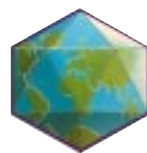


Recommendations from the
IHMF Management Strategies Workshop and
3rd Annual Meeting

Editors: Dr E Sandström
Professor RJ Whitley

THE INCREASING IMPORTANCE OF CYTOMEGALOVIRUS, EPSTEIN-BARR VIRUS AND THE HUMAN HERPESVIRUSES TYPES 6, 7 AND 8

Jointly sponsored by the University of Alabama School of Medicine,
University of Alabama at Birmingham, USA and
the *International Herpes Management Forum* (IHMF)



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The above were participants in the *Management Strategies* Workshop.

The contribution of the participants at the 3rd Annual Meeting of the IHMF is also acknowledged.

The *International Herpes Management Forum* (IHMF) was established to improve the awareness, understanding, counselling and management of infections caused by herpesviruses. Steered by an IHMF Board of Professor Richard Whitley, Dr Martin Wood, Dr Larry Corey, Professor Paul Griffiths, Dr Susanne Kroon, Dr Antonio Volpi and Dr Koichi Yaminishi, the IHMF involves international Opinion Leaders in all aspects of medical management of herpesvirus infections including herpes simplex virus (HSV), varicella zoster virus (VZV) and cytomegalovirus (CMV) infections.

Two *Management Strategies* Workshops were held in 1995, leading up to the 3rd Annual Meeting of the IHMF in November 1995 when recommendations on specific issues affecting the management of herpesvirus infections were debated.

The seventh IHMF workshop was held on 3–4 April 1995 to discuss latency and its implications for the clinical management of herpesviruses. All herpesviruses can exist in a latent state, but the implications of reactivation depend on the virus involved and the immune status of the host. Presentations highlighted populations at greatest risk of the consequences of latent herpesvirus infections and reviewed the strategies that have been implemented to reduce these risks. The aim of the seventh workshop was to improve understanding of the nature of latent herpesvirus infections so recommendations could be developed to limit the consequences for the affected individual in terms of discomfort and disease and for the population as a whole in terms of transmission.

The draft recommendations from the workshop were discussed at the 3rd Annual Meeting of the IHMF which took place on 17–19 November 1995. Following the Annual Meeting it was decided that the workshop topics were best illustrated in two separate *Management Strategies* publications entitled *Genital and Orofacial Herpes Simplex Virus Infections – Clinical Implications of Latency* and *The Increasing Importance of Cytomegalovirus, Epstein-Barr Virus and the Human Herpesviruses Types 6, 7 and 8*.

The editors would like to thank all the participants at the 3rd Annual Meeting for their contribution and especially the Co-Chairs of the working groups.

This series of monographs is jointly sponsored by the University of Alabama School of Medicine, Division of Continuing Medical Education and the IHMF. This publication is CME accredited for American and Canadian physicians (see inside back cover for details).

Objectives

The information contained in this publication should enable the physician to:

- ◆ Appreciate the worldwide seroprevalence of cytomegalovirus, Epstein-Barr virus (EBV) and human herpesviruses types 6, 7 and 8
- ◆ Recognize populations at greatest risk of infection and strategies for its prevention and/or control
- ◆ Understand the concerns for EBV-associated disease in different areas of the world
- ◆ Expand their knowledge of the most recently discovered human herpesviruses (types 6, 7 and 8) and the increasing number of diseases associated with them

Target Audience

The information contained in *The Increasing Importance of Cytomegalovirus, Epstein-Barr Virus and the Human Herpesviruses Types 6, 7 and 8* is aimed at physicians, healthcare workers and other individuals involved in the management of herpesvirus infections.

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Herpesviruses – A Continuing Challenge

Herpesviruses are extremely common in nature and around 100 have been at least partially characterized from a variety of vertebrate and non-vertebrate animal species. There is evidence that an extremely long coevolution existed between herpesviruses and mammals. It is not surprising therefore that rapid societal changes and profound changes in host immunocompetence have created conditions which are conducive for previously unknown or rare manifestations of herpesvirus infections.

In the past 10 years, the above factors have led to the discovery of three additional herpesviruses, bringing the number of human herpesviruses to eight: herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus type 6 (HHV-6), human herpesvirus type 7 (HHV-7) and human herpesvirus type 8 (HHV-8); also referred to as Kaposi's sarcoma-associated herpesvirus (Figure 1).¹

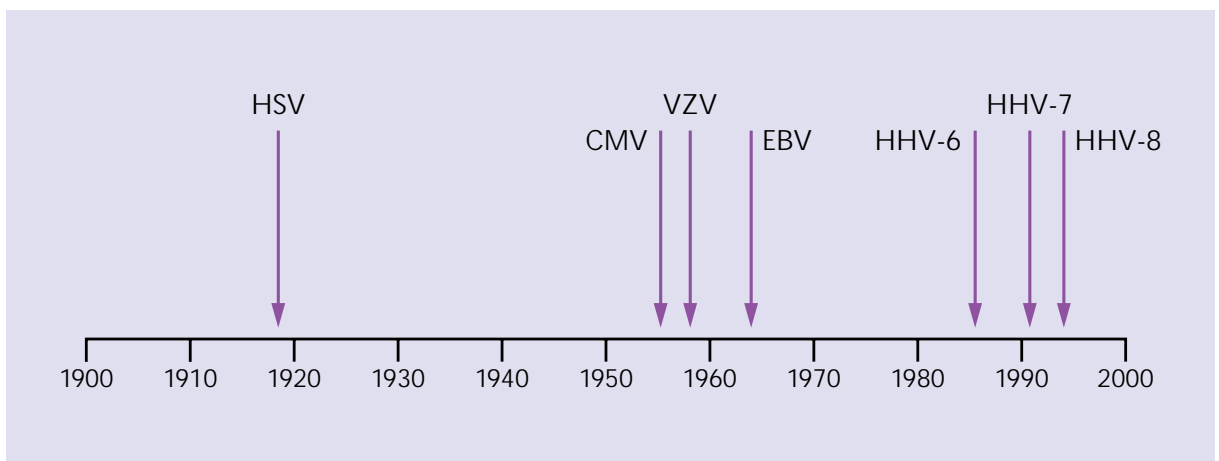


Figure 1: First detection of herpesviruses

An understanding of the natural history of herpesviruses has led to significant progress in controlling several diseases caused by them. With the addition of new members to the herpesvirus family, further progress in the management of herpesvirus infections will not only require improved drug discovery programmes, but also an understanding of the differences in pathogenesis.

During primary infection, herpesviruses establish latency, which allows the viral DNA to persist without expressing proteins that would be targets for an immune response. Intermittently, the latent genome can become activated to produce infectious virions. While the herpesviruses share aspects of molecular biology (replication, natural history and pathogenesis), they also differ extensively in important details. For instance, HSV-1 and HSV-2 infect a wide host-cell range, are recognized for their neurotropic characteristics, multiply efficiently and rapidly destroy the cells that they infect. EBV on the other hand is largely restricted to B lymphocytes but can induce malignant transformation. Herpesviruses also differ with respect to the cells in which they establish latency and in the clinical manifestations of disease with which they are associated.²

Chapter 1

Biological properties such as those described above have been used to classify the members of the family *Herpesviridae* into subgroups (Table 1).³ These depict evolutionary relatedness and serve a practical purpose in enabling the laboratory worker to identify and predict the properties of a new viral isolate by comparison with already established members.

Alpha herpesviruses	Beta herpesviruses	Gamma herpesviruses
● HSV-1	● CMV	● EBV
● HSV-2	● HHV-6	● HHV-8
● VZV	● HHV-7	

Table 1: Human herpesvirus subgroups according to the International Committee on the Taxonomy of Viruses (ICTV) classification

Numerous, diverse and often opposing trends will determine the frequency and severity of herpesvirus infections in the future. A major factor is the growing population of immunocompromised patients. Sociological changes will also be important, although the consequences of these, such as attempts to influence sexual practices, will be difficult to predict. Other changes, such as more frequent use of early child-care facilities, will predictably lead to early acquisition of most herpesviruses, thereby decreasing the incidence of severe disease in adulthood.

New diagnostic methods have already associated HHV-6, -7 and -8 with specific diseases. Other factors that might increase herpesvirus-related morbidity include: the discovery of new diseases caused by previously known herpesviruses and resistance of herpesviruses to antiviral therapy.

It is likely that the existing herpesviruses will assume increasing importance in medicine over the next few years. Strategies for the management of infection must apply what is currently known about herpesvirus natural history and pathogenic mechanisms to newer members of the family and maintain constant vigilance for developments in the fields of diagnostic methods and intervention strategies.

