VIRAL DISEASES AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Viral diseases are a major cause of morbidity and mortality after hematopoietic stem cell transplantation (HSCT). The risk of viral infection relates to a number of factors, including the type of transplant, processing of the graft, and posttransplantation immunosuppression. In many cases, viral infection after hematopoietic stem cell transplants results from reactivation of a latent virus, and herpes viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and herpes simplex (HSV) and herpes zoster (VZV) are common viral pathogens that cause disease after transplantation. In addition, respiratory viruses such as adenovirus, influenza, and respiratory syncytial virus (RSV) also pose a serious problem in posttransplantation patients, who usually acquire the viruses from contact with infected individuals [1-5].

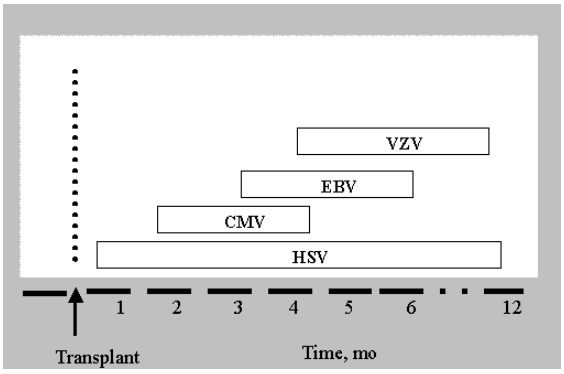


Figure 1: The reactivation of herpesviruses follows a predictable temporal pattern after. HSCT. HSV causes clinically apparent disease at about first month, and CMV usually occurs 2nd to 3rd month after, and EBV may also reactivate in the 3rd month after HSCT. VZV recurrence present at a median 5 months after transplantation

Hematopoietic stem cell transplantation is a potentially curative procedure for many types of hematopoietic malignancy but is associated with a period of intense immunosuppression, which may last for 1 to 2 years. Both the humoral and cellular arms of the immune system are affected, but most clinical problems follow impairment of the cellular immune response. T cell numbers are reduced for several months following an allograft, and T cell functional responses such as cell signaling and effectors function are also impaired. Peripheral blood stem cell grafts may improve immune reconstitution but such patients remain at high risk of infection. T cells play a major role in the control of viral infection. CD8+ cytotoxic T cells are able to recognize and destroy virally infected cells and are probably the most important cells in controlling many viral infections. CD4+ T cells may also be cytolytic but their prime role is in the support of humoral and CD8+ T cell responses. CD4+ T cell recovery is particularly sluggish after stem cell allografting, and typically the CD4:8 ratio is inverted for many months [6-9].

An additional factor contributing to progress was the development of rapid and sensitive diagnostic methods, such as the shell-vial culture, antigen detection assays, and the polymerase chain reaction (PCR), which permit the detection of viral infections at an early stage. Results obtained with these techniques enable clinicians to make timely therapeutic decisions. Rapid diagnostic tests have also facilitated the introduction of the preemptive treatment strategy, which consists in initiating antiviral drug therapy only when a viral infection is documented, to prevent the occurrence of viral disease [10,11]. In contrast to antiviral drug prophylaxis, the preemptive treatment approach restricts antiviral treatment to patients at the highest risk for viral disease, which is particularly important in view of the toxicity and costs associated with some of the antiviral compounds currently available.

HUMAN HERPESVIRUSES

Members of the herpesviruses family are the cause of significant morbidity and mortality in the post-HSCT setting. They all possess the unique characteristics of latency and reactivation, and each virus emerges during a specific time period after transplantation. Herpesviruses are among the most common causes of viral disease after allogeneic and autologous HSCT [12,13]. So far, eight viruses have been identified that belong to the human herpesviruses family. Treatment strategies have been established for infections with HSV types 1 and 2, VZV, and CMV. A possible therapeutic effect of licensed antiviral drugs against Epstein-Barr virus and human herpesviruses 6, 7, and 8 in HSCT recipients has not been investigated in controlled trials, and firm recommendations on the treatment of these viruses are therefore not possible **[Figure1]** [14].

