CHAPTER 33

Herpesviruses

The herpesvirus family contains several of the most important human viral pathogens. Clinically, the herpesviruses exhibit a spectrum of diseases. Some have a wide host-cell range, and others have a narrow host-cell range. The outstanding property of herpesviruses is their ability to establish lifelong persistent infections in their hosts and to undergo periodic reactivation. Their frequent reactivation in immunosuppressed patients causes serious health complications. Curiously, the reactivated infection may be clinically quite different from the disease caused by the primary infection. Herpesviruses possess a large number of genes, some of which have proved to be susceptible to antiviral chemotherapy.

The herpesviruses that commonly infect humans include herpes simplex virus types 1 and 2 (HSV-1, HSV-2), varicella-zoster virus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpesviruses 6 and 7, and herpesvirus 8 (Kaposi sarcoma-associated herpesvirus [KSHV]). Herpes B virus of monkeys can also infect humans. There are nearly 100 viruses of the herpes group that infect many different animal species.

PROPERTIES OF HERPESVIRUSES

Important properties of herpesviruses are summarized in Table 33-1.

TABLE 33-1 Important Properties of Herpesviruses

Virion: Spherical, 150–200 nm in diameter (icosahedral)
Genome: Double-stranded DNA, linear, 125–240 kbp, reiterated sequences
Proteins: More than 35 proteins in virion
Envelope: Contains viral glycoproteins, Fc receptors
Replication: Nucleus, bud from nuclear membrane
Outstanding characteristics:
Encode many enzymes
Establish latent infections
Persist indefinitely in infected hosts
Frequently reactivated in immunosuppressed hosts
Some cause cancer

Structure and Composition

Herpesviruses are large viruses. Different members of the group share architectural details and are indistinguishable by electron microscopy. All herpesviruses have a core of double-stranded DNA, in the form of a toroid, surrounded by a protein coat that exhibits icosahedral symmetry and has 162 capsomeres. The nucleocapsid is surrounded by an envelope that is derived from the nuclear membrane of the infected cell and contains viral glycoprotein spikes about 8 nm long. An amorphous, sometimes asymmetric structure between the capsid and envelope is designated the tegument. The enveloped form measures 150–200 nm; the "naked" virion, 125 nm.

The double-stranded DNA genome (125–240 kbp) is linear. A striking feature of herpesvirus DNAs is their sequence arrangement (Figure 33-1). Herpesvirus genomes possess terminal and internal repeated sequences. Some members, such as the HSVs, undergo genome rearrangements, giving rise to different genome "isomers." The base composition of herpesvirus DNAs varies from 31% to 75% (G + C). There is little DNA homology among different herpesviruses except for HSV-1 and HSV-2, which show 50% sequence homology, and human herpesviruses 6 and 7 (HHV-6 and HHV-7), which display limited (30–50%) sequence homology. Treatment with restriction endonucleases yields characteristically different cleavage patterns for herpesviruses and even for different strains of each type. This "fingerprinting" of strains allows epidemiologic tracing of a given strain.

The herpesvirus genome is large and encodes at least 100 different proteins. Of these, more than 35 polypeptides are involved in the structure of the virus particle; at least 10 are part of the viral envelope. Herpesviruses encode an array of virus-specific enzymes involved in nucleic acid metabolism, DNA synthesis, gene expression, and protein regulation (DNA polymerase, helicase-primase, thymidine kinase, transcription factors, protein kinases). Many herpesvirus genes appear to be viral homologs of cellular genes.