Implications for Transmission of Cytomegalovirus

Cytomegalovirus (CMV) has the most complex natural history of all the herpesviruses. Most body tissues are infected with CMV during productive infection and the virus can be detected in saliva, urine, blood and semen. CMV is transmitted by all organ allografts, including blood, and can be found at autopsy in most tissues of the body. CMV thus has the ability to replicate in many, if not all, cell growth types *in vivo*. This makes it unlikely that CMV has a single site of latency, although possible candidates include lymphocytes and monocytes.¹ The blood–brain barrier is easily crossed by these cells and is also a potential site for the establishment of latency.

Although a great deal has been learned about CMV, it remains the most important cause of congenital infection in the USA, a significant cause of transfusion-acquired infection and a frequent cause of morbidity and mortality among organ transplant recipients and other immunocompromised patients.

CMV infection is widespread with 40–100% of the world's adult population being seropositive. Sources of virus include oropharyngeal secretions, urine, cervical and vaginal excretions, semen, breast-milk, tears, faeces and blood. In the healthy host, primary infection is usually asymptomatic with 95% of adults who seroconvert having no recollection of any illness. CMV disease is generally associated with either immaturity of the immune system or immunodeficiency.

The immunocompromised host represents a large proportion of those at greatest risk of reactivation of latent CMV but a comprehensive discussion of the manifestations of CMV disease and its management in this broad patient group is too large a subject for the current chapter and will form the basis of a separate *Management Strategies* publication in 1997. Aspects of CMV management in the immunocompromised individual with HIV are discussed in a previous *Management Strategies* publication (*Herpesvirus and HIV Infections – Co-Factors and Opportunistic Infections*).² This chapter will review the implications for transmission of CMV to seronegative individuals, including pregnant women, day-care workers and transplant and transfusion recipients.

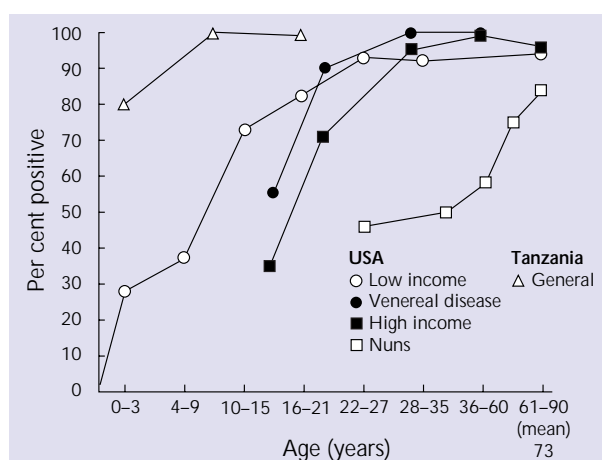


Figure 1: Age-related seroprevalence of CMV infection

Person-to-Person Transmission

The epidemiology of CMV varies widely in different areas of the world and between different age and socioeconomic groups (Figure 1). In general, those of higher socioeconomic status have a lower seroprevalence and acquire infection later in life.^{3,4}

Studies conducted at day-care centres in the USA have shown that in the first year of life, approximately 10% of children shed CMV.

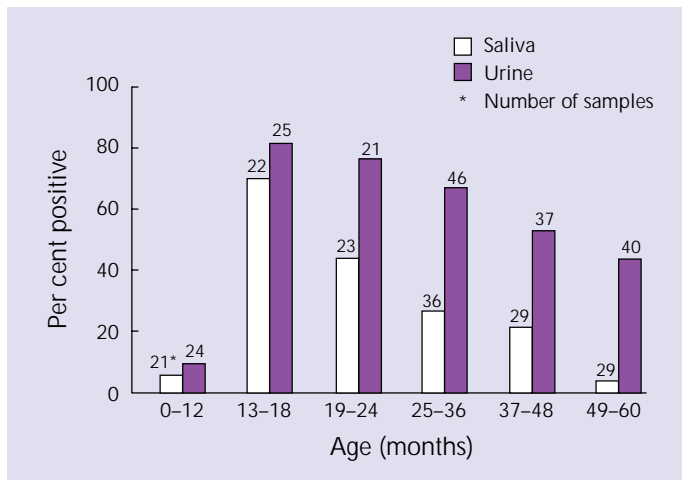


Figure 2: Excretion of CMV in saliva and urine among children in a single day-care centre in the USA

This figure increases significantly to approximately 80% by the time these children have reached 12–18 months of age (Figure 2), suggesting that the children are transmitting the virus to each other by close contact.⁵ In most developed countries, infection rates increase slowly until the age of entry into school at which time they rise more rapidly. It is estimated that 40–80% of children are infected before puberty in developed countries. In other areas of the world 90–100% of the population may be infected during childhood.

Congenital CMV infection

Person-to-person transmission of CMV in the healthy population is generally of no clinical consequence except for the risk of congenitally acquired CMV infection. Congenital infection can be observed either after a primary infection or recurrence of a previous infection, but the probability of transmission is higher and the outcome is generally more severe if the congenital infection follows a primary maternal infection during pregnancy (Figure 3).⁶

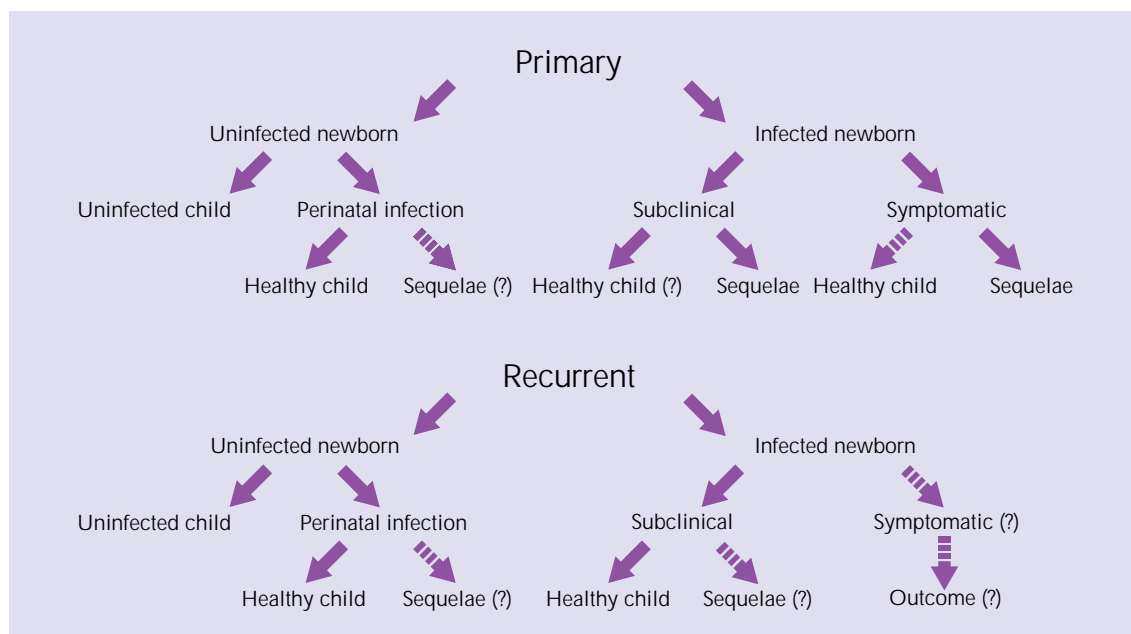


Figure 3: Type of maternal CMV infection and effect on offspring

Maternal factors

The proportion of babies who are affected by congenital CMV infection depends on a number of factors, including antibody status of the mother, breast-feeding and age. For reasons that are not known, shedding of CMV in the genital tract decreases steadily with age from up to 30% in women in their mid-teens to undetectable levels in women over 30 years old.⁷

There is considerable evidence that CMV-specific antibodies are important in protecting against CMV disease. In CMV-seronegative women who become infected during pregnancy, intra-uterine transmission occurs in 35–40% of cases, whereas it occurs in only 0.2–2% of women previously infected with CMV.⁶ Newborns infected after reactivation of maternal CMV infection rarely have clinically apparent disease or severe sequelae, while congenital infection after a primary maternal CMV infection during pregnancy, may result in damage to the fetus with long-term sequelae.⁶

Routes of transmission

There are three routes of CMV transmission from mother to child and it is estimated that about 10% of all babies born in the USA acquire CMV through one of these routes:⁵

- ◆ Transplacental
- ◆ Infected secretions in birth canal
- ◆ Breast-milk

Between 0.2% and 2.2% of live-born infants are infected *in utero*.⁸ Another 8–60% become infected perinatally as a result of infected cervical secretions in the birth canal or from breast-milk. Intra-uterine transmission of CMV can occur whether a mother has prior immunity or acquires CMV for the first time during pregnancy.⁸ The degree of protection afforded to an infected infant by the presence of antibody in the mother before conception is uncertain.⁶ It is possible for a woman seropositive for one strain of CMV to become infected with another strain of CMV during pregnancy. In post-partum women, the breast is the most common site of reactivation. Thirty per cent or more of seropositive women can intermittently excrete CMV into breast-milk during the first year after delivery.⁹

Populations at risk

Subclinical shedding of CMV can provide a reservoir for transmission. Virus excretion in urine and saliva can persist for years after congenitally, perinatally and early postnatally acquired CMV infections (Figure 4); a fact that has important implications for children looked after in day-care centres. These children are excellent vectors for

the transmission of CMV because of the type of contact they have with other members of society and the duration for which they are shedding virus.