HERPES SIMPLEX VIRUS

Herpes simplex virus infections occur during the early, neutropenic or pre-engraftment period soon after the initiation of immunosuppressive therapy. Primarily HSV infection begins after close contact of a susceptible individual with someone excreting virus. This usually involves exposure to HSV at mucosal surfaces or abraded skin. Following HSCT, primarily HSV lesions develop at mucocutaneous sites and frequently with severe and extensive ulcerative lesions on the palate, tongue, lips and nose, but esophageal HSV disease is also fre-

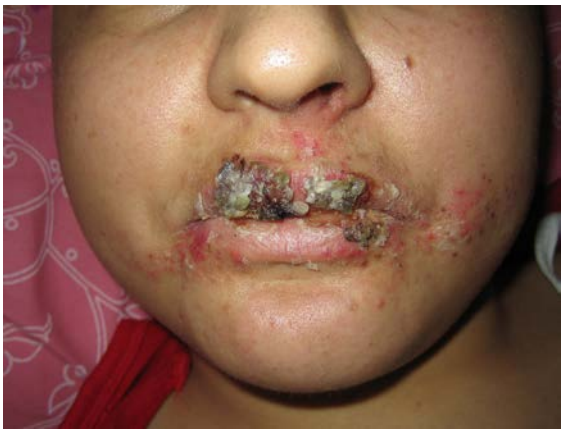
quent and is present in about 10% of patients with upper gastrointestinal symptoms [3].

In the days prior to the use of antiviral prophylaxis, approximately 80 % of HSV seropositive HSCT recipients would shed the virus and, of these, 70% would develop reactivate HSV disease. With the advent of acyclovir prophylaxis, the incidence of HSV disease has dropped below 5% . But while the problem of HSV infection after HSCT has substantially diminished in the early post-transplant period, HSV infection has shifted to the period after prophylaxis has ended, and the occurrence of acyclovir-resistant HSV strains has emerged [15]. HSV type 2 lesions in the genital and perinea regions were less often seen. Approximately 90% of infections involved the oral mucous membranes (HSV-1), while 6% involved the genital area (HSV-2). Fatal pneumonias due to HSV were also seen. HSV disease results from reactivation of latent virus in most cases, and antiviral drug prophylaxis is thus primarily aimed at HSV seropositive patients. The pain suffered by the patient can become a major management problem, but the damage done to the oral mucosa can lead to portals of entry and sites of infection for bacteria (Viridans streptococci) and fungi (Candida). It can also lead to extension of infection into the esophagus and lung. HSV pneumonia probably results as an extension of oropharyngeal infection and usually presents as an interstitial pneumonitis. HSV interstitial pneumonitis has a high fatality rate and does not appear to have changed in the era of prophylaxis [3].

Table1: General approaches to HSV infections in HCT recipients.

Prophylaxis:	
Acyclovir	250 mg/m2 or 5 mg/kg IV q.12h or ; 200 mg, PO, t.i.d.
Valacyclovir	500 mg, PO, q.d.
Treatment:	
Acyclovir	250 mg/m2 or 5mg/kg, IV, q.8 h or; 400 mg, PO, 5x/day
Valacyclovir	500-1000 mg, PO,b.i.d.
Famciclovir	500 mg , PO, b.i.d.
For visceral disease:	
Acyclovir	500 mg/m2 or 10 mg/kg IV q.8 h

Diagnosis of HSV infection relies upon both clinical and laboratory criteria. A clinical diagnosis of cutaneous HSV infection can be made when clumps of vesicular lesions on an ertythematous base near or around the perioral or genital areas are present **[figure2].** In the past, rapid diagnosis of cutaneous lesions was made with adequate scrapings of fresh, early lesions examined microscopically after Giemsa (Tzanck preparation), Wright or papanicolaou staining. The standard of diagnosis of HSV infection is virus isolation. Cytopathic effect may develop within 24-48 h, but definitive identification may take from 48 to 96 h. A more rapid cultural technique is the spin-amplified culture, or shell vial, technique with subsequent staining for specific HSV antigen (3).



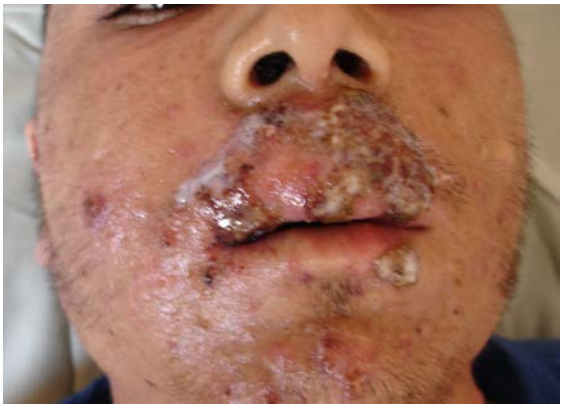


Figure 2: HSV in patients with allogeneic transplantation.[Dedeman Hematology Oncology Hospital, Capadocia Transplant Center, Archive No: AA-124, AA-067]

