# Advances in the Management of Viral Infections

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**Abstract**

Viral infections are common in cancer patients. The risk and severity of infection are influenced by patient, disease, treatment, and viral factors. Severe viral infections are more likely to occur in treatment regimens that are more immunosuppressive. Historically, the most frequent severe infections have been due to herpesviruses, but more recently, other pathogens, especially community respiratory and hepatitis viruses, have received increasing attention as major viral pathogens in cancer patients. Because of the new diagnostic assays and the introduction of better therapeutic options, knowledge of viral infections is important in optimizing antineoplastic therapies.

**Keywords**

Herpesviruses · Viral pathogens · Cytoreductive regimens · Hematopoietic cell transplantation · Neoplastic diseases · Antineoplastic diseases · Purine analogs · Monoclonal antibodies

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## Contents



## 1 Introduction

The immunocompromised cancer patient is vulnerable to a wide spectrum of viral pathogens (Table 1). There has been an increasing recognition for viruses as clinically important pathogens in cancer patients during the past two decades. In part, this is attributable to improved diagnostic techniques to better recognize viral pathogens as causes for illness. In part, this is also due to the increasing dose intensity of cytoreductive regimens used to control cancer, the increasing use of hematopoietic cell (also known as bone marrow) transplantation (HCT) in the treatment for neoplastic diseases, improvements in supportive care that permit patients to survive bacterial and fungal infections that in the past might have led to death before viral illness became manifest, and the introduction of antineoplastic agents (including purine analogs and monoclonal antibodies) that have potent immunosuppressive properties. Thus, there are greater numbers of highly immunosuppressed patients with severe compromise in cell-mediated immunity, the major host defense against most viral pathogens.

Not only are viral infections increasingly recognized today, but a wider array of pathogens have been noted to cause complications of cancer therapy that in the past have been attributable to toxicities. Pneumonitis, cystitis, myelosuppression, mucositis, enteritis, and hepatitis are examples of syndromes that in the past have been attributable to toxicities from cytoreductive regimens, or in the case of HCT patients, graft-versus-host disease (GVHD) (Table 2); in a number of instances, however, it is clear that viral pathogens are either sole causes for the syndrome, or there is an interplay between viral pathogenesis, tissue damage, and disordered immune responses to the virus in the development, severity, and type of manifestations of the syndrome.

**Table 1** Viral pathogens in immunocompromised cancer patients

| |
|---|
| *Herpesviruses* |
| Herpes simplex type 1 |
| Herpes simplex type 2 |
| Cytomegalovirus |
| Varicella zoster virus |
| Epstein–Barr virus |
| Human herpesvirus 6 |
| Human herpesvirus 8 |
| *Hepatitis viruses* |
| Hepatitis A |
| Hepatitis B |
| Hepatitis C |
| Non-A, non-B, non-C hepatitis |
| *Adenoviruses* |
| *Intestinal viruses* |
| Rotavirus |
| Norwalk virus |
| Adenoviruses |
| Astroviruses |
| Coxsackieviruses |
| Caliciviruses |
| *Respiratory viruses* |
| Respiratory syncytial virus |
| Influenza |
| Parainfluenza |
| Metapneumovirus |
| *Papovaviruses* |
| JC |
| BK |
| Human papillomavirus |
| *Retroviruses* |
| HTLV1 |
| HIV |

**Table 2** Syndromes due to viral pathogens often attributed to treatment toxicity

| Syndrome | Patient population | Viral pathogen |
|---|---|---|
| Oral mucositis | Lymphoma, leukemia, HCT | HSV |
| Esophagitis | Lymphoma, leukemia, HCT | HSV, CMV |
| Hepatopathy | HCT | Hepatitis viruses, adenovirus, CMV, VZV |
| Myelosuppression | HCT | CMV, HHV-6 |
| Interstitial pneumonia | HCT | CMV, HHV-6, adenovirus. RSV, influenza, parainfluenza, metapneumovirus |
| Hemorrhagic cystitis | HCT | BK virus, adenovirus, CMV |
| Diarrhea | Leukemia, HCT | CMV, adenovirus, rotavirus, coxsackie |
| Fever of unknown etiology | HCT | CMV, EBV, HHV-6 |
| Treatment-related lymphoma | HCT | EBV |

*HCT* hematopoietic cell transplantation, *CMV* cytomegalovirus, *EBV* Epstein–Barr virus *HHV-6* human herpesvirus-6, *HSV* herpes simplex virus, *RSV* respiratory syncytial virus

The increased recognition for viral pathogenicity has fortunately been accompanied by the introduction of new diagnostics and therapeutics. Several nucleoside analogs, biologic agents, and new vaccines all offer the clinician tools to prevent or reduce the morbidity associated with these organisms. Thus, prompt diagnosis of these potentially treatable syndromes and an understanding of how to use these new therapeutic modalities are important for optimal management of the cancer patient.