Parents

There is a relationship between parental acquisition of CMV infection, secretion of virus by their child and the age of the child; age determining the type of contact a parent has with their child and the amount of contact with bodily secretions.

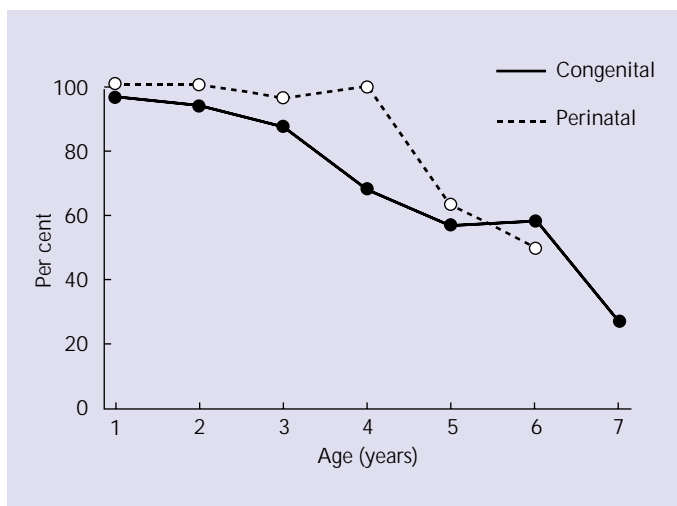


Figure 4: Duration of viruria in children with congenital or perinatal (intrapartum and breast-milk) CMV infection

Parental seroconversion rates in families who have children attending day-care centres are approximately 20% per year. This increases to approximately 30% if the child is shedding virus and up to 40% if the child is also under 18 months of age.

A control group of parents whose children were not attending day-care centres showed no evidence of infection and therefore did not seroconvert.⁵

This has important implications for CMV-seronegative mothers with a child at a day-care centre who are planning or expecting another child because of the risks of acquisition of primary CMV infection and congenital CMV infection.

Day-care workers

Day-care workers also have an increased risk of acquiring CMV infection compared with the expected annual seroconversion rate of 2% per year (Table 1). This again has implications for women of child-bearing age working in this environment.¹⁰

Study	Conversion rate/year (%)	Risk ratio*
Adler ¹⁰	11.0	5.5
Murph <i>et al</i> ²³	7.9	4.0
Pass <i>et al</i> ²⁴	20.0	10.0

* Assumes expected rate of seroconversion of 2%/year

Table 1: Transmission of CMV to day-care workers – summary of cohort studies

Hospital workers

Little evidence has been found of a greater risk of acquisition of CMV in hospital workers.¹¹ Hygiene is at a standard that could not be achieved in a day-care centre or in the home, and of the proportion of patients hospitalized the number likely to be shedding CMV is small.

Sexually active individuals

Sexual transmission of CMV has been suggested as the explanation for the increase in prevalence of CMV infection with increasing age after puberty.⁴ Recurrences are associated with intermittent shedding of CMV from many sites and a number of findings indicate that CMV can be transmitted during sexual contact. In addition, increased seroprevalence and excretion of virus have been found among women attending sexually transmitted disease clinics.¹²

Populations at risk of CMV transmission by person-to-person contact

- ◆ Parents of children in day-care centres
- ◆ Day-care workers
- ◆ Sexually active populations who are CMV seronegative

Strategies for the prevention of transmission

Because the majority of primary infections with CMV are subclinical and because of the high seroprevalence in most populations, little can be done at present to prevent acquisition. Thorough cleansing after contact with bodily secretions of young children is recommended, but it is not known if this is successful or if the level of hygiene required is readily achievable in the home.

In the future, a vaccine may be available and, although it may not prevent transplacental infection, it might reduce the sequelae observed in infants born to mothers with primary infections during pregnancy to the rate observed in seropositive mothers. In the USA, this would reduce the number of children with morbidity and mortality as a result of CMV infection from approximately 8000 to 1000 per year.

Transfusion-Associated Transmission

Populations at risk

Patients at greatest risk of transfusion-acquired CMV infection are those with an immature immune system or those who are immunosuppressed. For CMV-seropositive patients receiving blood from seropositive donors, the risk of CMV infection varies from 5% to 67%, with an average of 14%. Approximately 30% of infected patients become symptomatic. In these patients, reinfection with donor CMV may cause more severe disease than reactivation of the recipients' latent virus.¹³

Infection rates with transfusion of infants are only slightly increased over those in older individuals, but with primary infection in premature babies CMV-induced disease is much more common. Between 50% and 90% of the seronegative infants develop various forms of CMV-induced diseases and mortality rates can range as high as 40%.¹³

Exactly which blood components actually harbour infectious virus in seropositive individuals and can transfer it to the recipient is not known, but development of both primary and recurrent CMV infection post-transfusion depends on the amount of blood or blood products transfused and the number of seropositive donors. A risk of 3–4% per unit of unscreened blood has been estimated.¹⁴

Strategies for the prevention of transmission

Screening

The transmission of CMV by blood transfusions can pose a serious risk to certain immunocompromised patients and, therefore, a sensitive method is needed for detection of the virus when screening blood. However, there have been inconsistencies with isolation of CMV from the blood of healthy donors, with some but not all studies, being able to isolate virus.^{15,16} There are also inconsistencies with CMV detection by the polymerase chain reaction (PCR). One study detected CMV DNA in 100% of seropositive donors as well as 50% of seronegatives.¹⁷ However, other authors failed to confirm these data.¹⁸

Ideally, susceptible individuals undergoing blood transfusion should be given blood from CMV-seronegative donors to reduce the incidence of infection. However, this cannot be done routinely in settings where the prevalence of CMV infection is very high due to an obvious shortage of donors and the costs involved. In this situation it is advisable to use blood components from seronegative donors to protect those at greatest risk from infection, such as premature infants and those who will require frequent or large volume transfusions (Table 2).

- ◆ CMV-seronegative pregnant women
- ◆ Premature infants
- ◆ Allogeneic bone marrow transplant recipients
- ◆ Individuals with advanced HIV disease
- ◆ CMV-seronegative patients receiving multiple transfusions
- ◆ CMV-seronegative cancer patients receiving high-dose chemotherapy
- ◆ CMV-seronegative burn patients
- ◆ Patients with severe combined immunodeficiency

Table 2: Populations at risk of severe disease from transfusion-associated CMV infection

Vaccination

There is considerable evidence that antibodies provide protection from CMV disease. For instance, about 85% of transplant patients with primary infection become symptomatic compared with only 20–40% of patients suffering recurrent infection.¹³ In addition, studies in mice have illustrated the importance of neutralizing antibodies in protecting mice from lethal challenge.²¹

There are several different strains of CMV, however, which present different epitopes²² and immune individuals may become re-infected with a different strain. A vaccine would therefore need to be broadly immunogenic because of the genetic disparity among different CMV strains.

If such a vaccine were to become available it would prove beneficial for a considerable number of patients, including CMV-seronegative patients undergoing transplantation, HIV-positive individuals to prevent re-infection with another CMV strain and susceptible females wishing to start a family.

Treatment of blood products

Considerable literature has accumulated indicating that leucocytes present in allogeneic cellular blood components intended for transfusion are vectors for infectious agents such as CMV.¹⁹ Although the threshold leucocyte number at which disease manifests is still to be determined, leucocyte-depleted blood is thought to be relatively safe.