The antiviral drugs acyclovir (ACV), valaciclovir and famciclovir are licensed for treatment of HSV infection and disease **[Table1].** Valaciclovir and famciclovir have an oral bioavailability 3–5 times that of oral acyclovir, which permits less frequent dosing and replacement of intravenous acyclovir for some indications. Prophylactic intravenous or oral acyclovir has become a standard of care for HSV seropositive HSCT recipients [16,17]. ACV prophylaxis initiate from time of conditioninig regimen and continue until absolute neutrophil count greater than 500/ µl: 250 mg/m^2 q 12 hours IV (5 mg/kg q 12 hours IV) or 200 mg QID PO (800 mg q 12 hours PO). The duration of prophylaxis is usually 3–5 weeks after the start of the conditioning regimen, but may be longer in allograft recipients who develop acute graft-versus-host

disease. Oral valaciclovir and famciclovir have not been systematically studied for the prevention of HSV infection after HSCT, but are probably as efficient as acyclovir [3]. Treatment of herpetic infections after prophylactic period is discouraged for several reason: 1) late infections usually resolve without treatment; 2) treatment in this context frequently (up to 18) results in emergence of resistant virus; 3) prolonged treatment delays the development of immune responses to HSV. Treatment is justified if the herpetic lesions are painful, interfere with nutrition, produce fever that complicates interpretations concerning other possible infections or are thought to be responsible for clinically significant neutropenia or thrombocytopenia. Intravenous acyclovir (250-500 mg/m^2, IV q. 8 h, 7-10 days) is the therapy of choice for severe mucocutaneous or visceral HSV disease in HSCT recipients. Oral acyclovir (200-400 mg/m^2 q. 8h IV, 7-10 days) , valaciclovir, or famciclovir may be considered as therapeutic alternatives for less serious forms of HSV disease.

ACV resistant virus rarely occurs during prophylaxis (0,4%) but frequently emerges during treatment of established infections in the post-prophylaxis period (up to 18%). In this condition, dose of ACV can initially increase to 500 mg/m^2 every 8 hours intravenously if renal functions is normal. Therapy should switch to foscarnet immediately if there is severe, life threatening infection with resistant virus. If renal function is adequate, treatment should be with foscarnet at 40-60 mg/kg every 8 hours intravenously until clinical resolution.. For ACV and foscarnet resistant HSV: Cidofovir 5 mg/kg, weekly x 2, IV then q.2 weeks.

VARICELLA-ZOSTER VIRUS

Varicella-zoster, like other pathogens of the herpesviruses family, can cause severe infections in hematopoietic cell transplantation recipients. VZV is a member of the alpha-herpesviruses subgroup of the herpesviruses genus. It is an enveloped virus that has a double-stranded DNA genome. Primary VZV infection causes chickenpox (varicella), is much less common than disease caused by VZV reactivation during the 1-st year after HSCT, accounting for only about 5% of VZV infections in this population. Patients who acquire varicella infection during the first 9-12 months after transplantation appear to be at highest risk of developing severe disease. In one large series, 32 % of these patients developed visceral dissemination in the course of varicella, with VZV infection of the lungs, liver, and central nervous system (CNS). The clinical complications that result include pneumonia, hepatitis, DIC and encephalitis. The mortality that accompanies VZV reactivation is almost always due to viral pneumonia, but fatal fulminant hepatitis and DIC without VZV pneumonia have been reported [4].

Serum immunoglobulin G (IgG) antibodies to VZV provide evidence of a past primary infection and indicate that the individual is latently infected with the virus. Reactivation of VZV results in herpes zoster **[Figure3]**. The reported incidence of recurrent VZV infection after HSCT ranges from 23% to 59%. In general, the risk of recurrent VZV infection is highest between 2 and 10 months after transplantation, although cases have been reported within the 1st week and continue to occur after the 1-st year. Localized herpes zoster is the most common clinical presentation of VZV infection in HSCT recipients who are seropositive at the time of transplantation. The rash of localized herpes zoster is usually preceded by pain and parasthesias in the involved dermatome. These symptoms may begin as long as 5 days before the eruption and vary from mild discomfort to very severe debilitating pain. In high-risk patients, the average time for cessation of new lesion formation was 8 days, and crusting was not complete until an average of 18 days. Immuno suppressed patients may occasionally develop a chronic cutaneous reactivation of VZV that persists for months. In one study showed that post-herpetic neuralgia in 25% of patients with herpes zoster after HSCT and some authors reported an incidence of 32%.

