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Human Herpesviruses in Hematologic Diseases

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1. Introduction

The members of the *Herpesvirales* containing more than 130 different herpesviruses have already been isolated from all animal species representing the higher steps of evolution. According to our knowledge, eight herpesviruses are classified as human herpesviruses: Herpes simplex virus 1 (Human herpesvirus 1, HHV-1), Herpes simplex virus 2 (Human herpesvirus 2, HHV-2), Varicella-zoster virus (Human herpesvirus 3, HHV-3), Epstein-Barr virus (Human herpesvirus 4, HHV-4), Cytomegalovirus (Human herpesvirus 5, HHV-5), Human herpesvirus 6 (HHV-6A and HHV-6B), Human herpesvirus 7 (HHV-7), and Human herpesvirus 8 (HHV-8 or Kaposi's sarcoma associated herpesvirus, KSHV).

It is a characteritic of herpesviral infections that after the frequently fulminant initial infection, they persist in the neurons or the B- and T-cells of the body throughout life. Sometimes they reactivate. With respect to lymphotropic human herpesviruses, HHV-4 and HHV-8 reproduce mainly in the B-cells, while HHV-5, HHV-6 and HHV-7 reproduce in T-cells. HHV-4 causes most of the infectious mononucleosis cases and can immortalize B-lymphocytes. HHV-5 can also cause infectious mononucleosis. A significant part of primary infections occurs in an asymptomatic way. Immunsuppression makes virus reproduction easier.

A wide range of diseases may appear in an immunodeficient state. HHV-6 was first described in 1986 and was isolated from patients suffering from lymphoproliferative disease. It infects CD4+ T-lymphocytes and it reproduces in them. Two variants of it, HHV-6A and HHV-6B, are known. Variant B is the pathogen of exanthema subitum (roseola infantum) and it can also cause latent infection with fever, diarrhoea, neural symptoms, and hepatitis. After transplantation, HHV-6 can reactivate and it is able to replicate in liver-cells. HHV-6 can activate the replication of HHV-4; it reduces or increases the replication of HIV, and accelerates the expression of antigens coded by HPV. HHV-7 was isolated from CD4+ cells in 1990 and was purified from a healthy patient. It is the pathogen of pityriasis rosea, but it can also cause exanthema subitum. Additionally, it can create latent infection in T-lymphocytes and productive infection in salivary gland epithelial cells. During pregnancy, viremia is more frequent and may adopt urogenital, perigenital and congenital transmission.

HHV-7 may play a role in cases of immunodeficient patients; in the case of immunosuppression HHV-6 and HHV-7 play the role of cofactor in states accompanied by

pneumonia. HHV-8 is the latest identified human tumorvirus; since its discovery in 1994 it has been in the limelight of research. It plays a critical role in the AIDS-associated body cavity B-cell lymphoma (BCBL). The new virus was named Kaposi's sarcoma associated herpesvirus (KSHV). Four clinical forms of Kaposi's sarcoma are known: 1. classical type (described by Kaposi), 2. epidemic-African type, 3. iatrogen, and 4. AIDS associated type. It is possible that KSHV plays a direct or indirect stimulating role: in BCBL in elderly patients or ones suffering from AIDS, and in Castleman disease.

Viral infections are important causes of morbidity and mortality for patients with haematological diseases and haematological malignancies. However, the true incidence and consequences of human herpesviral infections for these patients who undergo conventional nontransplantant therapy are poorly defined. The difference in incidence and outcome of viral infections among patient groups is wide, but dependent upon the infections among the intensity and duration of T-cell-mediated immune suppression. Infections are caused mainly by cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus (VZV) and less Epstein-Barr virus (EBV), human herpesvirus 6, 7, 8 (HHV-6, HHV-7, HHV-8).

Fortunately, a growing number of antiviral medications and vaccines are allowing for more effective prophylaxis against these pathogens.

Modern virology diagnostics use multiple methods for detecting viral infections. These include viral isolation in culture, cytologic staining, detection of viral antigens, nucleic acids, and viral antibodies.

Science has been examining the role of herpesviruses in haematologic malignant cases and in plasma-cell dyscrasias for decades now. Plasma-cell diseases (monoclonal gammopathies) are multiple myeloma (MM), Waldenstörm macroglobulinaemia (WM), and monoclonal gammopathy with unknown significance (MGUS). A potential role of HHV-8 has emerged in the pathogenesis of these diseases.

The increase in the number of histiocytes is characteristic of eosinophil granuloma (Langerhans cell histiocytosis, LCH). The causal role of lymphotropic herpesviruses has also been suggested in the pathogenesis of LCH. The rate of HHV-8 reactivation in patients suffering from monoclonal gammopathies significantly exceeds that of those suffering from Non-Hodgkins lymphoma. HHV-8 reactivation may refer to immunological lesion in patients suffering from monoclonal gammopathies. During its pathogenesis, HHV-8 might play a role in the formation of pathographies. HHV-4 is proportionately present in haematological pathographies. The data also indicate that in addition to HHV-8, the transient reactivation of HHV-4 might also play a role in the pathogenesis of monoclonal gammopathies.

2. Epidemiology, diagnosis and prevention of human herpesviruses infections in hematologic diseases

2.1 Human herpesvirus 1 (HHV-1) and human herpesvirus 2 (HHV-2) [Herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2)]

Herpes simplex viruses were the first of the human herpesviruses to be discovered and are among the most intensively investigated of all viruses. Herpes simplex virus (HSV) was first isolated by Lowenstein (Lowenstein, 1919). The ability of HSV to establish a life-long latent infection in its human host is one of the most intellectually challenging aspects of HSV biology.

Herpes simplex virus (HSV) belongs to the *Simplexvirus* genus of the *Alphaherpesvirinae* subfamily of the *Herpesviridae* family. It has two serotypes, HSV-1 and HSV-2. It was classified into two serologically distinct types by Schneweiss (Schneweiss, 1962). HSV-1 and HSV-2 are phylogenetically ancient viruses that have evolved together with their human host (Davison, 2002). In humans, latent virus is reactivated after local stimuli such as injury to tissues innervated by neurons harboring latent virus, or by systemic stimuli (e.g., physical or emotional stress, hyperthermia, exposure to UV light, menstruation, or hormonal imbalance), which may reactivate virus simultaneously in neurons of diverse ganglia (e.g., trigeminal and sacral).

Transmission of HSV depends on intimate, personal contact between a susceptible individual (namely, one who is seronegative) and someone excreting HSV. Thus, virus must come in contact with mucosal surfaces or abraded skin for infection to be initiated. Following oropharyngeal infection, usually caused by HSV-1, the trigeminal ganglion becomes colonized and harbors latent virus. Acquisition of HSV-2 infection is usually the consequence of transmission by genital contact. The epidemiology and clinical characteristics of primary infection are distinctly different from those associated with recurrent infection. HSV-1 causes acute gingivostomatitis, recurrent herpes labialis (cold sores), keratoconjunctivitis, blepharitis, iridocyclitis, encephalitis, tracheobroncitis, pneumonia, esophagitis, pharingitis, disseminalt infections, mucocutaneus lesions, herpetic whitlow, herpes gladiatorum, genital disease, neonatal infectio, and meningitis. HSV-2 causes genital disease, anal and perianal infection, proctitis, neonatal herpes, meningitis, mucocutaneus lesions, herpetic whitlow, oral disease, keratoconjunctivitis, esophagitis, pharingitis, and encephalitis.

A reappearance of HSV, known as recurrent infection, results in a limited number of vesicular lesions as occurs with HSV labialis or recurrent HSV genitalis. Reinfection with a different strain of HSV occurs, but it is uncommon in the normal host. Herpes simplex virus disease ranges from the usual case of mild illness, nondiscernible in most individuals, to sporadic, severe, and life-threatening disease in a few infants, children, and adults. Although HSV-1 and HSV-2 are usually transmitted via different routes and involve different areas of the body, much overlap is seen between the epidemiology and clinical manifestations of these two viruses. Historically, primary HSV-1 infections usually occurred in the young child, less than 5 years of age, and were most often asymptomatic. When the oropharynx is involved, the mouth and lips are the most common sites of HSV-1 infections, causing gingivostomatitis; however, any organ can become infected with this virus. Primary infection in young adults has been associated with only pharyngitis and a mononucleosis-like syndrome (McMillan et al., 1993). Genital herpes can be caused by either HSV-1 or 2. As infections with HSV-2 are usually acquired through sexual contact, antibodies to this virus are rarely found before ages of onset of sexual activity. Recurrent HSV-2 infection, as with HSV-1, can be either symptomatic or asymptomatic.