Other methods include de-glycerolized frozen red cells²⁰ and, currently under investigation, inactivation with photo-active compounds. A further strategy in the prevention of blood-borne infections in general must be to restrict transfusions only to those indications that are essential for the survival of the patient.

Implications for Reactivation and Transmission of Epstein-Barr Virus

Epstein-Barr virus (EBV) infection is widespread in all areas of the world and approximately 90% of the population is infected by adulthood.¹ In more developed countries, and in individuals of higher socioeconomic status, EBV infection tends to be acquired later in life compared with individuals from developing countries or lower socioeconomic status (Figure 1).

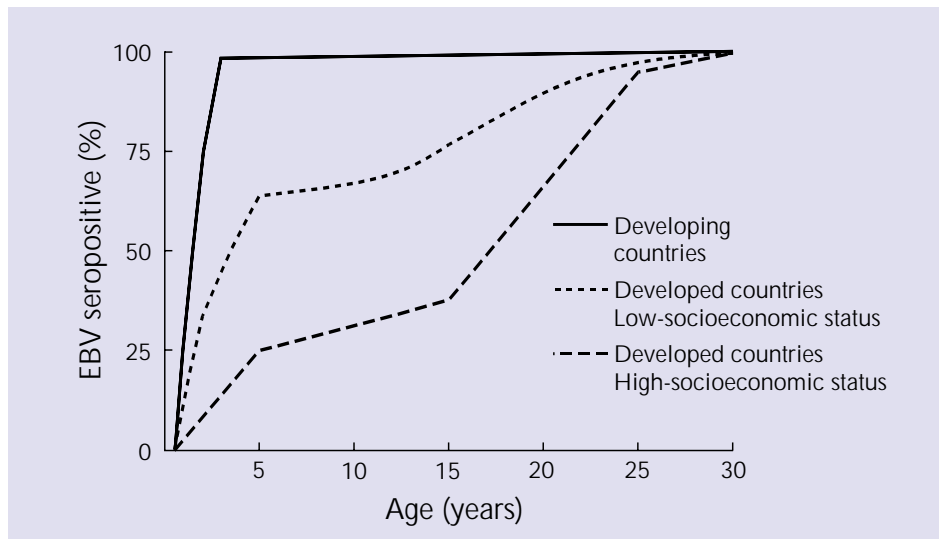


Figure 1: Seroepidemiology of EBV in developed and developing countries

Primary EBV infection usually occurs in childhood and passes unnoticed but establishes a subclinical infection in the majority of individuals. The virus is usually transmitted in saliva but in susceptible individuals blood transfusions and transplants may be the cause.¹ The oropharyngeal epithelium is the primary site of EBV infection. It is thought that lymphocytes become infected during passage through lymphatic tissue of the oropharynx in close proximity to infected epithelium.² Primary infection can manifest as infectious mononucleosis with symptoms of pharyngitis, lymphadenopathy and general malaise and fever.

Whether or not clinical symptoms occur as a result of primary infection, lymphocytes passing through the lymphatic tissue of the oropharynx become infected with EBV and it is in these cells that latency is established.

Efforts to characterize EBV latency have been facilitated by the availability of latently infected, transformed B cells, which are readily propagated in culture. This ability of the virus to cause indefinite *in vitro* proliferation of lymphocytes – a process termed immortalization – is the principal biological activity of EBV that underlies its role in the pathogenesis of lymphoproliferative diseases.

Despite the ubiquitous nature of EBV only a very small proportion of those latently infected go on to develop clinical symptoms of the diseases associated with the virus. For these individuals, disease outcome appears to be influenced by a combination of

factors, namely: the age of primary EBV infection, the immune status of the individual, as well as environmental, genetic, social and geographical factors.

Epstein-Barr Virus-Associated Lymphoproliferative Diseases

The clinical implications of EBV infection are very different from those of the other herpesviruses, as reactivation of EBV from latency may be associated with a number of lymphoproliferative diseases (Table 1).

Type of infection	Disease
Primary	Infectious mononucleosis
Chronic	Burkitt's lymphoma
	Hodgkin's disease
	Duncan's syndrome
Reactivation	Nasopharyngeal carcinoma
	Lymphomas in immunocompromised patients

Table 1: Lymphoproliferative diseases associated with EBV

Following its discovery in tumour cells from Burkitt's lymphoma biopsies, EBV has been associated with a number of other human cancers including nasopharyngeal carcinoma, Hodgkin's disease and several lymphoproliferative diseases in immunocompromised individuals. In addition, a wide variety of other diseases including chronic fatigue syndrome and autoimmune disorders have been indirectly associated with EBV, although a causal role for the virus in the pathogenesis of these conditions has not been demonstrated.

The precise role of EBV in these diseases remains unclear, but the oncogenic potential of this virus can be seen in laboratory studies where it readily infects human B lymphocytes, transforming them into permanently growing lymphoblastoid cell lines.

Infectious mononucleosis

Infectious mononucleosis occurs as the result of primary infection with EBV. When primary infection is delayed until the second decade of life or later, as is common in the industrialized world, it is accompanied by symptoms of infectious mononucleosis in about 50% of cases.³ Although generally self-limiting, infectious mononucleosis is not a trivial disease. The symptoms of malaise and lethargy may disrupt schooling for weeks or months and complications can range from mild hepatitis to haemolytic anaemia and thrombocytopenia and serious neurological disease.⁴

Burkitt's lymphoma

In sub-Saharan Africa, Burkitt's lymphoma is the most common malignancy in young children with an incidence of 8–10 cases per 100 000 people per year. The risk is greatest in equatorial Africa where there is a high incidence of malaria. A large study in Africa, which followed children for 10 years, showed that those who did develop the tumour had high levels of antibody to viral capsid antigen (VCA), a late gene

product, long before the diagnosis of Burkitt's lymphoma. This indicates that the tumour was associated with early infection by EBV followed by a long period of latency (Figure 2).⁵

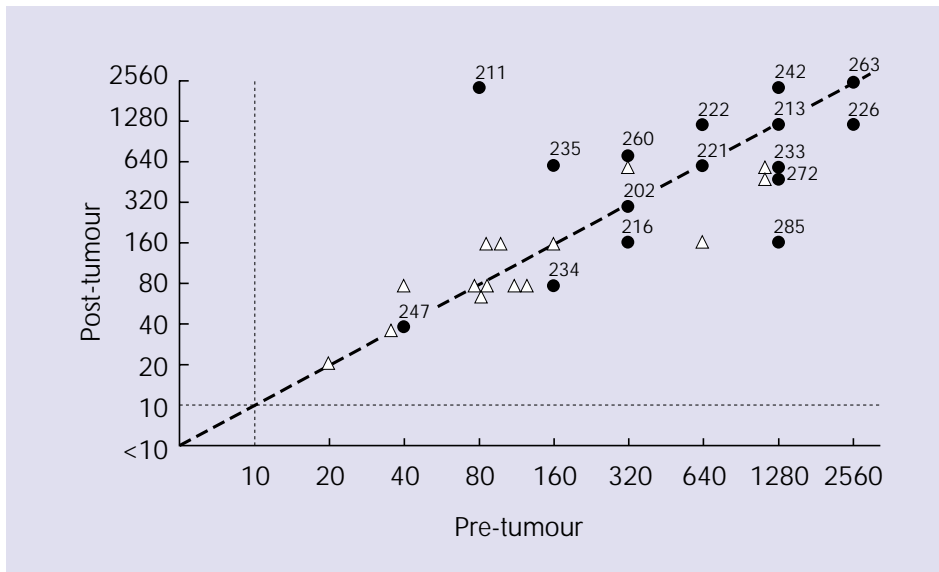


Figure 2: Levels of antibody to VCA both pre- and post-tumour

Burkitt's lymphoma is therefore thought to result from an early EBV infection which produces a large pool of infected B lymphocytes. Malarial infection may further increase the size of this pool because of its mitogenic properties and its ability to reduce EBV-specific T cell immunity. The subsequent chromosome translocation associated with Burkitt's lymphoma, which results in oncogene activation, may occur by chance; the large pool of B cells increasing the likelihood of it taking place.