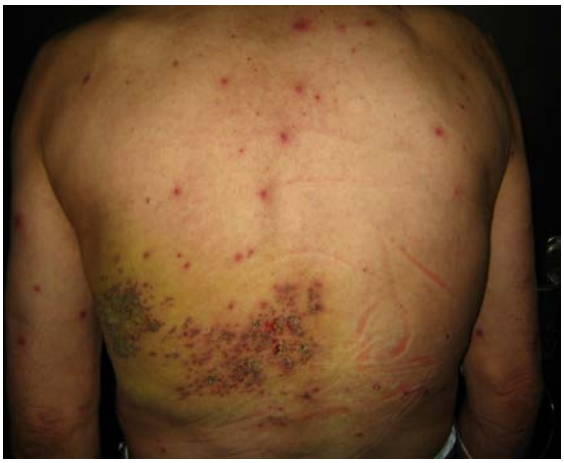


Figure 3: VZV in patient with allogeneic transplantation.[Dedeman Hematology Oncology Hospital, Capadocia Transplant Center ,Archive No: KL-025]

The optimal method for the rapid diagnosis of cutaneous VZV infection is to obtain epithelial cells from a fresh lesion and to stain the specimen using fluorescein-conjugated monoclonal antibodies to VZV antigens. VZV can be detected in clinical samples using standard tissue culture methods for viral isolation. VZV DNA sequences can be detected using radio labeled or biotinylated nucleic acid probes for in situ hybridization or southern blot procedures. The most sensitive serologic assays for

detection of VZV antibodies are fluorescent-antibody staining of membrane antigen (FAMA) and radio-immunoassay (RIA).

Both manifestations (primary & reactivation) of VZV infection require prompt treatment in HSCT recipients to inhibit disease progression and prevent visceral dissemination. Primary VZV infection in HSCT recipients occurring within the 1 st year after transplant should be considered to require intravenous acyclovir therapy. The goal of antiviral therapy for varicella in high-risk patients is to initiate drug treatment within 72 h after the appearance of the cutaneous rash. Varicella zoster immunoglobulin (VZIG) administration is indicated for high-risk children and adults who have never had VZV infection, whose exposure to VZV is identified within 96 h. Nevertheless, clinicians must be aware that severe varicella develops in some immune compromised patients despite the timely administration of VZIG. For moderately immune-deficient patients, high-dose oral acyclovir, oral valaciclovir, and famciclovir are possible treatment alternatives [18,19].

The dose of acyclovir is 500 mg/m^2 or 10 mg/kg intravenously (IV) given every 8 h. Therapy should be continued for 7 days or for 2 days after cessation of new lesion formation, whichever provides the longer treatment course. On average, early antiviral treatment should cause the cessation of acute pain within 4 days, crusting of lesions by 7 days and complete healing by 2-3 weeks. The average period to onset of varicella pneumonitis is 6 days, with most cases occurring within 4-8 days among untreated high-risk patients. In addition to preventing life-threatening dissemination, acyclovir therapy can also be expected to minimize the extent of the cutaneous disease and shorten the time to complete healing significantly. A randomized comparison of famciclovir and oral acyclovir for therapy of localized zoster in immune compromised hosts showed similar efficacy in terms of the time to cessation of new lesion formation, complete healing of lesions, or loss of acute pain, and the rates of zoster dissemination were no different between the two treatment groups [20]. Prevention of chickenpox in HSCT recipients requires strict isolation from infectious individuals. Isolation procedures may be too late in some cases, however, because patients with chickenpox can be contagious up to 2 days before the onset of skin rash. Following contact with an infected person, VZV-seronegative patients may benefit from infusions of VZV hyper immune globulins if these are administered within 96 h of exposure [21]. Immunization with a VZV vaccine might become an additional option for the prevention of chickenpox and zoster in HSCT recipients. In a non-comparative series of 15 children after HSCT, the use of a live attenuated VZV vaccine was effective in preventing VZV disease for up to 2 years after immunization. Among 75 VZV-seropositive HSCT recipients randomized to receive a heat-inactivated VZV vaccine or no intervention, immunization was furthermore associated with better reconstitution of specific cellular immunity and markedly less severe zoster. VZV reactivation can occur for a long period after allogeneic HSCT, but long-term antiviral drug prophylaxis is not advisable, since it only delays the development of zoster and carries the potential for induction of VZV resistance [22].

CYTOMEGALOVIRUS

Cytomegalovirus infection still remains a major cause of morbidity and mortality after HSCT. The pretransplantation serostatus of the recipient and the donor, the grade of human leukocyte antigen disparity between the donor and the host in the allogeneic setting, and modifications of the graft such as in vitro and in vivo T-cell depletion determine the risk of active CMV infection. The use of corticosteroids for management of GVHD is the single most important risk factor. Authors have shown that 1-2 mg/kg corticosteroid was associated with significant rise in CMV DNA in blood during ganciclovir therapy. At doses of 2 mg/kg or higher, there was a 10-fold likelihood of a rising CMV DNA load while on therapy [2].