## 2 Herpesviruses

The most frequently recognized viral pathogens in cancer patients are members of the herpesvirus family. These have long been recognized to be potential causes of serious and life-threatening illness. Patients receiving therapy for lymphoma, leukemia, and those undergoing bone marrow transplantation are especially susceptible. The human herpesviruses that cause clinically recognizable infection are herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), and human herpes virus type 6 (HHV-6). These DNA viruses are prevalent in the normal population. Initial infection often occurs early in life, is mild, is self-limited, and generally requires no therapy. After resolution of the primary infection, the virus typically establishes a latent infection that can be life long. HSV and VZV reside latently in sensory nerve ganglia; leukocytes harbor CMV, EBV, and

HHV-6. With compromises in cell-mediated immunity, reactivation can occur and lead to subsequent morbidity. In the nonimmunocompromised patient, reactivation can also occur but is generally associated with milder symptomatology than with the primary infection. In contrast, in immunocompromised patients, reactivation is both more likely to occur and more apt to lead to serious morbidity. The severity of manifestations tends to correlate with the degree of compromised immunity [1].

## 2.1 Herpes Simplex Virus

The lesions from HSV-1 infection are typically orofacial. Although labial vesicular lesions are common manifestations of active infection in nonimmunocompromised patients, they may be absent in compromised cancer patients after chemotherapy. Intraoral mucosal ulcerations may be the sole manifestation [2]. These lesions can be indistinguishable from the tissue damage that results from chemotherapy or radiotherapy. Thus, a pathogenic role for HSV in stomatitis has been often missed in the past; indeed, the reactivation of HSV and the occurrence of tissue damage from cytoreductive treatment often occur concomitantly, and these can result in severe oral mucositis. Most infections are due to reactivation in HSV seropositive patients. The likelihood of reactivation is a reflection of the intensity of the treatment: 70–80 % after HCT, 60–70 % after induction therapy for acute myelogenous leukemia, 40–50 % during treatment for lymphoma, and 10–25 % for patients undergoing various treatment regimens for solid tumors [3].

HSV-2 infection in cancer patients is less problematic because the virus is less common in the general population. However, reactivation can occur at high rates in patients who harbor latent HSV-2, and severe manifestations can result, especially, in patients with hematologic malignancies and HCT recipients. Genital lesions (especially ulcerations) are frequent manifestations, but extragenital vesicles, in the gluteal and anal regions, can also occur.

Although oral and genital mucosas are the major sites of HSV lesions, extension to the esophagus, urethra, bladder, and tracheal mucosa may also occur. Endoscopic biopsy may be necessary to distinguish a viral etiology from fungal or other possible causes. In profoundly immunocompromised patients, dissemination and involvement of visceral tissues can occasionally occur [4].

Culture of material from an infected lesion can confirm the diagnosis. Rapid detection methods using antigen detection or polymerase chain reaction (PCR) procedures offer quicker and easier alternatives [5–7]. Cytologic examination of cells removed from infected lesions using the Tzanck procedure can demonstrate multinucleated cells but do not permit distinction between HSV and VZV [8]. Serologic tests can be helpful in identifying patients harboring latent virus (and thus, susceptible to reactivation) but are of no value in documenting acute infection.

Acyclovir, a purine analog, is very active against HSV-1 and HSV-2 and has been shown in numerous clinical trials to be an effective treatment for HSV infection [9–13]. Several oral and intravenous regimens have been evaluated and

found to be effective and suitable for different clinical situations. Shortening of the time of viral shedding, time to cessation of pain, and time to healing of lesions have been demonstrated in various studies. Valacyclovir is the L-valyl ester of acyclovir and has excellent bioavailability, providing high blood concentrations of acyclovir, and approximating the levels achieved with intravenous acyclovir [14–16].