Classification

Classification of the numerous members of the herpesvirus family is complicated. A useful division into subfamilies

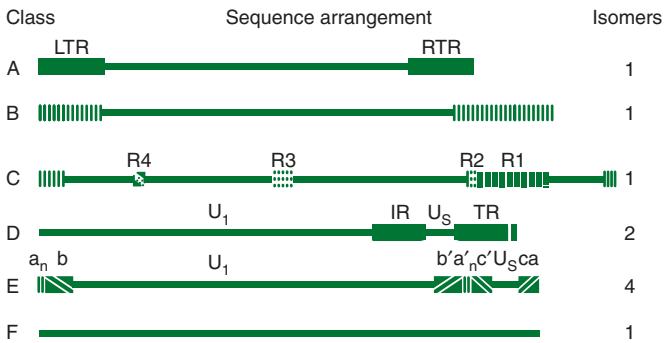


FIGURE 33-1 Schematic diagram of sequence arrangements of herpesvirus DNAs. Genome classes A, B, C, D, E, and F are exemplified by channel catfish virus, herpesvirus saimiri, Epstein-Barr virus, varicella-zoster virus, herpes simplex viruses, and tupaia herpesvirus, respectively. *Horizontal lines* represent unique regions. Reiterated domains are shown as *rectangles*: left and right terminal repeats (LTR and RTR) for class A; repeats R1–R4 for internal repeats of class C; and internal and terminal repeats (IR and TR) of class D. In class B, terminal sequences are reiterated numerous times at both termini. The termini of class E consist of two elements. The terminal sequences (ab and ca) are inserted in an inverted orientation separating the unique sequences into long (U_l) and short (U_s) domains. Genomes of class F have no terminal reiterations. The components of the genomes in classes D and E invert. In class D (varicella-zoster virus), the short component inverts relative to the long, and the DNA forms two populations (isomers) differing in the orientation of the short component. In class E (herpes simplex virus), both the short and long components can invert, and viral DNA consists of four isomers. (Reproduced with permission from Roizman B: Herpesviridae: A brief introduction. In Fields BN, Knipe DM [editors-in-chief]. *Virology*, 2nd ed. Raven Press, 1990, pp. 1787–1793.)

is based on biologic properties of the agents (Table 33-2). Alphaherpesviruses are fast-growing, cytolytic viruses that tend to establish latent infections in neurons; HSV (genus *Simplexvirus*) and varicella-zoster virus (genus *Varicellovirus*) are members. Betaherpesviruses are slow growing and may be cytomegalic (massive enlargements of infected cells) and become latent in secretory glands and kidneys; CMV is classified in the *Cytomegalovirus* genus. Also included here, in the genus *Roseolovirus*, are HHV-6 and HHV-7; by biologic criteria, they are similar to gammaherpesviruses because they infect lymphocytes (T lymphotropic), but molecular analyses of their genomes reveal that they are more closely related to the betaherpesviruses. Gammaherpesviruses, exemplified by EBV (genus *Lymphocryptovirus*), infect and become latent in lymphoid cells. KSHV, designated as HHV-8, is classified in the *Rhadinovirus* genus.

Many herpesviruses infect animals, the most notable being B virus (herpesvirus simiae or cercopithecine herpesvirus 1) in the *Simplexvirus* genus; herpesviruses saimiri and ateles of monkeys, both in genus *Rhadinovirus*; marmoset herpesvirus (genus *Simplexvirus*); and pseudorabies virus of pigs and infectious bovine rhinotracheitis virus of cattle, both in genus *Varicellovirus*.

There is little antigenic relatedness among members of the herpesvirus group. Only HSV-1 and HSV-2 share a significant number of common antigens. HHV-6 and HHV-7 exhibit a few cross-reacting epitopes.

Herpesvirus Replication

The replication cycle of HSV is summarized in Figure 33-2. The virus enters the cell by fusion with the cell membrane after binding to specific cellular receptors via envelope glycoproteins. Several herpesviruses bind to cell surface glycosaminoglycans, principally heparan sulfate. Virus attachment also involves binding to one of several coreceptors (eg, members of the