Hodgkin's disease

Hodgkin's disease is seen worldwide, but is particularly prevalent in the Western world, where it is the most common malignant lymphoma. An association between EBV infection and Hodgkin's disease, a B cell lymphoma, was first suggested by serological studies. Subsequently, analysis of tumour tissue from Hodgkin's patients showed the presence of EBV DNA, RNA and protein in 20–40% of cases. It has been suggested that those individuals who show clinical manifestations of acute infectious mononucleosis have a three- to four-fold increased risk of developing Hodgkin's disease.⁶

Duncan's syndrome

Duncan's syndrome or X-linked lymphoproliferative disorder is an immunodeficiency syndrome associated with high mortality, usually due to fatal infectious mononucleosis or malignant lymphoma.⁷ The syndrome is characterized by a deficient antibody response to EBV-specific antigens, which probably reflects a T-cell deficiency.⁸ Allogeneic bone marrow transplantation has been shown to correct the syndrome, suggesting that the abnormality is in bone-marrow derived cells.⁹

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is endemic in Southern China where it results in approximately 25% of the mortality from cancer. The association of EBV with this

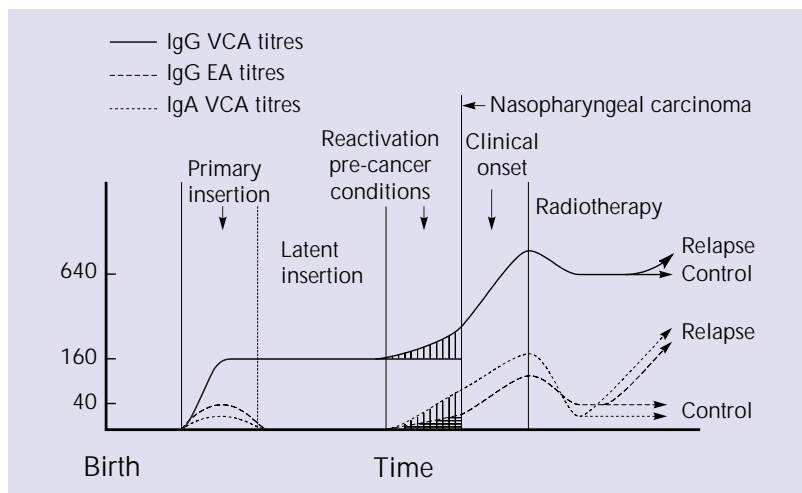


Figure 3: Use of serological screening for early detection of NPC

epithelial cell malignancy is constant and serological screening for increased IgA antibody levels to both VCA and early EBV antigens, which signal reactivation from latency, can be used for early diagnostic purposes (Figure 3).¹⁰

A study which followed 20 000 people for 10 years indicated that in almost 90% of cases NPC could be detected in its early stages and a simple course of radiotherapy resulted in a complete cure.¹¹

The high incidence of NPC among southern Chinese suggests that genetic or environmental factors in addition to EBV may also be important in the pathogenesis of the disease. In families with multiple cases of NPC among siblings it has been estimated that the risk of developing the carcinoma is increased by approximately 21%. This would suggest the existence of a disease susceptibility gene, inherent to individual families. Certain major histocompatibility complex (MHC) class I alleles have been associated with an increased risk of developing NPC, although this genetic susceptibility is based on familial rather than population studies.¹²

In southern China, studies have shown that nitrosamines found in salted fish are associated with a high incidence of disease.¹³ Another high-risk population is in Tunisia, where a food extract found in traditional harissa – the most used condiment in that area of the world – has been found to activate the BZLF-1 gene, which triggers EBV reactivation from latency.

It is currently thought that environmental carcinogens probably create the pre-cancerous conditions which then stimulate the virus to reactivate. A strong immune response results, which can be detected by serological screening, and the host can then either reject the pre-neoplastic condition or go on to develop NPC.

Lymphoproliferative disease in immunocompromised patients

A high percentage of post-transplant lymphoproliferative disorders are EBV-associated, the risk increasing following primary EBV infection. The incidence of lymphomas is reported as 1–2% following renal transplant and 5–9% following heart–lung transplant. In individuals with AIDS, lymphoproliferative disease develops in about 5–13% of patients, of which about 50% are EBV-associated. These malignancies are usually the result of reactivation, as the majority of the population is infected in childhood. The reversal of some transplant-related lymphoproliferation after a reduction in immunosuppressive therapy emphasizes the role of the immune system in controlling EBV infection in the normal host.¹⁴

Strategies for the Control of Epstein-Barr Virus-Associated Lymphoproliferative Diseases

Serological screening

In general, reactivation of EBV infection is defined by elevated antibody titres to VCA IgF, early EBV antigen (EA)-D (EA-R in cases of Burkitt's lymphoma), and the pre-existence of anti-EBV nuclear antigen (EBNA) IgG antibodies.¹⁵ A past EBV infection is identified by the absence of anti-VCA IgM antibodies and presence of IgG antibodies against both VCA and EBNA (Table 2).¹⁵

Disease condition	Antibodies								
	VCA			EA-D		EA-R	EBNA	EBNA Heterophil	
	IgM	IgG	IgA	IgG	IgA	(IgG)	(IgG)	(IgM)	(IgM)
Not infected	-	-	-	-	-	-	-	-	-
Silent primary infection	+	+	-	±	-	-	±	+	
Past infection	-	+	-	±	-	-	+	±	-
Reactivation with immunodeficiency	±	++	±	++	±	±	±	±	±
Infectious mononucleosis	+	++	-	+	-	±	-	±	+
Burkitt's lymphoma	-	++	-	±	-	++	+	ND	-
Nasopharyngeal carcinoma	-	++	+	++	+	-	+	ND	-

++ Elevated antibodies. + Positive antibodies. - Negative antibodies. ND: No data.

Table 2: Serological patterns of EBV antibodies in patients with EBV-associated diseases

Serological screening of populations at risk of NPC is a valuable strategy for early detection of this cancer. Elevation of IgA antibodies to VCA and EA has been linked to a 20–25% risk of developing a tumour and can also help predict the stage of clinical disease as tumour mass directly correlates with seroantibody levels. In the majority of cases early intervention with radiotherapy will then cure NPC. An IgA test may also be useful in detecting subclinical relapse, since elevated IgA levels can be detected up to 18 months before onset of the clinical symptoms. In a 10-year study of 1000 IgA-positive individuals without nasopharyngeal lesions, those who lost the IgA marker lost the risk of tumour development.

The possibility of using this technique for the detection of other lymphoproliferative diseases associated with reactivation of EBV at the subclinical stage, such as those in the immunocompromised, should now be investigated; particularly since a high percentage of post-transplant and HIV-related lymphoproliferative disorders are EBV associated.

Vaccines

There are two relevant issues when considering the development of an EBV vaccine. First, in Western societies, where the aim of vaccination would be to prevent the symptoms of infectious mononucleosis, it may not be imperative to induce sterile immunity or prevent the establishment of a latent EBV infection, because a reduction

in the EBV load during primary infection may avert clinical symptoms. On the other hand, any vaccine which aims to prevent Burkitt's lymphoma, NPC or Hodgkin's disease must be capable of preventing the establishment of a latent EBV infection, as all of these malignancies develop years after the primary infection with the virus. Development of a prophylactic vaccine to protect against EBV infection may not be feasible but a therapeutic vaccine which could be given to those individuals already infected could prevent development of clinical symptoms. Although there are several malignant diseases that could be amenable to an EBV vaccine, progress in this area has been relatively slow. However, an experimental subunit vaccine of the EBV major envelope glycoprotein, gp350, is in development.

Although it seems unlikely that a vaccine based solely on gp350 will be completely effective in preventing infection of every single epithelial or B-cell, such a vaccine could have the potential to reduce significantly the load of infectious virus and thus limit the long-lived EBV-positive B-cell pool.

For prevention of Burkitt's lymphoma, the target population for a vaccine trial would be newborn infants living in sub-Saharan Africa. Although theoretically feasible, this would be an extremely difficult logistical undertaking and there are many other more foreboding health problems affecting the population in this area.

In populations at high risk of NPC, initial exposure to EBV again occurs early in life and, because of the long latent period before the virus reactivates, the design of an appropriate vaccine trial would be difficult. However, the use of a therapeutic vaccine (to reduce IgA levels and boost IgG), which could be administered at the time of IgA testing, would be a feasible approach. The endemic nature of EBV-associated malignancies in certain areas of the world and the benefits that could be gained from the development of an appropriate vaccine should ensure continued research in this area.

Antiviral chemotherapy

The use of antiviral chemotherapy for the treatment of EBV infections is restricted because the clinical symptoms of EBV-associated disease generally become evident a long time after primary infection. In addition, it has also been suggested that the clinical symptoms may be associated with an EBV-induced polyclonal humoral response with only limited pathology caused by virus replication.