Acyclovir has also been shown to be effective as prophylaxis [17–21]. For patients at high risk of HSV reactivation and who are susceptible to serious morbidity, prophylaxis may be preferable to treatment [22–25]. In adult patients undergoing intensive induction therapy for acute leukemia and in patients undergoing HCT who are HSV seropositive, the high reactivation rate (60–70 %) and potentially severe manifestations provide justification for prophylaxis. Indeed, the emergence of drug resistance appears to be less common where acyclovir is used prophylactically than when used as treatment for established infections where repetitive courses of acyclovir may be necessary and the frequency of drug resistance increases with each subsequent treatment episode [24–26].

The emergence of acyclovir resistance has been noted in some patients with uncontrolled HIV infection. Resistance is less frequent in patients receiving cancer therapy but appears most frequent in HCT recipients who have received repetitive courses of acyclovir for repeated infection episodes. Acyclovir resistance usually is conferred by mutations in the genes encoding for the viral-specified thymidine kinase (TK) [27, 28]. This viral-encoded TK is necessary for acyclovir phosphorylation, and without it, little drug is converted to its active form. Thus, acyclovir and other nucleoside analogs that similarly rely on TK-mediated phosphorylation for their activity are inactive against acyclovir-resistant mutants.

Foscarnet is a pyrophosphate analog that directly inhibits viral DNA polymerase and does not require thymidine kinase for its activity. For patients with acyclovir-resistant HSV, Foscarnet is an alternative [29, 30].

## 2.2 Cytomegalovirus

CMV, another member of the herpesvirus family, infects a substantial proportion of the general population. Infection is generally asymptomatic in the nonimmunocompromised host, and although reactivation is frequent in immunocompromised patients, it rarely causes serious manifestations, except in highly immunocompromised patients such as HCT recipients, solid organ transplant recipients, and patients with the acquired immunodeficiency syndrome. Leukocytes are a reservoir of latent virus; thus, blood component transfusions as well as organ (including marrow and peripheral blood progenitor cells) grafts can be sources of viral transmission. CMV can cause fever, hepatitis, pneumonitis, leukopenia, thrombocytopenia, esophagitis, enterocolitis, retinitis, a mononucleosis-like syndrome, and occasionally central nervous system manifestations. In HCT patients, the most common and severe manifestation is interstitial pneumonitis, which if untreated results in death in 80–90 % of cases. Enterocolitis is less common but can represent a cause of severe diarrhea in the transplant recipient and

appears to be increasing in frequency. Chorioretinitis, a common clinical manifestation of CMV infection in HIV-infected patients, is uncommon in HCT recipients. Myelosuppression, a frequent accompaniment of cancer therapies, can have a variety of etiologies but CMV is one treatable cause [31–33].

Viremia can be diagnosed by culture [34, 35], but rapid diagnostic assays using detection of the pp65 antigen or CMV DNA or less commonly pp67 mRNA by quantitative PCR have largely replaced cultural assays [36–44], and such assays are capable of detecting virus 1–2 weeks earlier than culture. In tissue or cytologic specimens, the virus can be suspected by intracellular inclusions and confirmed by immunofluorescent assays or PCR.

Ganciclovir, a nucleoside analog structurally similar to acyclovir, is very active against CMV. It is effective in the treatment and in the prevention of CMV infection in transplant recipients. Ganciclovir exerts a potent antiviral effect in HCT patients with CMV pneumonitis, with a marked reduction in viral titers in infected tissue. However, when ganciclovir was used alone, there was no corresponding clinical benefit and most patients succumbed to relentless ventilatory failure [45]. Several studies have shown that when ganciclovir is used in combination with immunoglobulin both antiviral and clinical benefits ensue [46–48]. Thus, the mortality rate of 80–90 % from CMV pneumonitis has been reduced to approximately 50 %. For gastrointestinal CMV infection, ganciclovir alone and the combination of ganciclovir plus immunoglobulin have not been shown to be conclusively effective [49, 50], but ganciclovir alone is generally used. Foscarnet and cidofovir are alternative therapies to ganciclovir.