HSV-1 accounts for the majority of nongenital HSV-induced infections in humans, with 45% to 98% of the world population and 40% to 63% of the people in the United States reported HSV-1 seropositive (Ribes et al., 2001). Worldwide HSV-1 prevalence varies with age, race, geographic location, and socioeconomic status; a higher rate of seropositivity has been reported for less industrialized countries (Fatahzadeh & Schwartz, 2007; Chayavichitsilp et al., 2009). By the age of sixty, 60% to 85% of adults in the United States demonstrate HSV-1 seroconversion. Incidence is not seasonal. Over the past thirty years, HSV-2 seroprevalence

has increased dramatically, with 20% to 25% of US adults tested positive for HSV-2 antibodies by the age of forty (Fleming et al., 1997).

Risk factors for HSV-2 infection include older age, female gender, black race, poor socioeconomic status, low level of education, prior sexually transmitted disease, early age at first intercourse, and a higher number of lifetime sexual partners (Corey & Handsfield, 2000). Prepubertal detection of HSV-2 antibodies is rare. Prevalence of HSV2 seropositivity is strongly correlated with sexual maturity and promiscuity. Prevalence of HSV-2 antibodies is reported to be higher in women (Hettmann et al., 2008).

Patients compromised by immunosuppressive therapy, underlying disease, or malnutrition are at increased risk of severe HSV infections. Renal, hepatic, bone marrow, and cardiac recipients are all at a particular risk of increased severity of transplant HSV infection.

2.1.1 Epidemiology

HSV-1 and HSV-2 commonly cause mucocutaneus lesions in patients with haematological malignancies, but HSV-1 is more frequent (Gnann, 2003). Up to 80% of adult patients with leukemia are HSV seropositive. The rate of HSV reactivation among HSV seropositive allo-Stem Cell Transplant recipients was reported to be approximately 80%, with the majority of these infections occurring during the first four weeks after transplant. They are also common, ranging from 15% among CLL (chronic lymphocytic leukemia) patients treated with fludarabine to 90% of patients with acute leukemia (Sandherr et al., 2006; Anaisse et al., 1998). Most individuals undergoing conventional chemotherapy are at low risk of HSV reactivation; however, those receiving T-cell depleting agents (e.g. fludarabine, alemtuzumab) or proteasome inhibitors are at high risk of reactivation of both HSV-1 and HSV-2 (Sandherr et al., 2006).

The greatest risk of reactivation is seen in individuals with CD4 T-cell counts <50 cells/mm^3, and other contribuiting risk factors are corticosteroid use, prolonged neutropenia, renal insufficiency, and age above 65 years.

2.1.2 Clinical manifestations

HSV reactivation in leukemic patients is usually associated with localized mucocutaneous disease in the orofacial region (85-90%), and less frequently in the genital area (10-15%). The diagnosis of oropharyngeal HSV disease clinically can be difficult when severe mucositis is present. Mucositis and mucocutaneous ulcerations are common following high doses of chemotherapy, and occur at the same time as oral disease. Another frequent manifestation of HSV reactivations is esophageal disease. HSV esophagitis was found in about 10% of patients in studies of patients with leukaemia and other neoplastic disorders who had gastrointestinal symptoms. Uncommon HSV disease manifestations are pneumonia (2-3%), hepatitis, meningitis, and encephalitis (Kaufman et al., 1997; Angarone, 2011).

Recurrent HSV infection is a major cause of morbidity and occasional mortality in the immunosuppressed patient who experiences frequent, persistent and severe recurrences of HSV-1 and HSV-2 infection.

2.1.3 Monitoring and laboratory diagnosis of HSV infections

An important characteristic of modern diagnostic virology is the use of multiple methods for detecting viral infections. These include viral isolation in culture, cytologic staining for viral infection with the Tzanck smear (Tzanck & Aron-Brunietiere, 1949), detection of viral antigens, nucleic acids, and viral antibodies, which are all used to diagnose current viral

infection. Light microscopy is used to detect the effect of viral infection in tissue and to define the role of viral infection in producing disease. Clinicians may wish to utilize laboratory tests to establish definitive diagnosis when clinical presentation of HSV infections is atipical. Virus isolation remains the definitive diagnostic method; however, polymerase chain reaction (PCR) detection of viral DNA is gaining increased acceptance even for routine skin infections. If skin lesions are present, skin vesicles should be scraped and transferred in appropriate virus transport media to a diagnostic virology laboratory. Virus may be isolated from various samples including skin lesions, cerebrospinal fluid (CSF), ocular fluid, swabs from mucocutaneous lesions, blood, stool, urine, throat, nasopharynx, conjunctivae and cornea. The experience with PCR indicates that it is an especially useful tool for diagnosis of HSV encephalitis in cerebrospinal fluid (CSF).

The Tzanck smear is a rapid and reasonably priced diagnostic test that can confirm the presence of HSV infection. Although the test can confirm the presence of HSV or VZV, it cannot differentiate between the two herpes simplex serotypes and, therefore, cannot diagnose HSV-1 or HSV-2 infection definitively. The Tzanck smear has decreased in popularity as a diagnostic alternative to the direct fluorescent antibody assay (DFA) technique. In addition, DFA may be employed to serotype the HSV infection. Because DFA testing is rapid, inexpensive, and virally selective, it is often used to substantiate clinical suspicion and determine serotype. The biopsied cells are observed microscopically to detect degenerative cytopathologic changes commonly associated with the infection. The degenerative changes present in cells infected with HSV-1 and HSV-2 also are observed in cells infected with VZV. Thus, the specificity of the technique is low, and it cannot be used to serotype the infection.

As HSV PCR becomes more readily available and less expensive, it has the potential to become the most widely used means of detecting HSV for all types of infection because it is rapid, highly reliable, and valid. Serologic assay is employed to detect the presence of HSV antibodies when other techniques are impractical or ineffective. Such assay takes longer to complete than other techniques and should be considered primarily for diagnosing recurrent infections, in the presence of healing lesions and the absence of active lesions, or when partners of a person who has clinical herpes are at risk. Sera are collected at two sepatate times. Acute serum is obtained within three to four days after the onset of initial symptoms, and convalescent serum is gathered several weeks after the symptoms have abted. To confirm a diagnosis of primary HSV infection, the acute sample should be devoid of HSV-positive antibodies due to the delayed humoral response, and the convalescent sample should demonstrate the presence of both immunoglobulin G and M antibodies to HSV proteins. If any quantities of antibodies are observed in the acute sample, primary infection is ruled out and the diagnosis is recurrent herpes infection. Measurement of antiviral antibodies was one of the first methods used for the specific diagnosis of viral infections and it remains an important tool in the diagnostic virology laboratory.

The role of serology can be for the diagnosis of acute or current infection or for the determination of immune status to specific viruses. Serologic diagnosis of HSV infection is clinically valuable in the counseling of patients. Therapeutic decisions do not depend on the results of serologic studies. Immunoglobulin M (IgM) and IgG humoral responses have been well characterized. Antibodies [as detected by immunofluorescence assay (IFA), Enzyme immunoassay (EIA), enzyme-linked immunosorbent assays (ELISA)] are specific for HSV.

Serological tests are used for identification of seropositive patients before chemotherapy or hematopoietic stem cell transplantation (HSCT), but are not helpful in confirming the diagnosis of HSV reactivation. Routine surveillance for HSV reactivation could be done by culture or PCR, single (sPCR), nested PCR (n-PCR) and real-time or quantitative PCR (RT-PCR or Q-PCR). PCR for HSV DNA in CFS is indicated in the diagnosis of HSV meningitis and encephalitis.

2.1.4 Prevention of HSV diseases

Vaccination remains the ideal method for prevention of viral infection; however, prevention of HSV infections introduces unique problems because of recurrences in the presence of humoral immunity. Nevertheless, protection from life-threatening infection can be achieved in animal models with avirulent, inactivated, or subunit glycoprotein vaccines, each of which has unique differences. Future study of the immune response induced by natural HSV infections in both adults and neonates is needed to provide insight into the requirements for vaccination against acute disease and recurrences. Attempts to produce an effective vaccine against HSV have been largely unsuccessful. Perhaps a most effective vaccine will be needed to stimulate most, if not all, key parameters of innate and adaptive immunity, both systematic and mucosal (Jones & Cunningham, 2004; Stanberry, 2004).

HSV seronegative patients should attempt to prevent exposure to HSV. Early studies of intravenosus acyclovir in hematopetic stem cell transplantation recipients clearly documented its clinical efficacy: 0% to 2.5% of patients treated with acyclovir versus 50% to 70% of those treated with placebo developed HSV lesions (Lundgren et al., 1985; Angarone & Ison, 2008).