TABLE 33-2 Classification of Human Herpesviruses

	Biologic Properties			Examples	
Subfamily ("-herpesvirinae")	Growth Cycle and Cytopathology	Latent Infections	Genus ("-*virus*")	Official Name ("Human Herpesvirus")	Common Name
Alpha	Short, cytolytic	Neurons	*Simplex*	1	Herpes simplex virus type 1
				2	Herpes simplex virus type 2
			Varicello	3	Varicella-zoster virus
Beta	Long, cytomegalic	Glands, kidneys	*Cytomegalo*	5	Cytomegalovirus
	Long, lymphoproliferative	Lymphoid tissue	*Roseolo*	6	Human herpesvirus 6
				7	Human herpesvirus 7
Gamma	Variable, lymphoproliferative	Lymphoid tissue	*Lymphocrypto*	4	Epstein-Barr virus
			Rhadino	8	Kaposi sarcoma-associated herpesvirus

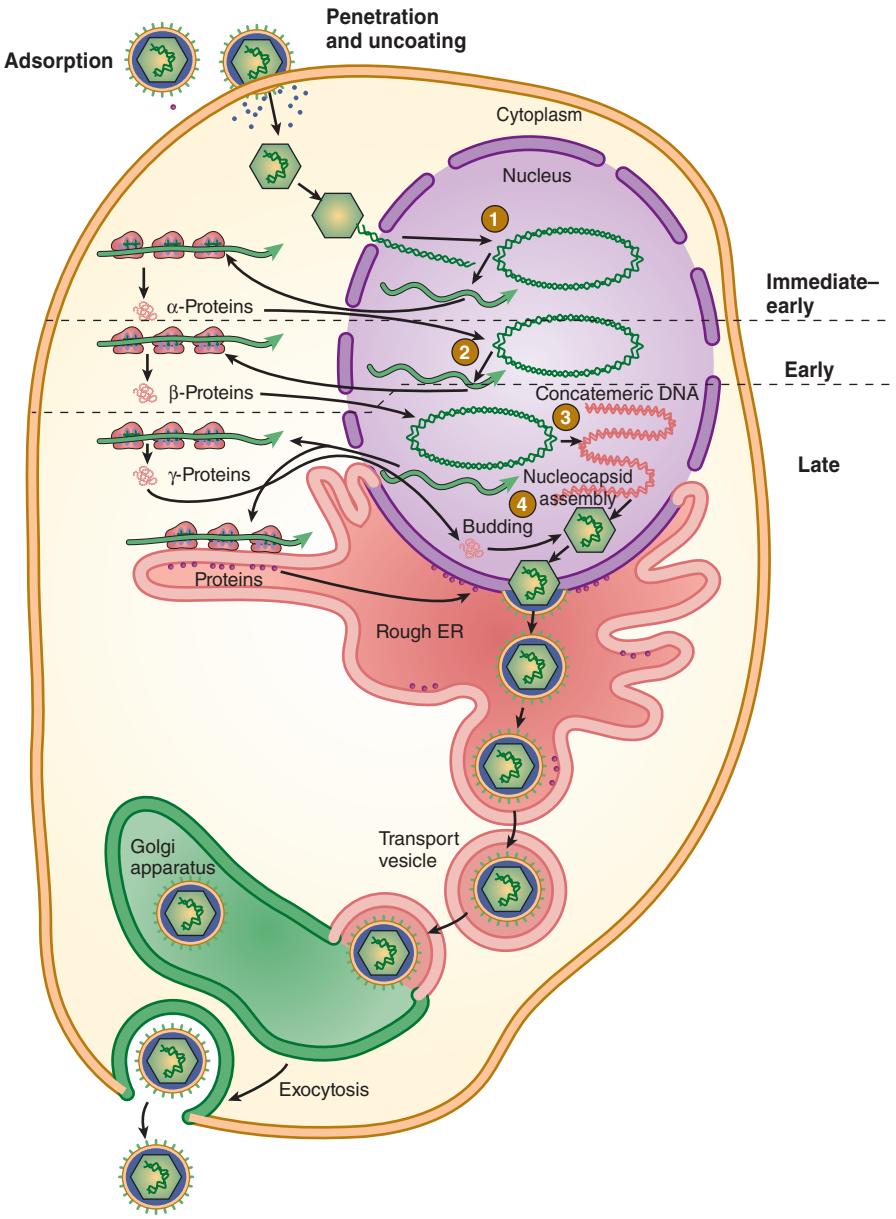


FIGURE 33-2 Replication cycle of herpes simplex virus. **(1)** Virus fuses with plasma membrane, and viral DNA is released from capsid at nuclear pore followed by circularization of genome and transcription of immediate-early genes. **(2)** α-Proteins, products of immediate-early genes, stimulate transcription of early genes. **(3)** β-Proteins, products of early genes, function in DNA replication, yielding concatemeric DNA. Late genes are transcribed. **(4)** γ-Proteins, products of late genes and consisting primarily of viral structural proteins, participate in virion assembly. Unit-length viral DNA is cleaved from concatemers and packaged into capsids. Enveloped viral particles accumulate in the endoplasmic reticulum (ER) and are transported from the cell. (Reproduced with permission from Willey JM, Sherwood LM, Woolverton CJ: *Prescott, Harley, and Klein's Microbiology,* 7th ed. McGraw-Hill, 2008. © The McGraw-Hill Companies, Inc.)

immunoglobulin superfamily). After fusion, the capsid is transported through the cytoplasm to a nuclear pore, uncoating occurs, and the DNA becomes associated with the nucleus. The viral DNA forms a circle immediately upon release from the capsid. Expression of the viral genome is tightly regulated and sequentially ordered in a cascade fashion. VP16, a tegument protein, complexes with several cellular proteins and activates initial viral gene expression. Immediate-early genes are expressed, yielding "α" proteins. These proteins permit expression of the early set of genes, which are translated into "β" proteins. Viral DNA replication begins, and late transcripts are produced that give rise to "γ" proteins. More than 50 different proteins are synthesized in herpesvirus-infected cells. Many α and β proteins are enzymes or DNA-binding proteins; most of the γ proteins are structural components.