Ganciclovir has also been evaluated as prophylaxis in allogeneic HCT patients who are seropositive and thus at high risk of CMV disease [51, 52]. This approach has been found to be highly effective in reducing the risk of serious morbidity from CMV. Unfortunately, ganciclovir's side effects, especially myelosuppression, have led to episodes of neutropenia and bacteremia; thus, survival has not been appreciably improved. An alternative strategy, frequently referred to as early "preemptive therapy," has also been explored [53, 54]. In this approach, patients undergo surveillance screening for viral reactivation. Those patients found to have active infection are then treated with ganciclovir to prevent the subsequent development of clinical manifestations, which generally do not occur for several days to weeks after reactivation. Screening is generally done weekly on specimens of blood. Oral ganciclovir, found to be potentially useful as maintenance therapy in HIV-infected patients [55, 56], is not useful because of poor bioavailability, low serum levels, and the risk of emergence of resistance. Valganciclovir, an oral prodrug of ganciclovir, achieves high blood concentrations of ganciclovir and has also been shown to be effective in preemptive therapy [57–61]. Foscarnet can be used alternatively [62].

Several reviews have discussed the advantages and disadvantages of prophylaxis versus preemptive therapy [63–66]. In general, ganciclovir prophylaxis is more effective in preventing CMV disease, with fewer breakthrough episodes of CMV disease, while early preemptive ganciclovir is associated with fewer episodes of neutropenia and spares a sizable proportion of patients (in which

reactivation does not occur) from the cost and toxicity of ganciclovir. With the introduction into clinical use of PCR and antigen detection assays, it can be expected that there will be fewer failures associated with the preemptive therapy approach. Although initially preemptive therapy was continued to the end of the risk period (typically 100–120 days), today, shorter courses have been shown to be effective. Many centers administer therapy for a minimum of 2 weeks and discontinue once the viremia has resolved. Foscarnet and, to a lesser extent, cidofovir have also been used as preemptive therapy for CMV; however, issues with renal toxicity have limited cidofovir's usefulness in the transplant population [67]. Following discontinuation of preemptive therapy, surveillance should continue since viremia recurs in many patients. If viremia recurs, reinstitution of preemptive therapy should be done.

Resistance to ganciclovir has occasionally been encountered in HIV-infected patients on chronic maintenance dose schedules [68] but is rare in cancer patients. Resistance occurs most commonly by mutations in the UL97 gene region [69], but mutations in DNA polymerase, the U54 gene, can also occur. Foscarnet can be used for most ganciclovir-resistant viral mutants [70].

Acyclovir has not been clinically useful in the treatment for CMV disease. However, several studies in both HCT and solid organ transplant recipients have indicated that prophylaxis acyclovir (or valacyclovir) is effective in reducing the risk of developing CMV disease [71–73]. The explanation for this is not clear, but it would appear that a low level of acyclovir phosphorylation occurs despite the fact that CMV does not encode for a viral-specific TK, the enzyme that most avidly phosphorylates acyclovir to its active metabolites. Thus, low levels of phosphorylated acyclovir may be effective when the viral burden is low, although not efficacious in instances in which the viral burden would be high (the treatment scenario).

For patients who are CMV seronegative, infection can occur through acquisition of virus from blood transfusion or organ donation because leukocytes are a reservoir of latent virus. Accordingly, use of only CMV-seronegative blood products is an effective strategy in preventing CMV infection and disease [74–77]. Unfortunately, a substantial proportion of healthy blood donors are CMV-seropositive and harbor potentially transmissible virus. Accordingly, significant costs are incurred in the provision of CMV-negative blood products by blood banks. An alternative approach is the use of leukocyte filters, which are capable of eliminating most leukocytes that are present in erythrocyte and platelet products [78, 79]. A controlled trial demonstrated that this approach is almost as effective as CMV screening [79] and this is an option if suitable CMV-negative products are not available. This may also have the added advantage of reducing the risk of alloimmunization, another concern for patients who receive multiple blood products.

CMV hyperimmunoglobulin and plasma have also been shown to reduce the risk of CMV disease in the HCT recipient [80–85]. Because the antiviral potency of CMV immunoglobulin appears modest in studies in which it was used for treatment for CMV disease, speculation has been raised as to the mechanism of its

action; it has been suggested that it may be acting more as an immunomodulatory agent affecting antigen presentation or immune responses to CMV antigens rather than as an antiviral agent. Indeed, conventional lots of immunoglobulin not specifically chosen for high antiviral titers against CMV seem to be comparable with high-titer lots of immunoglobulin in preventing CMV disease. It should be noted that most studies have been conducted in CMV-seronegative patients. Only one study conducted in seropositive patients has shown a benefit, and the benefit was modest [85]. It is generally not used today because of its high cost and the advent of antiviral drug alternatives for prevention. An inactivated CMV vaccine is under study in HCT patients.