HSV seropositive patients: Based on the data, most cancer centers routinely use antiviral prophylaxis against HSV reactivation for leukemia patients' chemotherapy, especially those at high risk of ractivation such as those treated with purine analogs or alemtuzumab (Styczynski et al., 2009). Antiviral agents are routinely used as prophylaxis against HSV reactivation, using either i.v. acyclovir, oral acyclovir or valacyclovir, until three–five weeks after chemotherapy has been stopped (Angarone, 2011).

2.1.5 Therapy of HSV diseases

Advances in the treatment of HSV infections have led the way in the development of antiviral therapeutics. In the 1970s, vidarabine (adenine arabinoside) became the first licensed antiviral therapeutic for the treatment for herpes simplex encephalitis and neonatal HSV infections. Quickly, however, vidarabine was replaced by acyclovir in the the treatment of all HSV infections. Today acyclovir, valacyclovir, penciclovir, famciclovir, ganciclovir, valganciclovir, cidofovir and foscarnet are the most useful and widely used therapeutics for the treatment of HSV-1 and HSV-2 infections (Knipe & Howley, 2007; Gilbert et al., 2010; Jancel & Penzak, 2009; Angarone, 2011).

2.2 Human herpesvirus 3 (HHV-3) [Varicella-zoster virus (VZV)]

Varicella-zoster virus (VZV) is a human alphaherpesvirus, which belongs to the *Varicellovirus* genus of the *Alphaherpesvirinae* subfamily of the *Herpesviridae* family. It causes varicella, commonly called chickenpox, during primary infection. Varicella, which is characterized by fever and a generalized, pruritic vesicular rash, is most prevalent in childhood. Varicella is highly contagious, producing annual epidemics among susceptible

individuals during winter and spring in temperate climates. Among the alphaherpesviruses, VZV is unique in its tropism for T lymphocytes, which allows dissemination of the virus to skin. VZV also infects and establishes latency in cells of the dorsal root ganglia. Its reactivation from latency produces herpes zoster, commonly referred to as shingles, an illness observed most often in older adults and immunocompromised patients of any age. The vesicular rash of herpes zoster is largely confined to regions of the skin served by a single sensory dermatome. Unlike varicella, herpes zoster infections are associated with acute pain that can be severe and prolonged. Pain that persists after the onset of herpes zoster for more than 30 days is called postherpetic neuralgia (PHN).

Varicella and herpes zoster were described in very early medical literature. Once thought to be the same disorder, Heberden distinguished smallpox and varicella as two diseases in 1867. In 1892, Bokay suggested an infectious etiology for varicella and herpes zoster and postulated that they were related (von Bokay, 1909), an idea supported by the demonstration that varicella occurs in children following inoculation with vesicular fluid from herpes zoster lesions and that virions from varicella and herpes zoster vesicle fluids are identical in appearance by electron microscopy (Almeida, 1962). The isolation of VZV in tissue culture was reported by Weller in 1953 (Weller, 1953). Primary VZV infection is presumed to be initiated by inhalation of respiratory droplets or by contact with infectious vesicular fluid from an infected individual. The potential for aerosol transmission is suggested by epidemiologic reports, and VZV DNA is detected in air samples from rooms occupied by patients with varicella or disseminated herpes zoster (Sawyer, 1994).

Varicella-zoster virus latency is established during primary infection. VZV persists in sensory nerve ganglia. VZV can access neural tissues, either hematogenously or by centripetal neural transport from mucocutaneous lesions.

Varicella-zoster virus reactivation, although possibly asymptomatic at times, typically presents as herpes zoster, a vesicular rash that is usually confined to the dermatomal distribution of a single sensory nerve. Because herpes zoster is caused by the reactivation of latent virus, susceptibility requires previous primary VZV infection. Given the high incidence of varicella, most adults are at risk of VZV reactivation. Herpes zoster is rare in childhood, but varicella during the first year of life, or VZV infection acquired by intrauterine transmission, are associated with an increased risk.

The attack rate for previously uninfected household or day care center contacts exposed to varicella is about 90%. Varicella pneumonia in healthy adults presents with fever, cough, tachypnea, and dyspnea and may be associated with cyanosis, pleuritic chest pain, or hemoptysis. Varicella pneumonia is often transient, resolving completely within 24 to 72 hours, but interstitial pneumonitis with severe hypoxemia progresses rapidly to cause respiratory failure in severe cases.

Varicella hepatitis can occur subclinically, although it may be associated with severe vomiting. Aspirin is contraindicated in children with varicella because it predisposes to liver damage (Reye's syndrome). Patients with encephalitis typically have a sudden onset of seizures and altered sensorium, whereas those with cerebellar disease show a gradual progression of irritability, nystagmus, and gait and speech disturbances. Some patients have fever, headache, and meningismus, only without any altered consciousness or seizures. Acute thrombocytopenia causes petechiae and purpuric skin lesions, hemorrhage into the varicella vesicles, epistaxis, hematuria, and gastrointestinal bleeding. Hemorrhagic complications are usually transient. Purpura fulminans, caused by arterial thrombosis and

hemorrhagic gangrene, is a rare but life-threatening complication. Postinfectious thrombocytopenia occurs from 1 to 2 weeks or longer after varicella. Varicella nephritis causes hematuria, proteinuria, diffuse oedema, and decreased renal function, with or without hypertension. A few cases of nephrotic syndrome and hemolytic-uremic syndrome have been reported in children with varicella. Varicella arthritis is rare; it resolves spontaneously, with no residual joint disease. Other unusual complications of varicella include myocarditis, pericarditis, pancreatitis, and orchitis. Varicella vesicles are common on eyelids and conjunctivae, but eye disease is unusual.

Reactivation of VZV in the trigeminal ganglion can produce ophthalmic disease, including conjunctivitis, dendritic keratitis, anterior uveitis, iridocyclitis with secondary glaucoma, and panophthalmitis. Loss of vision associated with herpes zoster is predominantly caused by retrobulbar neuritis and optic atrophy.

2.2.1 Epidemiology

The high incidence of herpes zoster in elderly and immunocompromised patients suggests that waning host immune responses to the virus have a significant impact on whether reactivation occurs and whether it will lead to symptomatic disease. Herpes zoster in young children after intrauterine or early postnatal varicella and the short interval between primary and recurrent VZV infections in children with HIV infection probably reflect their development of suboptimal cell-mediated immunity. Diminished in vitro T-cell proliferation to VZV antigens in elderly patients and in patients receiving immunosuppressive therapy correlates with higher susceptibility to herpes zoster.

The incidence of VZV infection ranges from 2% among patients with chronic myelogenous leukemia (CML) receiving imatinib mesylate, to 10-15% in patients with chronic lymphocytic leukemia (CLL) receiving flurdarabine or alemtuzumab, to 25% of patients with Hodgkin lymphoma, myeloma treated with bortezomib or autologous stem cell transplant recipients, and to 45-60% among allogenic stem cell transplant recipients (Locksley et al., 1985; Anaisse et al., 1998; Sandherr et al., 2006; Wade, 2006). Infection risk is the greatest within the first twelve months following treatment or transplant. The majority of VZV infections in adult patients with a hematological malignancy are reactivation infections and 80% with localized disease (Locksley et al., 1985). After exposure to an individual with VZV infection (varicella or herpes zoster) seronegative leukemia patients and HSCT recipients are at risk of developing varicella, wich can be very severe. After HSCT, the risk of varicella is the highest in the first 24 months, or beyond this time if undergoing immunsuppressive therapy and having chronic graft-versus-host-disease (GVHD). Other risk factors include the pretransplantant diagnosis of leukemia and other lymphoproliferative disorders.

2.2.2 Clinical manifestations

Varicella manifests as a generalized, pruritic, vesicular rash. In leukemic patients and in those following HSCT, there is a risk of progressive severe varicella characterized by continuous eruptions of lesions, high fever, visceral dissemination, encephalitis, hepatitis, pneumonia, nausea, vomiting and diarrhea. Hemorrhagic varicella may sometimes occur.

In herpes zoster, grouped painful vesicular lesions appear in the distribution of one to three dermatomes in the immuncompetent patients. In leukemia patients and HSCT recipients, varicella zoster may disseminate to several more dermatomes or throughout the whole

body, with the risk of visceral involvement, which may prove fatal. This visceral dissemination may sometimes occur without skin vesicles, which makes diagnosis difficult.

2.2.3 Laboratory diagnosis

Laboratory diagnosis is not necessary for the clinical management of most VZV infections in the immunocompetent host, but rapid diagnostic techniques are useful to guide decisions about antiviral treatment, especially for high-risk patients.