Nucleoside analogues, such as aciclovir and ganciclovir, are effective against oropharyngeal EBV replication. In clinical trials, however, aciclovir alone appears to have only a marginal clinical benefit on the severity or duration of EBV disease.^{4,16} A combination of intravenous aciclovir and prednisolone has been tried for severe cases of infectious mononucleosis and demonstrated a reduction in the duration of clinical symptoms such as fever and an improvement in general health.¹⁶ Virological assessments of oropharyngeal shedding suggested that aciclovir in combination with prednisolone inhibited oropharyngeal EBV shedding to the same extent as aciclovir therapy alone. Preliminary results from other studies suggest that oral aciclovir (800 mg five times daily for 10 days) in combination with prednisolone may have a beneficial effect on upper respiratory obstruction and clinical symptoms induced by the formation of autoantibodies, the predominant cause of cytopenia in infectious mononucleosis. Prophylactic antiviral therapy for reduction of lymphoproliferative disorders has not been evaluated.

Clinical Implications for Human Herpesviruses Types 6, 7 and 8

The past decade has seen the discovery of three new human herpesviruses: types 6, 7 and 8 (HHV-6, HHV-7 and HHV-8), and as yet information on their epidemiology is incomplete. As a result, there has been much speculation in the literature about the role of these viruses in disease. The following chapter reviews the evidence on these disease associations and indicates where there are likely to be causal relationships.

Human Herpesvirus Type 6

Natural history

HHV-6 was first isolated in 1986 from peripheral blood mononuclear cells of patients with lymphoproliferative disorders and subsequently named human B-lymphotropic virus (HBLV).¹ Electron microscopy of HBLV revealed morphological features consistent with a herpesvirus classification; although serological studies demonstrated a lack of immunological cross-reactivity with the other known human herpesviruses (herpes simplex virus [HSV], cytomegalovirus [CMV], varicella zoster virus [VZV] and Epstein-Barr virus [EBV]).¹ Analyses of HBLV genomes led to the conclusion that this herpesvirus was distinct from other previously characterized human herpesviruses and it was designated HHV-6.² HHV-6 has now been classified into two distinct variants, 6A and 6B, based on molecular and immunological techniques using restriction enzymes, polymerase chain reaction (PCR) and specific monoclonal antibodies. It is not yet clear whether HHV-6A causes any disease and at present no adequate method exists to differentiate antibodies to the two HHV-6 variants.³

It has been postulated that HHV-6 can persist in healthy individuals in a latent state.⁴ The potential of HHV-6 to become latent and to reactivate has been suggested by reports of increases in antibody levels during concurrent illnesses and by recovery of virus from blood and respiratory secretions in previously infected immunocompromised patients.⁵ Although the molecular biology of HHV-6 latency is not known it appears to have some similarities to CMV and has been detected in circulating mononuclear cells, saliva and brain. HHV-6 has also been detected in the cerebrospinal fluid of children under 3 years old both during and after primary infection, and it has been suggested that the central nervous system may be the site of persistent or latent HHV-6 infection.⁶

Although HHV-6 was initially recovered from immunocompromised adults,¹ subsequent reports from Japan have shown that primary infection occurs early in childhood, predominantly as *exanthem subitum*.^{7,8} It has been reported that 92% of adults excrete HHV-6 in their saliva and therefore the most likely route of infection in young children is by contact with infected secretions following a decline in maternal antibody levels.^{9,10} Infection may also be acquired by intra-uterine or perinatal transmission from the mother. The level of maternal antibody may influence the degree and duration of protection and therefore the age at which infection occurs (Figure 1).¹¹

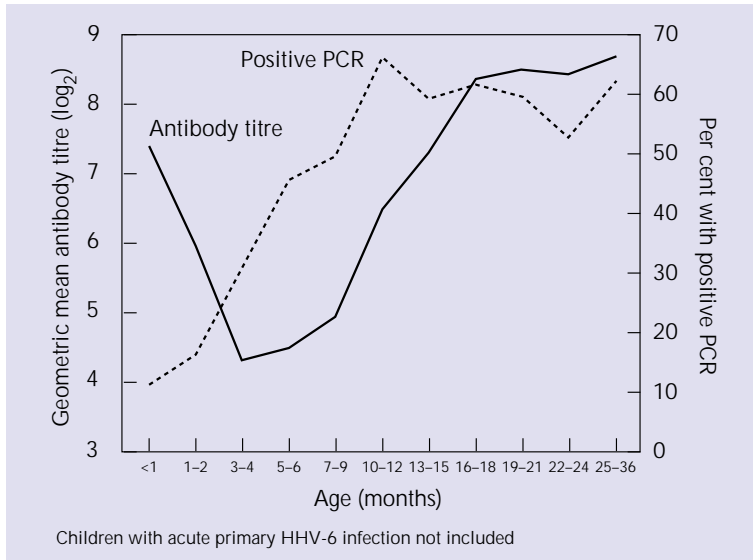


Figure 1: Geometric mean antibody titres to HHV-6 in 2427 children and the proportion in whom the HHV-6 genome was detected in peripheral blood mononuclear cells by PCR, according to age



Figure 2: Typical rash during exanthem subitum

HHV-6-associated diseases

Exanthem subitum (roseola infantum)

Exanthem subitum is a common childhood illness usually characterized by fever and the appearance of a rash (Figure 2). Symptoms are usually mild, but febrile convulsions have been reported. Since blood-borne transmission of this infection was first documented in the 1950s,¹² it has been widely believed that the disease was caused by a virus. In 1988, Yamanishi and colleagues successfully cultured a virus isolated from peripheral blood lymphocytes of children with *exanthem subitum* and showed the virus to be antigenically related to HHV-6.⁸ Their

results strongly suggested that the newly isolated virus was identical or closely related to HHV-6 and the causal agent of *exanthem subitum*.⁸ HHV-6 samples isolated from children with *exanthem subitum* have subsequently been shown to be of the HHV-6B subtype.

Acute febrile illness

A large 3-year prospective study in the USA of children under 3 years of age has established HHV-6 as an important cause of undifferentiated febrile illness in children. The study evaluated both normal children and those presenting with acute illnesses in a hospital emergency room for HHV-6 infection. Of the 1653 children with acute febrile illness, approximately 10% had primary HHV-6 infection, whereas none of the 582 children with acute non-febrile illness or the 352 without acute illness had primary HHV-6 infection. These results demonstrate a strong association between acute febrile illness and HHV-6, which appears to be responsible for

approximately one-third of all febrile fits within this population.¹³

Association with other diseases

HHV-6 infection has also been implicated in some cases of severe hepatitis, meningoencephalitis, lymphadenopathy and mononucleosis (Table 1).¹⁴⁻²⁰ However, it is not clear whether these diseases are due to primary infection with HHV-6 or a result of reactivation. An association of HHV-6 with the pathogenesis of multiple sclerosis has also been suggested.²¹

Cases of reactivation or re-infection with HHV-6 have been reported after kidney,²² liver²³ and bone marrow transplants.^{24,25} HHV-6 viraemia is observed more frequently

- Meningitis
- Encephalitis
- Lymphadenopathy
- Mononucleosis
- Hepatitis
- Pneumonitis
- Suppression of marrow function

Table 1: Conditions associated with HHV-6 infection

after bone marrow than renal transplants, suggesting that replication of HHV-6 is associated with the degree of immunosuppression. HHV-6 has also been implicated in graft failure and meningoencephalitis after bone marrow transplantation²⁶ and as a novel cause of marrow suppression.²⁷ To determine the pathogenic role of HHV-6 in this patient cohort the clinical courses of 16 adults following allogeneic bone marrow transplantation were examined. It was suggested that HHV-6 may persist in the stromal cells of the bone marrow and mediate cytokine release, thereby creating an unfavourable environment for haematopoiesis.²⁷

Treatment

To date, there have been few studies reporting on the responses of HHV-6 to antiviral agents. However, the susceptibility of HHV-6 to aciclovir, ganciclovir and foscarnet has been investigated *in vitro*.^{28,29} HHV-6 displayed greatest sensitivity to ganciclovir and foscarnet (Figure 3), but a study of HHV-6 infection in bone marrow transplant recipients has shown that aciclovir-treated patients had lower levels of HHV-6 DNA than patients who did not receive aciclovir.³⁰