## 2.3 Varicella Zoster Virus

VZV infection is highly prevalent in the general population. Cancer treatment regimens are associated with a risk of reactivation that is, compared with the nonimmunocompromised host, slightly greater in solid tumor patients, substantially greater in patients treated with hematologic malignancies, and greatest in patients undergoing HCT. The most common manifestation is a dermatomal vesicular eruption, which may be preceded by a prodrome of localized pain and pruritus. Postherpetic neuralgia can persist for many months, especially in older individuals. Dissemination only occasionally occurs, but with highly immunocompromised patients such as allogeneic HCT recipients, dissemination can occur in up to 30–40 % of individuals [86, 87]. Cutaneous dissemination, the most common form of spread, can be complicated by bacterial superinfection. Visceral dissemination can be life threatening, and VZV pneumonia is the most common lethal manifestation. Fulminant hepatitis and pancreatitis are rare manifestations that can occur even in the absence of or before onset of cutaneous lesions [88]. It can be life threatening if not recognized and if treatment is not initiated promptly.

Acyclovir is very active against VZV and has become the treatment for choice [89–93]. Higher concentrations of acyclovir are required to control VZV than HSV. Because of acyclovir's poor bioavailability, intravenous administration is the preferred method of treatment in immunocompromised patients, or alternatively valacyclovir. Although high-dose oral acyclovir, valacyclovir, and famciclovir have shown efficacy in nonimmunocompromised hosts, they have not been well studied in the immunocompromised host. Acyclovir-resistant VZV has only been rarely encountered to date [94]. Foscarnet can be used for resistant pathogens [95]. Immunoglobulin can be given to susceptible immunocompromised patients if exposure is recognized within 3–4 days [96]. An attenuated vaccine has been found to be safe and protective for susceptible children with acute lymphoblastic leukemia [97–100]. Safety has not been evaluated in the early convalescent HCT period [101, 102]. An inactivated VZV vaccine is under study in HCT patients.

## 2.4 Epstein–Barr Virus

EBV, the cause of infectious mononucleosis in the nonimmunocompromised host, only occasionally causes morbidity in the immunocompromised host despite high rates of reactivation. However, in transplant recipients, severe morbidity can result from a mononucleosis-like syndrome or a variety of lymphoproliferative disorders. These can range from polyclonal lymphadenopathy to rapidly progressive monoclonal malignancy. Although these lymphoproliferative diseases are clearly EBV associated, molecular techniques have demonstrated mutations of oncogenes such as C-*myc* and tumor-suppressor genes, which occur in the transition from benign to malignant disease [103, 104]. The risk of EBV-associated lymphoproliferative diseases correlates with the degree of immunodeficiency. The use of multiple immunosuppressive agents, especially anti-thymocyte globulin, the use of T-cell-depletion techniques, the use of mismatched donors in the HCT setting, and the occurrence of multiple rejection episodes in the solid organ transplant setting [105], or severe graft-versus-host disease in the HCT setting [106] all contribute to the risk of these disorders [107, 108]. Although antiviral agents such as acyclovir and ganciclovir are active in vitro against EBV, their effectiveness in treating EBV-associated lymphoproliferative diseases has been disappointing in most cases. Once mutations in oncogenes and tumor-suppressor genes occur, most treatment approaches have been largely ineffectual. The treatment approach that has been most fruitful is reduction in immunosuppressive therapy, which can effect a remission in the benign lymphoproliferative disorders. Rituximab or anti-B cell lymphoma chemotherapy regimens are also usually administered. Serial monitoring for EBV viremia in high-risk patients has been advocated by some. In high-risk patients, weekly monitoring of EBV viremia with preemptive use of rituximab in patients with high levels of circulating viral DNA may be effective in preventing the subsequent development of EBV-associated lymphoma [109].

## 2.5 Human Herpesvirus Types 6 and 8

HHV-6 rarely causes clinical illness in the normal population despite being very prevalent. A self-limited eruption, exanthem subitum, has been noted in children. HHV-6 has been implicated as a potential pathogen causing some cases of interstitial pneumonitis, several CNS syndromes, rash, and sometimes HHV-6 appears to be a cause of myelosuppression (especially thrombocytopenia) in HCT recipients [110–114]. Ganciclovir, cidofovir, Foscarnet, and several other nucleoside analogs are active against HHV-6 in vitro, but to date, there are no clinical trials to establish clinical efficacy [115, 116] (see chapter Central Nervous System Infections in Cancer Patients and Hematopoietic Stem Cell Transplant Recipients).