After HSCT, patients are at increased risk of developing severe CMV disease following primary infection, reinfection, or reactivation of virus. The most frequent manifestations of CMV disease are interstitial pneumonia, gastroenteritis, and hepatitis. Rare manifestations are CMV retinitis and encephalitis. CMV pneumonia is defined as a progressive interstitial pulmonary process, as evidenced by chest X-ray, with concomitant evidence for other causes of pneumonitis **[Figure4]**. CMV enteritis is defined as a gastrointestinal disease with pain, nausea and vomiting, or diarrhea and evidence of CMV infection at the site of an erythematous or ulcerative mucosal lesion. In general, other CMV-associated organ-related syndromes, such as hepatitis and encephalitis, are defined as syndromes with specific organ dysfunction and concomitant presence of active CMV infection. With the exception of CMV retinitis, the diagnosis of CMV disease cannot be made with confidence without histologic evidence of CMV infection in the involved organ [12,13].

CMV infection per se in HSCT recipients is usually defined as the isolation of CMV in tissue culture. The antigenemia assay based on the detection of number of pp65-positive leukocytes the by immune-fluorescence was developed and was found to correlate with viremia and CMV disease[23]. In-

creasing use is now being made of the amplification of viral DNA and RNA. By monitoring the patient with sensitive detection methods such as polymerase chain reaction (PCR) assays of whole blood for CMV-DNA, the incidence of CMV disease and CMV-related mortality has been reduced through the early introduction of antiviral therapy[24]. Thus a fourfold or higher rise in CMV antibody titer and antigenemia and quantitative PCR assays are increasingly used to diagnose active CMV infection after transplantation and to initiate antiviral therapy. CMV infection arises either from exogenous introduction of virus via blood elements and transplanted tissue or from reactivation of endogenous virus. Persons who have had CMV infection prior to HSCT form the group at risk for most problems after HSCT. The seronegative transplant recipient is at much lower risk for serious infection so long as exposure to exogenous sources of infection can be minimized. Convincing evidence has been provided that granulocytes are a major source of exogenous CMV after HSCT arises by contact with random blood products. For this reason, CMV-seronegative HSCT recipients of stem cells from seronegative donors need to be protected from potentially infectious blood products. In the absence of prophylactic measures, the incidence of CMV infection is 60–70% in HSCT recipients when the graft donor or recipient is CMV seropositive, and one-third of allograft recipients and 10–20% of autograft recipients with documented CMV infection develop CMV pneumonia [25]. The high rates of infection and disease fell dramatically with the introduction of CMV-negative blood support **[Table2].**

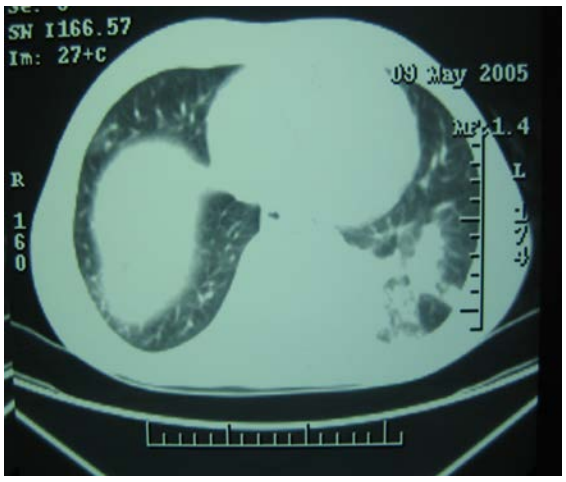


Figure 4: CMV induced interstitial pneumonia in patient with allogeneic transplantation. [Dedeman Hematology Oncology Hospital, Capadocia Transplant Center, Archive No: MN-011]

The use of antiviral agents at the time of engraftment or when CMV infection first occurs reduces the incidence of CMV disease in the first 100 days post-HSCT to 1-2 %. Because the poor prognosis of therapy of established CMV disease, preventive measures are very important and consist either in prevention of CMV infection (prophylaxis) or prevention of development of disease after CMV reactivation has been documented (preemptive therapy)

Not all HCT recipients will do well with preemptive anti-CMV management, especially those at the highest risk for CMV infection. The alternative approach to prevention of CMV in high-risk patients is to treat all patients prophylaxis with ganciclovir, usually at time of engraftment. Authors assessed the early routine use of GCV in high risk group; GCV was given at a dose of 5 mg/kg twice daily in the course of conditioning regimen, and resumed when the ANC equaled 1,000/µL at 5 mg/kg IV three times /week until day 84 or 120 post HSCT. Prophylaxis with GCV; CMV infections were reduced, however, there was no survival advantage. Furthermore, because of the toxicity (severe neutropenia) of these agents and their expense, general use of GCV in all CMV seropositive persons is currently not recommended.