The differentiation of the VZV infections from HSV and bullous dermatitis is an important indication for virological diagnosis. VZV infections of pregnant women and of newborn infants, atypical infections of immunodeficient patients, and suspected VZV infections of the central nervous system must be confirmed by laboratory diagnosis.

VZV can be isolated in tissue culture, but it is not as easy as for HSV. Tzanck smear cannot differentiate between HSV and VZV. Nucleic acids are readily detected by PCR and detection of VZV antigens by immunohistochemical assays of cells from cutaneous lesions allows rapid diagnosis. The most sensitive methods are the fluorescent-antibody membrane antigen assay (FAMA) (Gershon et al., 1999). Latex agglutination methods provide a useful, sensitive alternative to FAMA (Steinberg & Gershon, 1991).

Assays for VZV IgG antibodies are most useful for determining the immune status of individuals whose clinical history of varicella is unknown or equivocal. The enzyme-linked immunosorbent assay (ELISA) and the immunfluorescence technique are especially suited for the detection of VZV specific immunglobulin of classes IgG, IgM and IgA. Detection of IgM and high titered IgA anti-VZV antibodies usually indicates a reactivated VZV infection regardless of whether lesions are visible or not (Gross et al., 2003).

PCR techniques (sPCR, n-PCR, RT- PCR or Q-PCR) for VZV DNA are considered the best diagnostic tools because they are very specific and sensitive and can detect viral DNA in vesicle samples, crusts, and throat swabs from patients with varicella or herpes zoster. PCR can be used for tissue specimens as well. VZV encephalitis following HSCT is diagnosed by PCR of cerebrospinal fluid. PCR of blood samples (serum, plasma) can document VZV DNA viremia in an HSCT recipient with herpes zoster, and quantitative monitoring (RT-PCR or Q-PCR) of circulating VZV DNA may be useful for the diagnosis and for assessing the response to treatment of visceral VZV infection without skin manifestation. PCR can also distinguish vaccine strain from wild-type VZV in clinical specimens (Kalpoe et al., 2006).

2.2.4 Prevention

The live attenuated Oka varicella vaccine is the first human herpesvirus vaccine licensed for clinical use in several countries. Its development and initial clinical evaluation were first reported by Takahashi in 1974 (Takahashi et al., 1974). The vaccine virus derived from a clinical isolate of VZV, the Oka strain; was isolated from a healthy Japanese child with varicella and atteunated by serial passage in cell culture; initially propagated in guinea pig embryo fibroblasts, and then in WI38 human cells. Clinical studies in Japan demonstrated the safety, immunogenicity, and clinical efficacy of Oka vaccine, which protected susceptibile immuncompetent and immuncompromissed children against varicella, even when administered shortly after exposure. Oka vaccine also boosted VZV specific cell-mediated immunity in immunocompetent and immunocompromised adults. Varicella vaccine (Varivax; Merck) was licensed by the US Food and Drug Administration (FDA) in 1995. Zoster vaccine (Zostavax; Merck) was licenced by the FDA in 2005. Recent

development of genetic analysis of VZV Oka strains isolated from vaccine-associated rashes and cases of herpes zoster may help identify specific single nucleotid polymorphisms (SNPs) that differentiate Oka vaccine from wild-type strains of VZV, and which contribute to attenuation of the vaccine and the pathogenicity of wild type VZV (Oxman, 2010).

Oka vaccine is the most attenuated of all currently licensed live, attenuated virus vaccines, and it has been safely administered to VZV-susceptible children and VZV-seropositive children and adults, including susceptible children with human immunodeficiency virus 1 infection and leukemia. Oka vaccine strain of VZV is fully susceptible to acyclovir, famciclovir, and valacyclovir; thus, effective antiviral therapy is available if complications involving vaccine virus replication occur.

Inactivated zoster vaccines for administration to immuncompromised patients are potentially beneficial. Heat-inactivated VZV vaccine has been safely administrated to autologous bone marrow transplant recipients, in whom it accelerated recovery of VZV-cell mediated immunity and reduced the occurence of herpes zoster (Hata et al., 2002). Encouraged by these results, several groups are exploring the development of inactivated VZV vaccines, with and without adjuvants, to permit immunization of profundly immunsuppressed patients.

2.2.4.1 Passive antibody prophylaxis

Varicella zoster immune globulin (VZIG) and the related product are made from high-titer immune human serum. VZV antibody prophylaxis is recommended for passive immunization of individuals at high risk of serious varicella who were recently exposed to people with acute varicella or herpes zoster.

2.2.4.2 VZV seronegative patients

Fortunately, VZV can be prevented by minimizing exposure, passive immunization, and antiviral prophilaxis. VZV seronegative family members and contacts of HSCT candidates should be vaccinated against VZV no later than four weeks before conditioning begins. Contact with patients after vaccination must be avoided, especially if post-vaccination eczema occurs. In VZV seronegative patients, who have been in contact with varicella or herpes zoster and hence potentially contagious, airborne precautions should be instituted seven days after the first contact and continued until 21 days after the last exposure or 28 days post-exposure if the patient received passive immunization against VZV (VZIG-varicella-zoster immune globulin or ZIG-zoster immune globulin). Prior to the start of chemotherapy, VZV serologies should be evaluated and, if negative, exposure should be minimized. The role of direct prophylaxis and duration of that has yet to be tested in clinical trials (Wade, 2006; Styczynski et al., 2009).

2.2.4.3 VZV seropositive patients

Most HSCT recipients are VZV seropositive, following varicella in their childhood or following immunization with varicella vaccine, and are at risk of virus reactivation. There have been several retrospective studies of the use of acyclovir prophylaxis to prevent VZV reactivation in HSCT recipients. Arguments for the use of passive immunisation for VZV-seropositive leukemia and HSCT recipients include the theoretical potential for supplementing immunity against VZV. The arguments against include scarity of VZIG and ZIG, their cost, the low incidence of reinfection, lack of proven efficiency in VZV-seropositive recipients, and the possible adverse effect and discomfort associated with passive immunization (Weinstock et al., 2004).

2.2.5 Therapy

Treatment of VZV disease should include the early institution of antiviral therapy (valacyclovir, acyclovir or famciclovir). Acyclovir therapy diminishes the clinical severity of varicella in immunocompromised children by ensuring that cell-associated viremia is terminated efficiently despite the impaired host response. Early antiviral therapy prevents progressive varicella and visceral dissemination. Acyclovir and valacyclovir are highly effective. Yet, despite its efficiency in preventing disease, antiviral prophylaxis is not routinely recommended by many of the clinical care guidelines (Sandherr et al, 2006).

In addition to preventing life-threatening dissemination, early acyclovir therapy minimizes cutaneous disease, which may reduce the risk of secondary bacterial infections. Immunocompromised patients who have pneumonia, hepatitis, thrombocytopenia, or encephalitis require immediate treatment with intravenous acyclovir. Oral acyclovir can be used to diminish varicella symptoms in healthy children, adolescents, and adults when administered within 24 hours after the appearance of the initial cutaneous lesions. Adults with varicella pneumonia, including pregnant women, require immediate treatment with intravenous acyclovir. Acyclovir is effective for the treatment of recurrent VZV infection in healthy and immunocompromised patients. Among healthy individuals, the period of continued new lesions in the involved dermatome was shortened, as was the time to complete healing.

Acyclovir treatment is especially important in patients who are immunocompromised because of their risk of disseminated disease, and it is important in healthy adults with ophthalmic zoster because of their risk of developing acute uveitis and chronic keratitis. Acute neuropathic pain is reduced by early treatment with acyclovir, valacyclovir, or famciclovir, but effects on rates of subsequent PHN are less obvious. Acyclovir is given intravenously to immunocompromised patients who are at high risk of disseminated disease. Daily acyclovir (or suitable alternative) appears to be effective at preventing herpes zoster virus in patients with myeloma who are receiving bortezomib, with or without corticosteroids (Vickrey et al., 2009). Acyclovir prophylaxis effectively prevented VZV disease after allogenic transplantation. This regimen is highly effective, safe, inexpensive, and does not appear to interfere with VZV specific immune reconstruction (Boeckh et al., 2006). At present, acyclovir prophylaxis is not a universal practice in all transplant centers, because the prompt initiation of acyclovir for the treatment of recurrent VZV infections is effective (Weinstock et al., 2004) and long-term use can be associated with emergence of drug-resistant VZV mutants.