HHV-8 is the causative agent of Kaposi's sarcoma. HHV-8 disease is infrequent in cancer and HCT patients. Treatment and prevention strategies have not been adequately evaluated for HHV-8 disease.

## 3 Immune Responses to the Herpesvirus Family

Both humoral and cellular immune responses occur in response to infection by all of the herpesviruses. The immune responses, felt to be most important in the control of active infection, are the cytotoxic response mediated by T lymphocytes or natural killer (NK) cells. This has been most convincingly demonstrated in CMV infection [117–119]. In the HCT recipient, resolution of active infection occurs only with the development of cytotoxic T cell or NK responses. In the absence of the development of these responses, most patients succumb from infection. In HCT recipients with GVHD, the orderly development of cytotoxic responses may be severely impaired and patients are at much greater risk of more frequent and more severe CMV infection and illness. Similarly, patients who are the recipients of T-lymphocyte-depleted bone marrow grafts are unable to mount robust T-cell responses and are similarly more susceptible to more frequent and severe CMV infection and disease. These observations have led to consideration of cloning cytotoxic T cells (CTL) with anti-CMV activity and expanding them ex vivo for use as lymphocyte transfusions to bolster host immunity in an attempt to prevent severe CMV disease [120–123]. Clinical trials are currently under way.

EBV-specific cytotoxic T-cell precursors are more frequent in the circulation than CMV-specific CTL precursors. Buffy-coat transfusions have been successfully used in the treatment for EBV-associated lymphoproliferative disorders in transplant recipients without the need for ex vivo clonal expansion [124]. These approaches to adoptive transfer of cellular immunity appear quite promising for preemptive therapy as well [125–127].

Bolstering the host immunity through the use of viral vaccines has been hampered by the lack of safe and highly immunogenic vaccines. A live-attenuated varicella vaccine is useful in children with acute leukemia (as noted earlier); however, it have been felt to be too risky for use in the HCT setting, except in patients two or more years after transplant without active GVHD. Attenuated CMV vaccines have been tested in clinical trials in solid organ transplants, but have been similarly felt to be too risky in the HCT setting. Inactivated CMV and VZV vaccines are being evaluated in HCT patients.

## 4 Hepatitis Viruses

The hepatitis viruses are a heterogeneous group of RNA (hepatitis A and C) and DNA (hepatitis B) pathogens. The portal of entry for hepatitis A is generally the enteric route, with transmission by fecal–oral contact, while for hepatitis B and C, sexual and blood transmission are the primary routes of acquisition. Recognition for the potential of transmission through blood products and the development of screening tests have led to a marked reduction in transmission of hepatitis B and C.

For cancer patients who are seropositive for hepatitis B and C prior to treatment, the likelihood of reactivation and disease progression is related to viral and patient treatment factors. Patients with evidence of a high viral load (DNA/RNA in blood) and those receiving more immunosuppressive therapies (e.g., lymphoma and HCT patients) are at greater risk. Accordingly, patients should be screened for prior hepatitis prior to antineoplastic chemotherapy or HCT.

Inactivated hepatitis A and hepatitis B vaccines have been found to be safe and highly immunogenic. Hepatitis B immunization is recommended for seronegative patients. Immunoglobulin can be protective for those who must come in close contact with infected individuals to reduce the risk of infection. After exposure, immunoglobulin can also be efficacious against hepatitis A and B.

For patients with prior infection with hepatitis B, reactivation is likely with immunosuppressive chemotherapy regimens and the risk is greater after more highly immunosuppressive therapies and in patients with higher viral loads before therapy. Mild elevations of transaminases are most common, but severe, even fatal hepatitis can occur in 5–10 % of cases [128]. Lamivudine given prophylactically is highly effective in preventing reactivation, flares of hepatitis, and fewer antineoplastic treatment delays due to liver complications and should be given to patients with circulating HBV DNA [129]. For patients without circulating HBV DNA but with serologic evidence of prior infection (e.g., presence of hepatitis B core antibody), either close monitoring for reactivation in less intensively treated patients or lamivudine prophylaxis in more intensively treated patients should be considered. The optimal duration of lamivudine is not known. Since hepatic injury often occurs (or peaks) with HBV infection at the time of immune reconstitution due to the pathologic effects of the immune response, lamivudine should be continued until immune reconstitution has occurred. Experts recommend its continuation for a minimum of six months after completion of chemotherapy or immunosuppressive therapy [130, 131]. Resistance to lamivudine can occur, especially in patients with actively replicating virus receiving long-term therapy [132]. Other antivirals such as adefovir or entecavir are acceptable alternatives, but there is to date only limited experience with these.