Table2: Transfusion politics according to the CMV serostatus in allogeneic HSCT*

CMV serostatus	Blood product support
R^- & D^-	CMV negative blood products are recommended as a successful strategy to prevent exposure
R^- & D^+	The utility of providing seronegative blood products to seronegative recipients who have seropositive donors is controversial, but should be if feasible.
R^+ & D^+ Or R^+& D^-	It is not necessary to restrict patient to CMV negative blood products.

*CMV seronegative autologous HSCT; Ideally, the provision of CMV negative products if the transplant center can provide such products. (R: recipient, D: donor)[44]

Preemptive treatment is applied either from the first positive test result until day 100 after transplantation resulting in a duration of 6–8 weeks of therapy in the majority of patients or until the indicator test becomes negative, usually resulting in 2–4 weeks duration of therapy. In a cohort of 86 PCR-monitored and preemptively treated patients, CMV disease before day 100 after transplantation occurred in 3.5% and late onset CMV disease thereafter in 6% of patients. Ganciclovir is the drug of choice for pre-emptive treatment and is administered at an “induction” dose of 5 mg/kg twice daily for at least 7-14 days or until evidence of falling CMV load. CMV infection will clear in most patients within 2 weeks but for those with stable or

increasing CMV levels, the induction period should continue. Maintenance therapy consists of ganciclovir (GCV) 5 mg/kg/day for 5-7 days/week for an additional period of time based on the patient's risk factors. For example, if the CMV levels are negative on two occasions, and the subject is not receiving corticosterioids or in vivo T-Iymphocyte depletion, then maintenance can stop after 3-6 weeks. For patients on steroid or other secondary therapy for GVHD, treatment should continue for up to 100-day post-HSCT. For patients for whom immunosuppressive therapy of GVHD is lessening and in whom there are at least 2 weeks of negative surveillance points for CMV in blood, pre-emptive ganciclovir can be stopped. For patients in the 2nd and 3rd months after HSCT, for whom there are no major risk factors relating to GVHD and immunosuppressive therapy, pre-emptive management can be tentatively stopped. However, if secondary treatment for GVHD is required, and corticosteriod use is ≥1mg/kg/day, the pre-emptive surveillance program should be reactivated **[Table3]** [2].

CMV-IP occurred in 15-30% of marrow allograft recipients. No matter whether CMV-IP occurs before or after day 100 after HSCT, hypoxia is the major physiological abnormality observed, and radiological abnormalities suggestive of interstitial pneumonitis are the frequent pattern on X-ray films. However, as noted earlier, it is recognized that CMV level in blood is predictive of risk for late onset CMV disease Although the diagnostic procedure of choice in the past was lung biopsy, since the mid-1980s BAL has become the preferred method of diagnosis of CMV-IP. In a study, for the treatment of CMV-IP with combination of antiviral agent (GCV 5 mg/kg/IV q.12h) and CMVIg: 20 patients received a regimen of IVIg consisting of 500 mg/kg every other day for 10 doses and then every 2 weeks for 8 doses. Fourteen (70%) of the 20 patients were alive at 6 weeks and 10(30%) were alive at 6 months, with a median follow-up time of 24 months. In another study; 40 patients were treated with therapy which included antiviral induction treatment lasting 3 weeks, or until there was documented clearing of pulmonary CMV infections, followed by a maintenance treatment lasting until immunosuppressive medications were stopped. In this regimen, ganciclovir was given at 10 mg/kg daily and Ig at 500 mg/kg every other day for 21 days, followed by ganciclovir at 5 mg/kg daily 5 days/week and IVIg at 500 mg/kg weekly until day 180 after treatment was started and 16(40%) were alive at a median follow-up time of 18 months. Thus, ganciclovir combined with IVIg has produced improvement in the outcome of this disease. Although these results were derived from uncontrolled studies, ganciclovir plus Ig has become the recommended [2].