2.3 Human herpesvirus 4 (HHV-4) [Epstein-Barr virus (EBV)]

The discovery of Epstein-Barr virus (EBV) by Epstein, Achong, and Barr, reported in 1964 (Epstein et al., 1964), was stimulated by Denis Burkitt's recognition of novel African childhood lymphoma and his postulation that an infectious agent was involved in the tumor etiology. Human herpesvirus 4 (HHV-4 or EBV) was classified as belonging to the *Lymphocryptovirus* genus within the subfamily *Gammaherpesvirinae* of the *Herpesviridae* family. With respect to biology, it causes two types of infection: primary infection, mainly in children and adolescents, and reactivation of latent infection. The syndrome caused by primary infection includes infectious mononucleosis, chronic active EBV infection and X-linked lymphoproliferative syndrome. Most EBV reactivations are subclinical and require no therapies; however, it may be manifest as encephalitis, myelitis, pneumonia, and

hepatitis. HHV-4 associated tumors (reactivation syndromes) include lymphoproliferative disease (LPD), Burkitt's lymphoma, non-Hodgkin's lymphoma, nasopharyngeal carcinoma, natural killer (NK)-cell leukemia, Hodgkin's disease, hemophagocytic lymphohistiocytosis, and angioblastic T-cell lymphoma (Ambinder, 2007; Delecluse et al., 2007).

2.3.1 Epidemiology

EBV infection occurs in more than 90% of the normal population, and immuncompromised patients are predominantly at risk of disease due to EBV reactivation. The incidence of PTLD (post-transplant lymphoprolifertaive disease) varies with the organ transplanted, and ranges from 1% for renal to 14% small bowel transplant recipients.

2.3.2 Clinical manifestations

A significant number (at least 25%) of serologically confirmed primary infections in adolescence or early adult life are manifested as infectious mononucleosis, as they are a small number of infections in childhood. Symptoms can range from mild transient fever to several weeks of pharyngitis, lymphodenopathy, and general malaise. The period of acute disease correlates much more closely with that of CD8 T lymphocytosis than with high virus shedding and, indeed, treating patients using infectious mononucleosis with oral acyclovir to block virus shedding brings little if any clinical benefit.

The main manifestation of EBV infection after allogenic HSCT is the development of post-transplant lymphoprolifertaive disease (PTLD) in the presence of reactivated infection, which has a very poor prognosis. The clinical manifestation of EBV-associated PLTD may include fever, lymphadenopathy, tonsillitis, hepatosplenomegaly, and symptoms and signs from other affected organs. Although the incidence is low (0.5-2.0 %), it may rise as high as 20% in the presence of three or more risk factors. The morbidity risk is highest during the six months post HSCT (Islam et al., 2010). Risk factors for developing EBV related PLTD are: *ex vivo* T-cell depletion, treatment with antithymocyte globulin for preventing or treating GVHD, anti–CD3 antibodies for GVHD therapy, and unrelated or HLA-mismatched transplant.

2.3.3 Laboratory diagnosis

Viral detection and *in situ* hybridization techniques fall into the former category whereas immunohistochemistry is useful for distinguishing latent from replicative infection and for identifying the prevailing from of EBV latency. Fluorecence *in situ* hybridisation (FISH) is the method of choice for visualisation of viral nucleotide sequences in the infected cells, interphase nuclei or on chromosomes (Wilson & May 2001). Using PCR with this sensitivity can be used to quantitate absolute numbers of infected cells in a given population. Virus can be isolated on cell line.

The serologic profile, therefore, can be a useful marker of past infection. Because patients who are B-cell deficient do not naturally acquire EBV, we have no direct information from clinical observation about the biological importance of the antibody response. Antibodies to VCA, EA, and the EBNAs target intracellular antigen complexes and, therefore, seem unlikely to play any major effector role in controlling virally infected cells *in vivo*.

EBV reactivation prospective monitoring of EBV viraemia by Q-PCR is recommended after high risk allo HSCT. Screening for EBV DNA should start at the day of HSCT, and last for three months with frequency of at least once a week in high-risk cases.

Diagnosis of LPD or PTLD must be based on symptoms and/or signs consistent with lympoproloferative processdeveloping after HSCT, together with detection of EBV by an appropriate method applied to specimen from the involved tissue. EBV detection in a biopsy specimen requires detection of viral antigen or *in situ* hibridization for the EBER (Epstein-Barr-encoded RNA).

2.3.4 Prevention

The sheer range of EBV-associated diseases emphasizes the importance of developing either prophylactic vaccines to reduce disease burden or therapeutic strategies that specifically target virus-positive lesions. A number of approaches are currently being pursued. The first clinical testing of a gp350-expressing recombinant viral vaccine, based on the Chinese Tien Tan strain of vaccinia virus, was carried out on small groups of EBV-seronegative and EBV-seropositive children (Gu et al., 1995). Phase I and II trials of a gp350 subunit vaccine in young adults have induced a neutralizing antibody response; this did not prevent primary infection within the vaccinated group, but it did significantly reduce the incidence of infectious mononucleosis symptoms compared with the placebo controls.

2.3.4.1 EBV seronegative patients

Seronegative individuals should undertake behaviour that minimizes the likelihood of EBV exposure. If a patient is found seronegative, the risk of PTLD is higher. Also, HSCT donors should be tested before transplantation for EBV serology. When there is choice, the selection of a seronegative donor might be beneficial as EBV might be transmitted with the graft. Prevention of PTLD has focused on EBV DNA monitoring and use of the donor–derived cytotoxic T-cells.

2.3.4.2 EBV seropositive patients

Reactivation of EBV is common after allo-HSCT, but rarely causes significant problems through direct viral end-organ disease. The important complication of EBV replication is PTLD. Poor or negative data are available regarding EBV prophylaxis. Ganciclovir can reduce EBV replication, but neither ganciclovir and foscarnet nor cidofovir therapy and prophylaxis have any impact on the development of PTLD.

2.3.5 Therapy

Anti-CD20 antibodies (rituximab), reduction of immunsuppression or adoptive immunotherapy are recommended as a first-line therapy for PTLD. Four to eight doses of rituximab are needed to obtain clincal improvement and reduce the EBV DNA load. Chemotherapy is a second–line option.

2.4 Human herpesvirus 5 (HHV-5) [Cytomegalovirus (CMV)]

Human herpesvirus 5 (HHV-5 or CMV) was classified as belonging to the *Cytomegalovirus* genus within the subfamily *Betaherpesvirinae* of the *Herpesviridae* family. The virus usually infects the population in early childhood, and later, at the time of sexual activity. The primary infection of immuncompetent patients is generally symptomless, or causes self-limiting diseases, such as certain cases of infectious mononucleosis. The primary CMV infections of seronegative pregnant women's transplacental transmission during pregnancy leading to fetal damage may cause severe

congenital damage in the neonates, including deafness and mental retardation. Reactivation or primary CMV infection in immunocompromised patients can give rise to a wide range of complications in many organs of the host. Ho provides a comprehensive summary of work leading to the recognition of CMV as a separate medically important herpesvirus subfamily (Ho, 1991).

By the early 1950s, cytomegalic inclusion disease was diagnosed based on the presence of inclusion-bearing cells in urine, and viral etiology was predicted based on the detection of approximately 100 nm viruslike particles with low-resolution electron microscopy (EM). The unrelenting efforts of Margaret Smith, which led to isolation of this virus from urine of congenitally damaged newborns, followed her earlier success isolating the related mouse salivary gland virus (now called murine CMV) commonly used a viral strain that bears her name (Knipe & Howley, 2007). As with all herpesviruses, CMV latency is likely to be maintained in everyone who experiences primary infection. The propensity of virus to reactivate following immunosuppression or immunodeficiency is an important factor leading to CMV-associated diseases. CMV also remains medically prominent as an opportunistic infection in the immunocompromised host and this drives initiatives for therapeutic intervention.

CMV reactivation remains a significant cause of morbidity and mortality due to the extended period of immunodeficiency after allogenis HSTC. The CMV status of the recipients before HSCT has strong influence on HSCT outcome (Zhou et al., 2009).

2.4.1 Epidemiology

CMV has a worldwide distribution and infects up to 50-85% of the population in industrialized countries. CMV is predictably transmitted in settings where susceptible persons have contact with body fluids from persons excreting virus. Transmission appears to require direct contact with infectious material; spread by the airborne route or through aerosols does not occur. Following initial acquisition of CMV, infectious virus is present in urine, saliva, tears, semen, and cervical secretions for months to years. Two types of exposures have consistently been linked with horizontal transmission of CMV: sexual activity and contact with young children. Vertical transmission from mother to fetus or newborn not only occurs but is common and plays an important role in maintaining infection in the population. In this context, CMV is spread by three routes: transplacental, intrapartum, and via human milk.