For patients with prior hepatitis C, chronic infection is typical and elevated transaminases may wax and wane during chemotherapy or after HCT. After HCT, HCV infection increases the risk of hepatic veno-occlusive disease; alternatively, hepatic abnormalities may be most prominent several months after immunosuppression is stopped. The risk of late cirrhosis years later is also increased. The combination of pegylated interferon plus ribavirin is the most effective therapy for HCV infection. Genotype 1 virus responds less well to therapy compared with genotypes 2 and 3. Because of myelosuppression and the concern for provoking or worsening GVHD after HCT, treatment is generally delayed if possible until after immunosuppressive therapy is completed. The magnitude and durability of clinical benefit have been debated. Generally, early treatment after transplant is not necessary or advisable due to the toxicities of the treatment. Much later, after the patient has completed immunosuppressive therapy, the presence of chronic active hepatitis may alter the risk benefit balance [133].

A hematopoietic graft from a seropositive individual has the potential for transmitting hepatitis B or C to the recipient. Different reports have suggested different rates of transmission and different degrees of severity of illness in the recipient of such transmission [134]. Donors who have circulating viral RNA/DNA are at higher risk of transmitting virus than those who are seropositive but not viremic. Donors who are hepatitis seropositive should be excluded if possible. If they must be used, they should be treated with antiviral therapy if time permits to reduce the risk of transmission. Donors who are HBV DNA positive should be treated with lamivudine [131] to reduce the likelihood of transmission. Adoptive transfer of immunity to hepatitis B in the HCT setting from an immune donor may be a possible option for some patients [135]. Consideration can be given for treatment for hepatitis C donors with pegylated interferon and ribavirin.

## 5 Adenovirus

Adenovirus is a viral pathogen capable of causing respiratory illness, conjunctivitis, gastroenteritis, interstitial pneumonitis, and hepatitis. Type 11 has been associated with hemorrhagic cystitis. Adenovirus isolation is noted in 5 % of all allogeneic HCT recipients. Illness ensues in approximately 20 % of infected individuals. Types 1, 5, and 7 appear to be the most common types causing invasive disease, which can be fatal in approximately half of cases. HCT patients who are the recipients of unrelated donor grafts, mismatched grafts, cord blood, or grafts in which T-cell depletion has been performed, younger-aged patients, and those given total body irradiation appear to be at greater risk [136, 137]. Currently, there is no known effective antiviral therapy. Cidofovir is active against adenovirus in vitro and case series suggest clinical activity, although there are no controlled clinical trials. Ribavirin also has some activity, but treatment responses have been inconstant. Since high-level viremia is often a harbinger of subsequent development of invasive disease, some centers monitor viremia in high-risk cord blood or haploidentical transplant recipients on a weekly basis and initiate cidofovir preemptively if high-titer viremia develops [138].

## 6 Intestinal Viruses

Outbreaks of a variety of enteric pathogens occur in the community with seasonal variation. Immunocompromised patients can become infected during these community outbreaks. Common pathogens include coxsackievirus, rotavirus, the Norwalk agent, caliciviruses, and astroviruses. The allogeneic HCT recipient is especially vulnerable to severe, even life-threatening, and diarrheal illness. There are no effective antiviral therapies. Electrolyte and fluid replacement are important adjunctive measures. Immunoglobulin given orally has been suggested as a treatment for these illnesses, but adequate clinical trials are lacking.

## 7 Community Respiratory Viruses

Respiratory syncytial virus (RSV), influenza, and parainfluenza viruses are frequent causes of upper- and lower-respiratory-tract illness. Transmission is frequent in the community and often is the source of infection in immunocompromised cancer patients. The degree of immune compromise (e.g., lymphopenia) is a risk factor for severe illness from the community respiratory viruses [139–142] (see chapter Respiratory Infections).