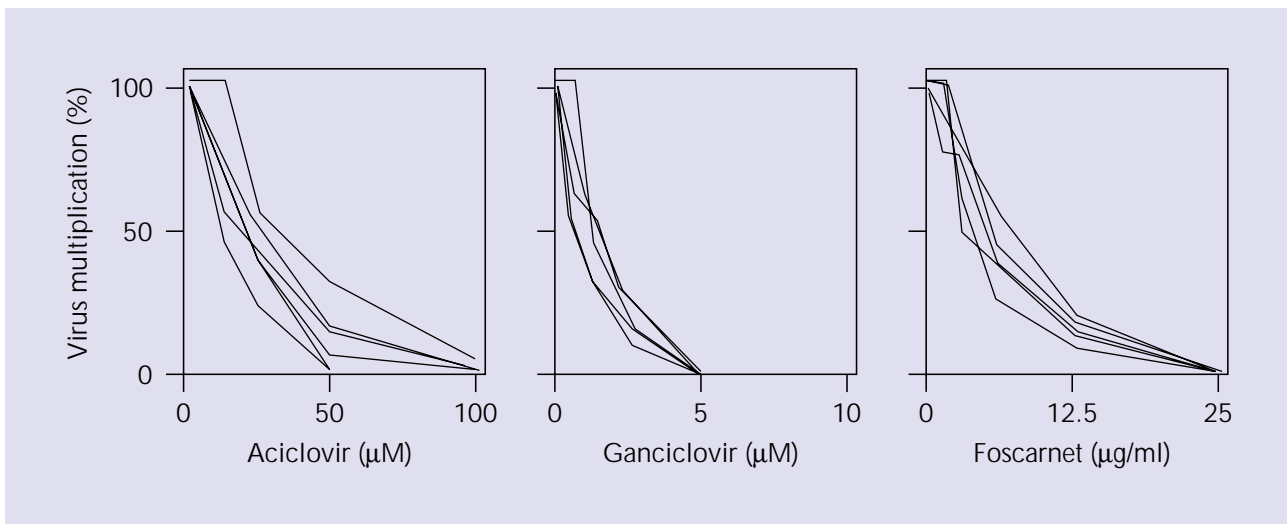


Figure 3: Inhibition of HHV-6 multiplication by antivirals. Infection with seven distinct HHV-6 strains was performed in the presence of various concentrations of aciclovir, ganciclovir and foscarnet²⁹

With the increasing amount of evidence implicating HHV-6 as a causal agent for a number of clinical conditions, there is clearly a need to conduct clinical trials on the effectiveness of new and existing antivirals. These could be instigated in paediatric populations with febrile fits or severe *exanthem subitum*, for example, with a suitably non-genotoxic antiviral such as aciclovir or valaciclovir. Furthermore, any clinical benefit provided by these drugs would indirectly imply that HHV-6 was the cause of these conditions.

Human Herpesvirus Type 7

Natural history

HHV-7 was isolated in 1990 from CD4+ T lymphocytes of a healthy individual.³¹ Examination of the purified CD4+ cells by electron microscopy revealed the characteristic herpesvirus structure. DNA hybridization showed no cross-reactivity with existing human herpesviruses and only limited cross-reactivity with HHV-6. The new virus was subsequently named HHV-7.

A further study conducted to determine whether HHV-6 and HHV-7 produce cross-reacting antibodies found that the two viruses appear to be antigenically distinct.³² Analysis of sera in this study revealed that seroconversion to HHV-6 was not associated with a parallel increase in anti-HHV-7 antibody titres. In some instances, HHV-7 infection occurred in the presence of high titres of HHV-6 antibodies, indicating a lack of protection in children seropositive for HHV-6 against subsequent infection with HHV-7.

Seroepidemiological data suggest that HHV-7 infection occurs later in childhood than HHV-6 (Figure 4).^{33,34} In one study, there was no detectable antibody before 2 years of age.⁸

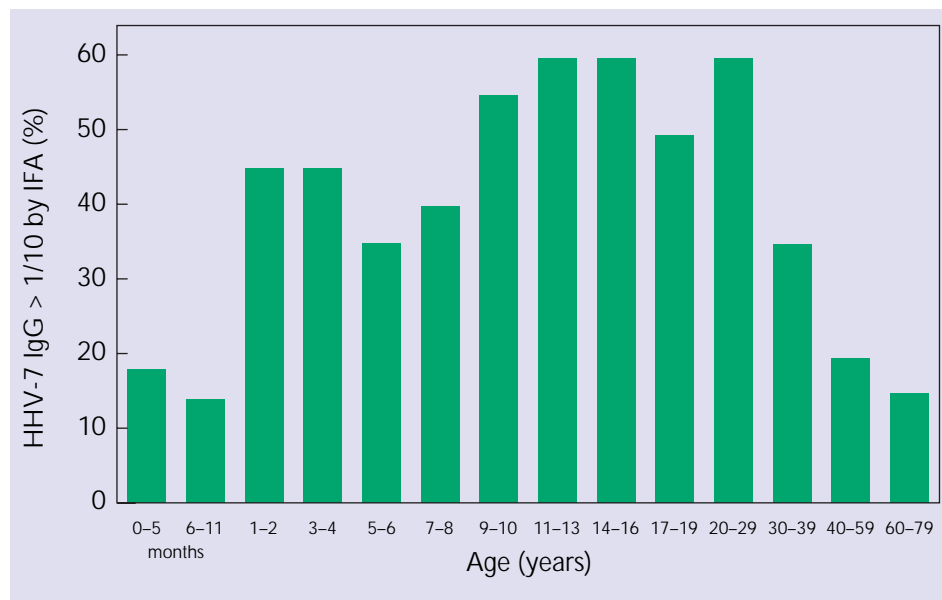


Figure 4: Seroepidemiology of HHV-7 in healthy children and adults in Japan, measured by positive antibody titres to HHV-7 (HHV-7 IgG > 1/10) by immunofluorescence assay (IFA)³³

The mode of transmission of HHV-7 has not yet been documented although several investigators have reported that the virus can frequently be isolated from the saliva of healthy adults.³⁵⁻³⁷ It is possible that the virus is transmitted by the same route of infection as HHV-6. Interestingly, antibody titres to HHV-6 are boosted during HHV-7 infection and it has been suggested that primary infection with HHV-7 may reactivate latent HHV-6.^{34,38}

HHV-7-associated diseases

Exanthem subitum

To date, there is very little evidence in the literature implicating a role of HHV-7 in disease, although a recent study has reported a causal role for HHV-7 in *exanthem*

subitum.³⁴ Out of a total of 24 HHV-7-seronegative children who were followed for up to 25 months, 17 seroconverted to HHV-7 and eight (47.1%) had *exanthem subitum* around the time of their seroconversion.³⁴

HHV-7 and HIV

HHV-6 and HHV-7 primarily infect T lymphocytes.³¹ CD4 is an essential component of the cellular membrane receptor for HHV-7 and a marked reciprocal interference between HHV-7 and HIV, which also uses CD4 as a receptor, has been observed.³⁹ It will be interesting to investigate whether active infection with HHV-7 influences the natural history of HIV infection *in vivo* either as an effective natural inhibitor of HIV infection or by enhancing its cytopathic effects, as has been suggested for HHV-6.⁴⁰

Human Herpesvirus Type 8

Natural history

Unlike HHV-6 and HHV-7, with Kaposi's sarcoma-associated herpesvirus (KSHV) or HHV-8, it was the case of a disease searching for a virus rather than a virus in search of a disease. Epidemiological studies had long suggested that Kaposi's sarcoma was caused by a sexually transmitted agent and the coincident increase in the disease with AIDS reinforced this notion. With the AIDS epidemic, the epidemiology of Kaposi's sarcoma changed drastically and is now primarily found in homosexual men with AIDS, among whom the risk has increased to 100 000 times compared with the general population. Specific behaviours linked to homosexual men have been sought to explain this relationship, but accumulating evidence favoured the involvement of an infectious agent in the aetiology of Kaposi's sarcoma.

The virus was discovered in 1994 by isolation of viral DNA sequences from an AIDS-associated Kaposi's sarcoma lesion using a technique known as representational difference analysis.⁴¹ Further studies showed the DNA sequences to be present in over 90% of AIDS-associated Kaposi's lesions examined. Using these subgenomic sequences, HHV-8 was subsequently detected in stably infected immortalized B cell lines which allowed initial virological characterization studies to be performed. The recent isolation of lytic virus should allow the development of serological tests which would prove invaluable for epidemiological studies.⁴² Following phylogenetic analysis the virus was assigned to the gamma herpesvirus subfamily along with EBV.⁴¹

HHV-8-associated diseases

Kaposi's sarcoma

The role of herpesviruses in the development of Kaposi's sarcoma has been the subject of much debate. Kaposi's sarcoma is the most common AIDS-related cancer, occurring in approximately 15–20% of individuals with AIDS.⁴³ The disease is characterized by disfiguring blotches on the skin and very rapid disease progression.