Effective antiviral prophylaxis and early intervention has led to an increase in active CMV infection and disease after day 100 after transplantation. Patients developing late-onset CMV disease are characterized by a delayed reconstitution of CMV-specific T-cell responses. In a prospective cohort study in CMV-seropositive patients, 26 of 146 patients (17.9%) developed late CMV disease at a median of 169 days after allogeneic SCT [37]. At 3 months after transplantation, preceding detection of CMV pp65 antigenemia, CD4 T+cell counts <50/µl, lymphocytopenia <100/µl, undetectable CMV-specific T-cell responses, and GVHD were associated with late CMV disease and death. In a pilot study in a limited number of patients at high risk for late-onset CMV disease, a single transfusion of a donor-derived *ex vivo* expanded polyclonal CMV-specific T-cell line was found to be associated with clearance of the viral load from the blood and reconstitution of CMV-specific T-cell responses in some of the patients, indicating a potential strategy to prevent late CMV disease [26,27].

Table3: General approaches to CMV infections in HCT recipients.

I. Prophylactic therapy
Ganciclovir, 5 mg/kg b.i.d.; daily
with conditioning regimen, and resumed when the ANC equaled 1,000/µL at 5 mg/kg IV 5-6 days /week, until day 84 or 120 post HSCT*
II. Pre-emptive therapy:
Ganciclovir, 5 mg/kg IV b.i.d. for 7-14 days Foscarnet, 60 mg/kg IV b.i.d.for 7-14 days
It is applied either from the first positive test result until day 100 after transplantation resulting in a duration of 6–8 weeks of therapy in the majority of patients or until the indicator test becomes negative (long course), usually resulting in 2–4 weeks duration of therapy (short course).
III Treatment of CMV-interstitial pneumonia
Ganciclovir, 5 mg/kg/IV q.12h for 21 days then 5 days per week until off immunosupression IVIg**, 500 mg/kg IV q.o.d., for 7-10 doses then weekly until off immunosupression or; CMVIg**, 125mg/kg IV q.o.d. 7-10 doses then weekly until off immunosupression
IV Treatment of CMV-enteritis
Ganciclovir, 5 mg/kg/IV q.12h

*If the (ANC)<1000/mL for 2 consecutive days, then stop GCV until count recovers.**IVIg or CMVIg used only for CMV-IP and not for other organ-specific syndromes.

OTHER VIRAL INFECTION AFTER HSCT

Epstein-Barr virus is a gamma-herpes virus that is present as a persistent asymptomatic infection in the majority (90%) of adults. Following an initial lytic infection the virus undergoes latency in a reservoir of approximately 1 in 100 000 resting memory B cells. EBV has a predominat tropism for B-lymphocytes. EBV is implicated in the pathogenesis of many human tumors and so it is perhaps no surprise that the major complication of EBV in the setting of immunosuppression is a malignancy, namely post-transplant lymphoproliferative disease (PTLD). PTLD is almost always of B cell origin and usually starts as a polyclonal proliferation that progresses to an aggressive monoclonal tumor. At least 85% of cases are EBV-positive. PTLD is seen most commonly in patients who have received solid-organ allografts and who are on long-term immunosuppression. Indeed, it is a rare complication of stem cell transplantation and is usually associated with intense post-transplant immunosuppression. The incidence of PTLD in HSCT varies widely according to the source of hematopoietic cells, the associated cell manipulations, and the type of immunosuppressive regimens. Clinical presentation is variable but in general there are two patterns of disease. Early PTLD tends to occur within weeks or months of transplantation and resembles a severe Infectious mononucleosis-like syndrome. Fever, generalized lymphadenopathy, respiratory compromise and rising liver transaminases are typical. This is usually rapidly progressive and may be Fulminant. Pathologically there is diffuse tissue infiltration and often no masses or lymphadenopathy. The diagnosis is difficult and sometimes may be determined only at autopsy following an episode of prolonged fever. Late disease occurs after 6 to 9 months and usually has a focal lymph node or extranodal pattern of organ involvement. Following stem cell transplantation PTLD is usually of donor cell origin and tends to occur within the first 6 months following transplantation [28]. Diagnosis of PTLD requires biopsy and immunohistochemical therapy or flow cytometry. Treatment of PTLD has traditionally centered around a reduction in immunosuppression. Unfortunately this is often difficult to achieve in a clinical situation in which survival of the organ graft is dependent on controlling the alloreactive immune response. If this approach fails, or is not an option, then chemotherapy may be tried. No particular regimen has been shown to be definitive, although the use of the anti-CD20 antibody rituximab has proven effective in some cases [29]. Anti-viral therapy with high-dose acyclovir, interferon, or surgery are also options. Cellular therapy for established PTLD certainly has a place in the setting of allogeneic transplantation. The initial report was with unmodified donor leukocyte infusions which had dramatic efficacy in several cases. Fives cases of PTLD which developed after T-cell-depleted stem cell transplantation were treated with 10^6 CD3+ T cells per kilogram. All the patients had complete pathological or clinical responses which developed 8 to 21 days after infusion, although two patients died of pneumonitis which may have been exacerbated by tissue damage following CTL infusion. The use of EBV-specific T cell lines was effective and without the side effect of graft-versus-host disease. [30]