Immuncompromised hosts are at elevated risk of serious CMV disease following primary infection, reinfection, or reactivation of latent virus (Sandherr et al., 2006). CMV is a leading infectious cause of morbidity and mortality in patients after HSCT and solid organ transplantation, and is an emerging problem in adults with leukaemia. CMV infection occurs in 60-70% of allogenic HSCT recipients when patient or donor are CMV seropositive, and is documented in about 50-60% of CMV seropositive autograph recipients. Other predisposing factors include the occurrence of acute GVHD, HLA-mismatched transplant, and a positive CMV serology of the graft donor in seronegative patients (Ng et al. 2005). The majority of CMV infections occur during the first three to four months after transplant largely controlled by preventive strategies using antiviral drugs; CMV infection remains a significant problem in this setting because of breakthrough disease in high risk patients, late onset disease, and indirect effects that adversely affect outcome.

2.4.2 Clinical manifestations

CMV infection is manifested clinically in the normal host. The illness is similar to mononucleosis that occurs with EBV infection. Estimates indicate that CMV is responsible for 20% to 50% of heterophile-negative mononucleosis and that it accounts for approximately 8% of all cases of mononucleosis. It is characterized by fever for more than 10 days, malaise, myalgias, headache, and fatigue. Splenomegaly, hepatomegaly, adenopathy, and rash are present in some patients. Compared to EBV-induced mononucleosis, pharyngitis, adenopathy, and splenomegaly are noted less commonly with CMV.

CMV disease manifestation includes pneumonia, enteritis, encephalitis, retinitis, hepatitis, cholangitis, cystitis, nephritis, sinusitis, and marrow suppression. CMV pneumonia was also increased among patients with lymphoma and acute leukemia. CMV-attributable mortality for these patients ranged from 30% to 60%.

Primary CMV infection is when CMV is detected in a previously CMV seronegative patient. Recurrent CMV infection is when CMV is detected in a CMV seropositive patient. At symptomatic CMV infection, patients develop symptoms (fever with or without bone marrow suppression) and carry detectable CMV virions, antigens or nucleic acid, but with no sign of CMV endorgan disease. CMV disease is when CMV can be detected by test with appropriate sensitivity and specificity in an organ, in a biopsy, or in samples from other invasive procedures, bronco-alveolar lavage (BAL), cerebrospinal fluid (CSF) together with symptoms and/or sings from the affected organ. For CMV retinitis, typical findings by ophtalmologic examination are sufficient.

2.4.3 Laboratory diagnosis

Several techniques exist allowing rapid diagnosis of CMV with high sensitivity. Serologic tests for antibody to CMV are useful for determining whether a patient had CMV infection in the past, a determination of great clinical importance for organ and blood donors, and in the pretransplant evaluation of prospective transplant recipients. The avidity of IgG antibody increases with time after initial infection and demonstration of low CMV-IgG avidity can improve the accuracy of identification of recent primary infection. Antibody tests are not useful in the diagnosis of CMV disease in the immunocompromised host. Serology determination of either IgG or IgM has no place in the diagnosis of CMV infection or disease but is useful to determine the risk of subsequent CMV infection. The most commonly used tests for diagnosis of CMV infection are the detection of antigen (pp65 antigenaemia assay), DNA, or mRNA. Use of a quantitative assay (Q-PCR) gives additional information valuable for patient management. CMV gastrointestinal disease is the combination of clinical symptoms, findings of macroscopic mucosal lesions on endoscopy, and demonstration of CMV by culture, histopathologic testing, immunohistochemistry or *in situ* hybridization in a biopsy specimen. PCR on biopsy material is insufficient for the diagnosis of CMV gastrointestinal disease.

2.4.4 Prevention

The different preventive strategies for CMV disease include the use of antiviral agents, such as chemoprophylaxis, pre-emptive therapy or treatment of symptomatic CMV infection. The currently available aniviral agents for prevention of CMV infection and disease are ganciclovir, valganciclovir, foscarnet and cidofovir (Ljungman et al.,2008).

CMV seronegative patients have low risk of contracting CMV infection. To reduce the risk of CMV transmission, blood product from CMV seronegative donors or leukocyte-depleted blood product should be used. CMV seronegative patients with CMV seronegative stem-cell donors have a lower risk of post transplant complications both from CMV and from the effect of CMV associated immunsuppression with its concomitant increased risk of bacterial and fungal infections.

Hyperimmune globulin preparations with high levels of antibody to CMV (CMVIG) have been evaluated for prevention of CMV disease in organ transplant recipients, premature newborns at risk for postnatal infection and pregnant women. Although attempts to develop a vaccine for prevention of maternal and congenital CMV have been pursued for more than 25 years, no vaccine is currently licensed or near licensure. Improved understanding of the role of specific viral proteins in eliciting protective immune responses and recent recognition of the potential benefit to society and cost-effectiveness of CMV vaccines, however, are stimulating development of new vaccines. Investigational vaccines using different formats have been evaluated in clinical trials; these include attenuated live virus, a recombinant protein in a fowl pox vector, a DNA vaccine, and a recombinant protein given with a new adjuvant (Sung & Schleiss, 2010).

2.4.4.1 CMV seropositive patients

The use of preemptive monitoring for CMV reactivation in patients receiving alemtuzumab for at least two months following the receipt of chemotherapy is recommended. Once CMV reactivation is recognized, either oral valganciclovir or intravenous ganciclovir may be used.

2.4.5 Therapy

The four antiviral agents (Ganciclovir, Valganiclovir, Foscarnet, and Cidofovir) are currently approved for treatment of CMV disease (Fellay et al. 2005; Knipe & Howley, 2007). Antiviral agents are commonly used in transplant medicine to prevent CMV disease, either as a daily prophylactic regimen or in a preemptive approach in which laboratory surveillance for CMV in blood is used to identify patients for antiviral therapy (Reusser 2002).

2.5 Human herpesvirus 6 (HHV-6)

Human herpesvirus 6 (HHV-6) belongs to the *Roseolovirus* genus of the *Betaherpesvirinae* subfamily of the *Herpesviridae* family. HHV-6 was first isolated in 1986 from B-lymphocytes of patients infected with HIV, HTLV, and lymphoproliferative disorders (Salahuddin et al., 1986). Because of tropism to B lymphocytes, the virus was first named human B-lymphotropic virus, but was later found mainly to infect and replicate in lymphocytes of the T-cell lineage. HHV-6 isolates are classified into two closely related groups, variants A (HHV-6A) and B (HHV-6B). HHV-6B is the major causative agent of exanthem subitum (roseola infantum), which is characterized by high fever, diarrhoea, and a mild skin rash along the trunk, neck, and face (Yamanishi et al., 1988). HHV-6A has been associated with several adult diseases, including cofactor in AIDS progression, and various neurological disorders including encephalitis, ataxia, seizure, liver disfunction, and chronic fatigue syndrome; however, the causal link between human diseases and virus infection remains to be fully elucidated (De Bolle et al., 2005; Ablashi et al, 2010).

Following primary infection, the genome of herpesviruses establishes latency as a nuclear circular episome. The *in vivo* and *in vitro* integration of HHV-6A and HHV-6B into the telomers of human chromosomaes during latency was demonstrated by Arbuckle et al. (Arbuckle et al., 2010; Arbuckle & Medveczky 2011). The integrate HHV-6 genome was also found to be vertically transmitted from parent to child in the germ-line. Characterisation of the integration sites in tumor samples and long-term follow up studies may elucidate the relationship between integration and leukemogenesis (Minarovits et al., 2007)

2.5.1 Epidemiology

Seroprevalence of HHV-6 decreases at five months of age, as maternal antibody wanes. Beginning at about 6 months, seroprevalence increases rapidly, with almost all children becoming positive by 2 years of age. Internationally, HHV-6 seroprevalence is high in almost all areas, but ranges from approximately 39% to nearly 100% among some ethnically diverse adult populations.

HHV-6 genomes and antigens are detectable in lymph nodes of patients with sinus histiocytosis with massive lymphadenopathy tubular epithelial cells, endothelial cells and histiocytes in kidney salivary glands and central nervous system tissues, where viral gene products have been localized to neurons and oligodendrocytes (Levine et al., 1992; Kurata et al., 1990). HHV-6 is also detected in lesions of Langerhans cell histiocytosis in the syndrome of Langerhans cell histiocytosis (Leahy et al., 1993; Csire et al., 2007a).