Several lines of evidence now reflect a strong association between HHV-8 and Kaposi's sarcoma (Table 2). In addition to AIDS-associated Kaposi's lesions, HHV-8 has been detected in all clinical/epidemiological subtypes of the disease, including classic, African endemic and post-transplant Kaposi's sarcoma.

Type of Kaposi's sarcoma	PCR results (number positive/number tested)	
	Kaposi's sarcoma	Autologous skin
Epidemic (HIV-positive individuals) ^{41,48-52}	72/75	7/24
Epidemic (HIV-negative individuals) ^{50,51}	5/5	1/2
Classic (elderly) ⁵⁰⁻⁵²	32/33	3/11
Endemic (African) ^{48,49}	15/19	5/5
Iatrogenic (transplant patients) ^{51,52}	9/9	0/1
TOTALS ($P < 0.001$)	113/141 (94%)	16/43 (37%)

Table 2: Detection of HHV-8 by PCR in Kaposi's sarcoma tissue versus skin biopsies not clinically involved with Kaposi's sarcoma

Further evidence for a causal role of HHV-8 in Kaposi's sarcoma has come from studies demonstrating HHV-8 DNA sequences in peripheral blood mononuclear cells of individuals with AIDS by PCR. The sequences were found in 24/46 (52%) of patients with Kaposi's sarcoma and detection increased with immunosuppression correlating with a reduced number of CD4 cells.⁴⁴ Moreover, HHV-8 detection in peripheral blood cells of HIV-infected individuals without Kaposi's sarcoma predicted the subsequent appearance of lesions.⁴⁴ This demonstration that infection precedes development of disease supports a causal role for HHV-8 in Kaposi's sarcoma.

B-cell lymphomas

HHV-8 has also been detected by PCR in an unusual subgroup of AIDS-related B-cell lymphomas.⁴⁵ The consistent presence of HHV-8 in these lymphomas suggests that the virus may play a role in their development.

Association with other diseases

Recent evidence suggests that HHV-8 may also be associated with lesions other than Kaposi's sarcoma in individuals with immunodeficiency not due to AIDS. A total of 33 skin lesions (including basal cell carcinomas, squamous cell carcinomas, actinic keratoses, verruca vulgaris, atypical squamous proliferations and seborrhoeic keratosis) from four organ transplant patients receiving immunosuppressive therapy were tested for HHV-8 by PCR.⁴⁶ HHV-8 was detected in 82% of these skin lesions. It is possible that the virus may also be involved in the pathogenesis of the various forms of proliferative skin lesions seen in organ transplant patients, although cross-contamination of the PCR reactions must be excluded.⁴⁶

Whether the finding of HHV-8 in peripheral blood can be a prognostic sign or pose a problem in blood transfusions requires further evaluation. However, Kaposi's sarcoma has not been frequently associated with transfusions.⁴⁷

Summary and Recommendations

The following guidelines for the management of cytomegalovirus infections (in terms of transmission) and summaries of the clinical implications for Epstein-Barr virus and the more recently discovered human herpesviruses types 6, 7 and 8 have been prepared following the IHMF workshop of 3–4 April 1995 and the 3rd Annual Meeting of the IHMF, held in Istanbul, 17–20 November 1995.

Implications for Transmission of Cytomegalovirus

While cytomegalovirus (CMV) infection is generally without consequences in the immunocompetent individual, it can be particularly severe in the neonate and in the immunocompromised host.

Person-to-person transmission

Newborns infected with CMV usually acquire the virus as a result of infected cervical secretions in the birth canal or in the breast-milk. Because these children can then secrete virus for periods of up to 5 years, a particularly high rate of transmission of CMV has been found between children at day-care centres. If a mother of one of these children is seronegative and plans to have another child there is an increased risk of her seroconverting during pregnancy and of the neonate acquiring congenital CMV infection. Pregnant day-care staff are also at risk of transmission.

Little can be done at present to reduce these risks other than educating physicians, parents and day-care staff about the possibility of CMV infection. Physicians need to be able to counsel women about the sources of CMV infection and the risk to the fetus if the mother acquires primary CMV infection during pregnancy. It is recommended that women should be able to obtain up-to-date information from their physician on the risks of CMV infection during pregnancy. Such information may include: sources of maternal CMV infection, risk to the fetus and means of prevention. Institutions such as day-care centres and schools should also be provided with relevant information to develop policies, e.g. written guidelines on thorough cleansing after contact with body fluids, which can be followed in an attempt to limit transmission within these higher risk environments. Screening of all pregnant women and day-care staff is not recommended and probably not feasible. Serological testing accompanied by appropriate counselling may be useful for individual patients concerned about their risk of acquiring CMV infection.

In the future a CMV vaccine may be offered to women at risk. Until such a vaccine becomes available, educational efforts and stricter hygiene are considered the best approaches to limiting transmission. It is worth noting, however, that these approaches lack proven efficacy and do not address the possibility of congenital infection from reactivation or re-infection in women who have been infected with CMV in the past.

Transfusion-associated transmission

The transmission of CMV by blood transfusion can have serious consequences in susceptible individuals and is a frequent cause of disease. It is therefore desirable to

limit the use of blood transfusions in these patients wherever possible. To protect patients at greatest risk of infection, e.g. premature babies and seronegative individuals, it is advisable to use blood components from seronegative donors. However, this is not always possible where a large proportion of the population is infected with CMV and because of inconsistencies in screening. Other strategies to reduce transmission via blood transfusion are therefore being evaluated such as those which involve treatment of blood products.

The removal of blood leucocytes by filtration has been used with some success, although the efficacy of this method may not be consistent for all blood products and published data on the use of blood filtration to prevent transfusion-associated transmission of CMV in immunocompromised patients are limited.

Implications for Reactivation and Transmission of Epstein-Barr Virus

Unlike the other herpesviruses, Epstein-Barr virus (EBV) is linked to a number of lymphoproliferative diseases which are associated with the ability of the virus to immortalize B lymphocytes.

Malignancies associated with reactivation of the virus from a latent state include nasopharyngeal carcinoma (NPC) and most of the lymphomas found in immunocompromised patients.

In certain areas of the world NPC is endemic and responsible for a large proportion of the cancer deaths. However, the association of EBV reactivation with this carcinoma is so constant that routine serological screening for increased antibody levels can be used for diagnostic purposes, thus allowing early intervention. Other factors determining at-risk individuals include genetic and environmental factors.

Although a vaccine is not currently available, it is conceivable that several malignant diseases associated with EBV may be avoided if primary infection could be prevented. However, because the majority of populations are infected early in life, it may be difficult to design appropriate trials. In the future a therapeutic vaccine could be considered for use in association with serological screening for NPC.

Primary EBV infection in the adolescent or adult immunocompetent host varies in its duration and severity. Although antiviral drugs such as aciclovir and ganciclovir are effective against oropharyngeal EBV replication they appear to have only marginal clinical benefit on the severity or duration of primary EBV disease. In addition, clinical symptoms associated with EBV reactivation generally become evident a long time after primary infection. These factors have restricted the use of antiviral therapy for the treatment of EBV.

Clinical Implications for Human Herpesviruses Types 6, 7 and 8

With the introduction of more sensitive and rapid diagnostic methods the three latest members of the human herpesvirus family have all been linked to a disease. Human

herpesvirus type 6 and 7 (HHV-6 and HHV-7) appear widespread in the population and have been shown to be aetiological agents in the development of a usually mild childhood illness, *exanthem subitum*. In the immunocompromised the situation is less clear but reactivation appears to be associated with the degree of immunosuppression as a higher frequency of HHV-6 viraemia is observed after bone marrow compared with renal transplantation.

Human herpesvirus type 8 (HHV-8) was originally isolated from AIDS-associated Kaposi's sarcoma tissue and a large body of evidence now suggests that HHV-8 has a causal role in this disease. HHV-8 does not appear to be widespread in the general population and it is possible that it may be sexually transmitted as AIDS-associated Kaposi's sarcoma is primarily found in homosexual men. Whether this virus plays a role in the pathogenesis of other diseases in the immunocompetent or immunocompromised host has not been established.

Information on the epidemiology of these relatively recently discovered herpesviruses is accruing rapidly but is a long way from being complete and will require an understanding of the pathogenesis of disease in different patient groups. As yet there are no set guidelines for management of patients with these infections, but as HHV-6, HHV-7 and HHV-8 become causally linked to an increasing number of different diseases there is clearly a need for clinical trials to be conducted on the effectiveness of new and existing antivirals.

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