be tested for HCV-RNA (AII). If feasible, viral clearance with standard combination antiviral therapy before stem cell harvest may be attempted in donors with detectable HCV-RNA. However, there are few reports on the success of this method.[381,382] Both the donor and recipient should be counselled on individual risks (BIII).

Preventing disease progression
All HCT candidates with HCV infection must be assessed for evidence of chronic liver disease. To assess the risk of conditioning and HCT, liver biopsy is warranted in the following clinical situations (AIII):

- Associated iron overload
- History of excessive alcohol intake
- History of hepatitis C for >10 years
- Clinical evidence of chronic liver disease.

Patients with evidence of cirrhosis or hepatic fibrosis should not be considered for conventional myeloablative conditioning therapy that contains either CY or TBI $\geqslant 12$ Gy (DIII), as these regimens are associated with a 9.6-fold increased risk of fatal sinusoidal obstruction syndrome in these patients.[378] Instead, regimens that contain neither CY nor TBI, which pose a lower risk for fatal sinusoidal obstruction syndrome, should be used.[383] However, for patients with cirrhosis, even a reduced-intensity conditioning regimen poses a mortality risk.[384]

Treatment for chronic HCV should be considered in all HCV-infected HCT recipients, because limited data suggest improved outcome in those who respond to combination therapy (BIII).[385] To qualify for antiviral treatment, the patient must be in CR from the original disease; be $\geqslant 2$ years after transplant without evidence of either protracted acute GVHD or chronic GVHD; have been off immunosuppression for 6 months; and have normal blood counts and serum creatinine (BIII). Treatment should consist of full-dose peginterferon and ribavirin (BIII). Dose modifications should be made if intolerance develops (for example, development of cytopenias). In survivors whose neutrophil and plt counts are below normal at baseline, daily IFN-α can be substituted for peginterferon to assess hematological toxicity before moving to peginterferon. Treatment should be continued for 24–48 weeks, depending on response.

Human herpesviruses 6 and 7

Preventing exposure
Human herpesvirus 6 (HHV-6) is the cause of the classic childhood illness roseola, which is also known as exanthema subitum or Sixth Disease.[386] Clinical disease associated with HHV-7 infection remains to be defined. Nearly all children are infected with HHV-6 by 2–3 years of age[387–389] and with HHV-7 by the age of 5 years.[390]

Preventing disease and disease recurrence
The spectrum of HHV-6-associated complications after HCT has not been completely described. HHV-6 reactivation is common during the early allogeneic HCT transplant period, with viremia occurring in $\approx$40–60% of patients.[387,391–394] The clinical significance of detection of HHV-6 viremia is unknown, although it has been associated in the post transplant setting with hepatitis, fever, rash, idiopathic pulmonary syndrome and delayed plt and monocyte engraftment. HHV-6 can also be chromosomally integrated, potentially resulting in a false-positive PCR assay result.[395] A post transplantation acute limbic encephalitis syndrome associated with HHV-6 reactivation in the cerebrospinal fluid has been reported.[396] This syndrome is uncommon, occurring in $\approx$1–2% of HCT patients in some series. It typically occurs 1–2 months after

transplantation and seems to be more common after receipt of an umbilical cord blood or HLA-mismatched graft. Manifestations include profound memory loss, seizures, hyponatremia, mild cerebrospinal fluid pleocytosis and significant mesial temporal lobe abnormalities on magnetic resonance imaging.[396,397] In addition, HHV-6 may interfere with MHC class I Ag presentation and augment local immunosuppression;[398] however, the implications of this viral property are unknown. The role of HHV-7 in post transplant complications remains to be defined.

At this time, there are no data to guide a preemptive monitoring or a prophylactic antiviral strategy to prevent potential HHV-6-associated disease (DIII). Ganciclovir, cidofovir and foscarnet have variable *in vitro* activity against HHV-6 and may have a role in treating HHV-6-associated disease.[399,400] There are no data to support recommendations for monitoring of potential HHV-7-associated disease (DIII).

Human herpesvirus 8

Preventing exposure
Human herpesvirus type 8 is the cause of Kaposi's sarcoma and is also known as Kaposi's sarcoma-associated herpesvirus. Unlike other herpesvirus infections, HHV-8 infection is not ubiquitous. There is significant geographic variability in the prevalence of HHV-8 infection, with high infection rates reported in sub-Saharan Africa (50%), modest rates in the United States (about 5%) and low rates in Japan (<1%). In the United States, higher rates of HHV-8 infection have been identified in men who have sex with men, perhaps indicating sexual transmission or enhanced transmission through saliva.

Preventing disease and disease recurrence
Human herpesvirus type 8-associated disease (for example, Kaposi's sarcoma) occurs only rarely after HCT.[401–404] At this time, there are no data to guide monitoring or preemptive antiviral treatment for post transplant HHV-8-associated disease (DIII).

Human immunodeficiency virus

In patients infected with the HIV and receiving highly active antiretroviral therapy, cancer is now the leading cause of death.[405] Consequently, HCT may need to be considered for these patients.

Preventing exposure
As described in the Hematopoietic Cell Graft Safety section, regulations are in place in both the United State and the European Union for evaluation of donors to minimize risk of transmissible diseases.[78–80,82,83] Using a related donor with known HIV harbors significant risks that likely outweigh any benefits of transplantation to a seronegative recipient, and should not be considered (DIII).

Preventing disease and disease recurrence
Patients with HIV and a malignancy treated by transplantation should not automatically be excluded from this potentially life-saving therapy. Reports of autologous transplantation suggest that this is a feasible approach in patients with controlled HIV disease (BIII).[406–410] Outcomes after allogeneic transplantation are quite limited, although one report suggests that in the current era of highly active antiretroviral therapy, this may be considered (CIII).[411] Owing to significant complexity in the management of HIV-positive patients, it is recommended that any HIV-positive patient considered for HCT be enrolled in a clinical trial and the patient be co-managed by an HIV specialist.