2.5.2 Clinical manifestations

Asymptomatic HHV-6 reactivation is common after allogeneic bone marrow transplantation (Cone et al.,1999), but reactivation has also been linked to bone marrow suppression, encephalitis, gastroduodenitis, colitis, pneumonitis, rash, and acute graft-versus-host disease, all of which have been reviewed by others (De Bolle et al., 2005). Liver dysfunction is also associated with HHV-6 infection; although usually mild, it can be fatal hepatitis and chronic hepatitis. Primary HHV-6 infection has also been associated with cases of idiopathic thrombocytopenic purpura. Further, human herpesvirus 6 infection has also been associated with pneumonitis, with the infected cells being primarily intraalveolar macrophages, plus some lymphocytes.

Concentrations of HHV-6 genomes in lung tissue and their relation to changes in serologic titers support an association between HHV-6 infection and idiopathic pneumonitis in immunocompromised hosts. HHV-6 reactivates early after HSCT and is found in the blood in about half of all allo-HSCT recipients, making it difficult to make disease association. Two viral variants of HHV-6 have been identified (A and B), but the HHV-6B is most frequently associated with disease among immuncompromised patients. Longitudinal studies in HSCT recipients found the viral reactivation to occur at a median of 20 days after transplantation, and that viral shedding for some patients was prolonged, and correlated poorly with clinical improvement (Zerr et al., 2005). A clinical syndrome consisting of central nervous system dysfunction, impaired memory, secondary hypothyroidism, and delayed platelet engrafment are common disease manifestations. HHV-6 viraemia among allogenic transplant recipients is associated with the increase in all-cause mortality, and viraemia appears to be increased when patients are transplanted

for disease other than first remission, when donor and recipient are sex mismatched, and among younger patients.

2.5.3 Laboratory diagnosis

HHV-6 virus isolation is easily recovered from peripheral blood mononuclear cells of patients with exanthema subitum during the acute phase. Cytopathic effect (CPE) develops within 7 to 10 days. The refractile giant cells usually contain one or two nuclei and, after the occurrence of the CPE, lytic degeneration of the cells takes place. The rate of virus isolation from mononuclear cells was 100% on days 0 to 2 (just before appearance of skin rash), 82% on day 3, and 20% on day 4.

Numerous HHV-6 serologic assays have been described, including IFA, ELISA, neutralization, and immunoblot. IFA is the most commonly applied method, with HHV-6 infected cells being used as the antigens. For detection of IgM, separation of serum IgM from IgG and IgA significantly increases the specificity.

Antigenemia tests: such tests have been used for the diagnosis of HHV-6 infection in blood, but there is limited experience as their use has not been widespread.

HHV-6 DNA can be detected via PCR techniques (sPCR, n-PCR) from blood, cerebrospinal fluid (CSF), tissue samples, and other samples in view of the differing natural histories of variants A and B. Quantitative PCR (Q-PCR or real-time PCR) analysis on blood and CSF is the method of choice for diagnosis.

Possibile techniques include *in situ* hybridization and immunohistochemistry, but these are not generally available.

2.5.4 Prevention

Antiviral prophylaxis against HHV-6: foscarnet, ganciclovir and cidofovir have been shown to inhibit HHV-6 replication. Data from two small non-randomized studies of HSCT recipients suggest that prophylactic gancyclovir can prevent recurrent HHV-6 infection (Tokimasa et al., 2002, Rapaport et al., 2002).

2.5.5 Therapy

Foscarnet and gancyclovir, alone or in combination, have been used as treatment for HHV-6 infection. For treatment of HHV-6 encephalitis foscarnet or ganciclovir are recommended as first-line therapies after HSCT. Cidofovir is recommended as a second-line therapy.

2.6 Human herpesvirus 7 (HHV-7)

Human herpesvirus 7 (HHV-7) belongs to the *Roseolovirus* genus of the *Betaherpesvirinae* subfamily of the *Herpesviridae family*. HHV-7 was first described in 1990 (Frenkel et al., 1990). HHV-7 was isolated in 1990 from a healthy individual whose cells were stimulated with antibody against CD3 and then incubated with interleukin-2. The virus is one of the causative agents of exanthema subitum (Tanaka et al., 1994) and has been associated with febrile convulsions in young children (Ward et al., 2005). After primary infection of CD 4+T lymphocytes, HHV-7 infects (similar to HHV-6) epithelial cells of salivary glands and various organs (lungs, skin, mammary gland, liver, kidney and tonsils). HHV-7 could be reactivated from lately infected peripheral blood mononuclear cells by T-cell activation. Thus, HHV-7 can provide transacting functions, mediating HHV-6 reactivation from latency (Tanaka-Taya et al., 2000).

2.6.1 Epidemiology

HHV-7 infection appears to occur slightly later than HHV-6. As for HHV-6, seroprevalence declines over the first 5 to 6 months, as maternal antibody wanes, then increases fairly rapidly up to 4 years of age. HHV-7 is ubiquitous, with more than 44%-91% of adults having antibody to virus.

2.6.2 Clinical manifestations

Although the frequency of clinical illness is lower, primary infection with HHV-7 causes illness similar to that of HHV-6, including exanthem subitum, high fever, and neurologic symptoms (e.g., febrile convulsions).

In 1997, Drago et al. reported the association of pityriasis rosea with HHV-7 infection and proposed that it is a clinical presentation of HHV-7 reactivation. Peripheral blood mononuclear cell (PBMC) from patients with pityriasis rosea showed ballooning cells and syncytia after 7 days in culture, whereas PBMC from controls and patients recovered from pityriasis rosea did not. PCR identified HHV-7 DNA in PBMC, plasma, and skin from all patients with active pityriasis rosea, and only in the PBMC 10 to 14 months later. HHV-7 detection after HSCT is relatively infrequent, and there are only a handful of cases in which HHV-7 is associated with central nervous system disease (Yoshikawa et al., 2003).

2.6.3 Laboratory diagnosis

HHV-7 is sometimes isolated from peripheral blood of patients with exanthema subitum, and can be readily isolated from saliva by using methods as described above for HHV-6. Isolation of HHV-6 from saliva is uncommon, although its DNA is often detectable there. HHV-7 serology techniques are immunoblot, IFA, and ELISA assays for HHV-7 antibodies. The ELISA was the most sensitive, whereas the immunoblot was the most specific. As mentioned, antibody avidity assays enable identification of recent primary infections (Ward 2005). PCR techniques (sPCR, n-PCR, Q-PCR or RT-PCR) can be used to detect HHV-7 DNA of blood, cerebrospinal fluid (CSF), tissue, or other samples.

2.6.4 Prevention

In view of the limited data, no recommendations can be made regarding HHV-7 as a potential pathogen in leukemia patients or after HSCT.

2.6.5 Therapy

The majority of conditions due to infection do not require antiviral medication, but the severe complications may be treated with ganciclovir and its derivates or foscarnet and cidofovir.

2.7 Human herpesvirus 8 (HHV-8) [Kaposi's sarcoma associated herpesvirus (KSHV)]

Kaposi's sarcoma associated herpesvirus (KSHV; human herpesvirus 8, HHV-8) is the most recently discovered human herpesvirus (Chang et al., 1994). Kaposi's sarcoma (KS) is a complex, angioproliferative and inflammatory lesion that was first described by Kaposi in the late 19th century (Kaposi, 1872). HHV-8 belongs to the *Rhadinovirus* genus of the *Gammaherpesvirinae* subfamily of the *Herpesviridae family*. HHV-8 is the ethiologic agent of Kaposi's sarcoma, and has been implicated in other B-cell lymphoproliferative disorders including primary effusion lymphoma and a subset of multricentric Castleman disease. HHV-8 has been implicated in the pathogenesis of several other diseases, including multiple

myeloma, Waldenstörm macroglobulinaemia, and monoclonal gammopathy with unknown significance (Mikala et al., 1999).

2.7.1 Epidemiology

The prevalence of HHV-8 infection is very high in older children and adults in Africa and the Amazon basin (50-100%), medium in the Mediterranean (5-25%), and low in North America, North and West Europe (2-5%). Transmission of the virus is sexual; in homosexual and bisexual persons, seroprevalence rates are substantially lower among women than men. Transmission is possible via saliva in areas of high epidemicity. HHV-8 may be transmitted by blood transfusion and solid organ transplantation (Hladik et al., 2006).

2.7.2 Clinical manifestations

Transplant patients may acquire HHV-8 from the allograft, blood products, caregivers, or from family members. Cutaneuous or visceral Kaposi's sarcomas develop with a reported incidence of 0.5-5.0% in solid organ recipients (Jenkins et al., 2002).

2.7.3 Laboratory diagnosis

The first successful cultivation of HHV-8 used PEL cell lines explanted from patients with advanced AIDS (Renne et al., 1996). HHV-8 diagnostic serology techniques may include immunoblot, IFA, and ELISA assays for HHV-8 antibodies (Sarmati 2001; Juhasz et al., 2001). These are useful for donors and recipients in at risk population, but wherever available, are of variable sensitivity and specificity (Sergerie et al., 2004).