Adenoviral infection in stem cell transplant patients can lead to a variety of clinical syndromes of which haematuria is the most common. Adenovirus enters the mucosa and infects epithelial cell, may lead to infection of kidney, bladder, liver and lungs in HSCT recipients. Diagnosis of adenoviral infection is usually made by culture. The impact of adenoviral disease was assessed in a study of 2889 patients. Three percent of this group suffered adenoviral infection and the vast majority of infections were symptomatic. Upper respiratory tract infections were most common followed by enteritis, hemorrhagic cystitis, pneumonia and disseminated disease. The overall mortality rate was 26% but was greater than 50% in the latter two categories. Other groups have reported a higher incidence of gastrointestinal disease with a particularly high frequency in children who have undergone unrelated donor transplants. In this group overall mortality due to adenovirus was 1%. Fulminant hepatitis is another devastating mode of presentation. Treatment of established adenoviral disease is challenging. Withdrawal or reduction of immunosuppression is one option and ribavirin is often used but with limited evidence of its efficacy. Adoptive therapy with unmanipulated lymphocyte infusion has been reported as being associated with some improvement in viral disease but until adenoviral-specific immunity is more completely understood it remains a risky approach with respect to the possible induction of graft versus host disease[31-34].

The natural history and pathogenic potential of HHV-6 and HHV-7 are not yet well understood but they appear to be implicated in post-transplant disease. A recent study using a qualitative polymerase chain reaction for HHV-6 DNA was performed in 71 allograft patients and HHV-6 DNA was detected in 36% of the samples with a peak level at 4 weeks. Three patients had HHV-6 encephalitis, the major clinical problem associated with HHV-6 in this setting, and one patient had hepatitis. A possible association with graft-versus-host disease remains uncertain. In addition, there is a correlation between HHV-6 reactivation and delayed platelet

engraftment. The use of PCR for detecting HHV-6 and HHV-7 must be tempered with the fact that both viruses may be found at low levels in normal blood and bone marrow samples. One of the problems that investigators face in sorting out the unique clinical significance of HHV-6 is the fact that reactivation often occurs simultaneously with CMV reactivation. Sensitive viral load measurements are allowing the individual contributions of the herpes viruses to be teased apart. Studies have also been performed in CMV-seronegative donors, and in one case a primary infection with HHV-6 was associated with mild self-limiting disease. Use of peripheral blood stem cells as opposed to bone marrow appears to offer some protection against HHV-6-associated disease. For established disease such as encephalitis, foscarnet offers the possibility of successful treatment [35-38].

Parainfluenza, an enveloped paramyxovirus containing single stranded RNA, is classified into four serotypes. Parainfluenza virus serotype 3 is most common (approximately 90%). Upper respiratory infection is the predominant presentation. The more important risk factor for pneumonia is use of systemic corticosteroids and lymphopenia. Infection control is the mainstay of prevention strategies. Persistent outbreaks may be in HSCT units. Influenza viruses belong to family of orthomyxoviruses, single stranded pleomorphic RNA viruses. It is classified into three major types. Of which type A is most common, followed by type-B. Upper respiratory infection rarely progress to severe pneumonia. Effective prevention is available for influenza. Health care personnel and visitors may vaccinate against influenza. Amantadine and rimantadine are effective against influenza [5].

Respiratory syncytial virus is now recognized as a significant burden to adult populations, and immunosuppressed donors are at particular risk. RSV is an RNA virus (paramyxovirus) that causes a wide spectrum of respiratory diseases ranging from life thereating bronchiolitis in infants and potentially fatal pneumonia in transplant recipients. In a large study, winter season, male gender and use of bone marrow stem cell source were identified for the acquisition of RSV in HSCT recipients. One report has indicated a mortality rate of 19% following infection. Diagnosis of RSV infection is difficult because viral culture and antigen detection are relatively insensitive. Early bronchoscopy is valuable in transplant patients. Without treatment, RSV pneumonia is almost uniformly fatal in HSCT patients. Intermittent short duration (2g over 2h three times daily) or continuous aerolized ribavirin (20mg/ml for 16-18h a day by face mask or endotracheal tube) is considered the treatment of choice for RSV pneumonia. The role of intravenous gamma globulin or RSV-specific immunoglobin remains unclear[39-44].

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