Inactivated influenza vaccine is available and may be potentially protective for immunocompromised patients [143], but severely immunocompromised patients, such as early convalescent allogeneic HCT recipients, unfortunately do not respond reliably or adequately. Neuraminidase inhibitors, such as oseltamivir or zanamivir, are preferred treatment options for influenza A and B and have largely replaced amantadine and rimantidine because of less toxicity and emergence of resistance to the latter class of drugs. Early start of therapy (less than 48 h after onset of symptoms) is quite important. An ominous note is the recent observation of some influenza strains exhibiting resistance to oseltamivir (but retaining susceptibility to zanamivir). Neurominidase inhibitors can also be used in highly immunosuppressed patients exposed to influenza to prevent symptomatic infection.

Ribavirin, a nucleoside analog, can be clinically useful for RSV infection [144, 145]. As with influenza, early initiation of therapy is important. Lymphopenia and respiratory failure are adverse factors for response. Immunoglobulin with high-titer antibody against RSV or palivizumab, a RSV-specific monoclonal antibody, may have additive effects when added to ribavirin, but controlled trials have not been conducted. A controversial issue is whether administration of therapy for upper-tract infection will prevent the progression to lower-tract disease. A retrospective review on the use of ribavirin for RSV upper-tract infection in leukemia and in HCT patients suggested a reduction in subsequent pneumonia [146]; however, a small randomized trial in HCT patients suggested a reduction in viral load with aerosolized ribavirin, but no substantial reduction in subsequent development of lower-tract disease was evident [147]. A study of palivizumab suggested no benefit in its use in HCT patients to prevent progression of upper-tract infection to pneumonia [148].

There are no effective treatment approaches established for parainfluenza infections. Human metapneumovirus is a recently discovered RNA paramyxovirus. It has been isolated from a small percent of HCT patients undergoing bronchoscopy, mostly for idiopathic pneumonitis [149]. There is no known effective therapy, but ribavirin is active as well as immunoglobulin in vitro.

Cautionary measures must be exercised to avoid nosocomial transmission of these airborne organisms during community outbreaks [150–152]. Infection control measures are paramount to prevent spread of infection among patients, patient families, and health care workers during community outbreaks. These include respiratory isolation of patients with documented and suspected infection, use of masks, and restricting contact of patients with family and health care workers with

respiratory infections. Chemoprophylaxis of HCT patients exposed to influenza has been shown to be useful and well-tolerated in HCT patients [153] whether there is a role for prophylaxis in other immunocompromised patient groups is unclear.

## 8 Papovaviruses (Polyomaviruses)

JC and BK viruses cause asymptomatic infection in children but establish a persistent infection in renal and urogenital epithelial cells. JC virus has been associated with progressive multifocal leukoencephalopathy. BK virus has been associated with hemorrhagic cystitis in allogeneic HCT recipients [154–158]. At present, there are no effective therapies.

Cidofovir is active against polyomaviruses in vitro, and there are case reports and series describing its use, but its efficacy has not been documented [159]. DNA gyrase inhibitors, such as ciprofloxacin, may have efficacy in prevention in high-risk HCT patients [160].

## 9 Retroviruses

Human T-cell lymphotrophic virus type-1 (HTLV-1) is an endemic retrovirus in some areas of the world. Transmission can occur by breast feeding, sexual contact, or blood transfusion. It has been associated with the development of the adult T-cell 1eukemia/lymphoma syndrome. Latency between infection and onset of disease is often more than a decade, and the risk of development of disease may be dependent on the age of infection, with early childhood being most risky.

HIV (formerly HTLV-3) is a retrovirus that is the causative agent of AIDS. Sexual transmission and transmission via blood transfusion or organ transplant are well established. The institution of routine screening tests for blood products and organ donors has reduced the risk of transmission substantially. Several nucleoside analogs are active inhibitors of reverse transcriptase, and protease inhibitors have recently been found to be useful in the suppression of viral replication, with corresponding clinical benefits. There are multiple effective combination regimens that are effective in long-term suppression of viral replication and decline in immunity. The emergence of antiviral resistance has plagued the development of effective and enduring antiviral strategies, however.

## 10 Conclusions

The increase in viral infections in immunocompromised patients and the increasing numbers of immunocompromised patients have given a sense of urgency to improve our diagnostic techniques and to develop an armamentarium of antiviral agents for use in the control of these prevalent and opportunistic

microorganisms. Recognition of the relevant protective immune responses is likely to lead to new biologic strategies to supplement pharmacologic measures to control serious morbidity from these pathogens in the future.

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