HHV-8 DNA can be detected via PCR techniques (sPCR, n-PCR, Q-PCR or RT-PCR) from the whole blood, plasma or serum, cerebrospinal fluid (CSF), tissue or other samples. Possible techniques may include *in situ* hybridization and immunohistochemistry, but these are not generally available.

2.7.4 Prevention

In view of the limited data, no recommendations can be made regarding HHV-8 as a potential pathogen in leukemia patients or after HSCT.

2.7.5 Therapy

Antiviral agents that target herpesvirus DNA synthesis, such as ganciclovir, foscarnet and cidofovir, inhibit HHV-8 lytic replication and can prevent Kaposi sarcoma (Cohen & Powderly 2004). Several HIV protease inhibitors may interfere with tumor growth and angiogenesis, and one protease inhibitor, nelfinavir, directly inhibits HHV-8 replication *in vitro* (Gantt & Casper, 2011).

3. Conclusion

The spectrum of viral infections for patients with haematological diseases is expanding and diagnosis has increased because of new molecular diagnostic techniques. The group of human herpesviruses consists of eight members. Primary and reactivation infections are characteristic of these pathogens. Viral latency can be predicted by serological screening and it is useful for disease management. Antiviral therapy is now routinely used for prevention and therapy. Viral immunization remains investigational, except for the VZV vaccination (Cheuk et al., 2011).

Human herpesviruses are a major cause of related morbidity and mortality in hematologic diseases. This chapter focuses on the epidemiology and prevention strategies for human herpesviruses in this population (see Table 1.).

Virus	Disease ---------------------- Population	Surveillance ----------------- (Monitoring)	Recommended antiviral agent	Preventative measure	Timing and Duration
HHV-1 & HHV-2 (HSV-1 & HSV-2)	Reactivation, rare first infection Mucositis Esophagitis Pneumonitis or hepatitis	Baseline serologies Prophylaxis if seropositive ----------------- (No)	ACV GCV VACV VGCV FAM	Prophylaxis: IV ACV 5mg/kg BID oral ACV 200mg TID oral VACV 500mg BID	Initiate prophylaxis with start of chemotherapy Continue for 3-5 weeks post-chemotherapy
	HSCT			ACV 250mg per meter-squared IV q12h or oral ACV 200mg TID oral VACV 500mg BID FAM 750 mg po q24h or 500mg BID or 250mg TID	at least 30 days post-tranplantation
	Leukemia				during neutropenia
	Alemtuzumab therapy				2 months after therapy or until CD4> 100 cells/ul
HHV-3 (VZV)	Primary infection varicella, reactivation herpes zoster	Baseline serologies preventative therapy if seronegative	ACV GCV VACV VGCV FAM	post-exposure prophylaxis ACV 800mg QID, VACV 1g TID post-exposure passive immunization VZIG (0.2-1ml/kg IV) or IVIG (300-500 mg/kg IV	antiviral agents are until 21 days post-exposure passive immunization within 96 hours of exposure
		Monitor if seropositive		herpes zoster treatment with antivirals	
HHV-4 (EBV)	HSCT	Baseline serologies	GCV foscarnet cidofovir	No evidence for the use of prophylactic therapy	

Virus	Disease -------------------- Population	Surveillance ----------------- (Monitoring)	Recommended antiviral agent	Preventative measure	Timing and Duration
HHV-5 (CMV)	Reactivation CMV viraemia CMV syndrome Organ Disease (CNS, pneumonitis, GI)	Baseline serologies, weekly CMV PCR or pp65 antigenemia	GCV foscarnet cidofovir VGCV	Pre-emptive IV GCV 5mg/kg BID oral VGCV 900mg BID	chemotherapy to 2-6 months, post therapy treatment for at least 1 week or until CMV PCR is negative and patient asymptomatic
	HSCT				
	Alemtuzumab therapy	weekly CMV PCR or pp65 antigenemia			
HHV-6		Baseline serologies ?	foscarnet GCV	No evidence for the use of prophylactic therapy	
HHV-7		Baseline serologies ?	GCV foscarnet cidofovir	No evidence for the use of prophylactic therapy	
HHV-8 (KSHV)		Baseline serologies ?	GCV foscarnet cidofovir nelfinavir	No evidence for the use of prophylactic therapy	

Abbreviations: ACV-acyclovir, GCV-ganciclovir, VACV-valacyclovir, VGCV-valganciclovir, HSCT-hematopoietic stem cell transplantation, GVHD-graft-versus-host disease, IV-intavenous, BID-two times per day, TID-three times per day, QID-four times per day, VZIG-Varicella-zoster immunoglobulin, IVIG-intravenous immunoglobulin, FAM-Famciclovir, CNS-central nervous system, GI-gastrointestinal

Table 1. Recommendations for Surveillance and Prophylaxis in Patients with Hematologic Diseases

Viral infections remain a common complication in patients with hematologic diseases, especially in those receiving intensive chemotherapy. Fortunately, there are effective prophylactic and preventative mesures available to help control these infections.
Human herpesviruses have been implicated in the pathogenesis of several diseases. An increasing number of malignancies are being associated with EBV (e.g. LPD, non-Hodgkin's lymphoma, Hodgkin's diseases, Burkitts's lymphoma, NK-cell leukemia). HHV-8 has been suggested as a possible etiologic agent of several diseases. These include multiple myeloma, Waldenstörm's macroglobulinaemia, and monoclonal gammopathy with unknown

significance. Multiple myeloma is a genetically and clinically heterogeneous disease. Recently, (at least) 5 prognostically and biologically different subgroups have been described based on karyotype and type of cyclin expression (Gertz & Greipp 2004). HHV-8 infection may play a role in the disease process of only one or more subgroups of myeloma patients while not in others. In the history of HHV-8 research, it has been exceedingly difficult to obtain lymphoid cell lines (e.g. effusion lymphoma) devoid of EBV genome (Renne et al. 1996).

This brings up the point of possible interaction between these two lymphotropic herpesviruses, at least in diseases of the lymphoid system. A similar interaction of HHV-6 and 8 has been described *in vitro*. EBV-seronegative patients may be prone to HHV-8 reactivation, the possible interaction of EBV early proteins with the activation of latently harbored HHV-8 genomes. This might occur also in such cases when the two viruses are not replicating in the same cell, but viral membrane proteins i.e. ZEBRA or interleukin-like molecules shed (IL10) by the EBV producing B-cells might interact with B cells or bone marrow cells carrying latent HHV-8 mini-chromosomes.

It may be possible that the continuously replicating myeloma cells release both EBV and HHV-8, since latent virus infected cells are usually blocked in the G0-G1 phases of the cell cycle. When myeloma cells enter the S-phase, the availability of DNA replication machinery may activate the DNA viruses persisting in a small proportion of cells. The absence of CMV reactivation can be understood, since the sites of latency are the CD34+ progenitor cells of monocytes. The main site of replication is the B lymphocytes and many other cells in the human body. In conclusion, the data also indicate that in addition to HHV-8, the transitional reactivation of EBV may also play a role in the pathogenesis of MM (Csire et al. 2007b).

Prospective studies are needed to clarify the spectrum of viral infections and risk factors for disease better, and to define effective prevention and treatment strategies. Fortunately, clinicians and virologists are increasingly aware of the most appropriate therapeutic options based on improved monitoring and characteriziation of the antiviral therapy.

4. Acknowledgment

5. References

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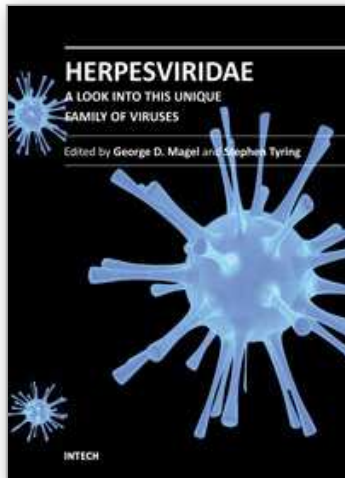
Herpesviridae - A Look Into This Unique Family of Viruses

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In order to fully understand the nature of viruses, it is important to look at them from both, their basic science and clinical, standpoints. Our goal with this book was to dissect Herpesviridae into its biological properties and clinical significance in order to provide a logical, as well as practical, approach to understanding and treating the various conditions caused by this unique family of viruses. In addition to their up-to-date and extensive text, each chapter is laced with a variety of diagrams, tables, charts, and images, aimed at helping us achieve our goal. We hope that this book will serve as a reference tool for clinicians of various specialties worldwide.

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