Viral DNA is transcribed throughout the replicative cycle by cellular RNA polymerase II but with the participation of viral factors. Viral DNA is synthesized by a rolling-circle mechanism. Herpesviruses differ from other nuclear DNA viruses in that they encode a large number of

enzymes involved in DNA synthesis. (These enzymes are good targets for antiviral drugs.) Newly synthesized viral DNA is packaged into preformed empty nucleocapsids in the cell nucleus.

Maturation occurs by budding of nucleocapsids through the altered inner nuclear membrane. Enveloped virus particles are then transported by vesicular movement to the surface of the cell.

The length of the replication cycle varies from about 18 hours for HSV to more than 70 hours for CMV. Cells productively infected with herpesviruses are invariably killed. Host macromolecular synthesis is shut off early in infection; normal cellular DNA and protein synthesis virtually stop as viral replication begins. Cytopathic effects induced by human herpesviruses are quite distinct (Figure 33-3).

The number of potential protein-coding open-reading frames in herpesvirus genomes ranges from about 70 to more than 200. In the case of HSV, about half the genes are not needed for growth in cultured cells. The other genes are probably required for viral survival in vivo in natural hosts.

Herpesviruses have recently been found to express multiple microRNAs, small (~22 nucleotides) single-stranded RNAs that function posttranscriptionally to regulate gene expression. It is predicted that these viral microRNAs are important in regulating entry into or exit from (or both) the latent phase of the virus life cycle and may be attractive targets for antiviral therapy.

Overview of Herpesvirus Diseases

A wide variety of diseases are associated with infection by herpesviruses. Primary infection and reactivated disease by a given virus may involve different cell types and present different clinical pictures.

HSV-1 and HSV-2 infect epithelial cells and establish latent infections in neurons. Type 1 is classically associated with oropharyngeal lesions and causes recurrent attacks of "fever blisters." Type 2 primarily infects the genital mucosa and is mainly responsible for genital herpes. Both viruses also cause neurologic disease. HSV-1 is the leading cause of sporadic encephalitis in the United States. Both types 1 and 2 can cause neonatal infections that are often severe.

Varicella-zoster virus causes chickenpox (varicella) on primary infection and establishes latent infection in neurons.

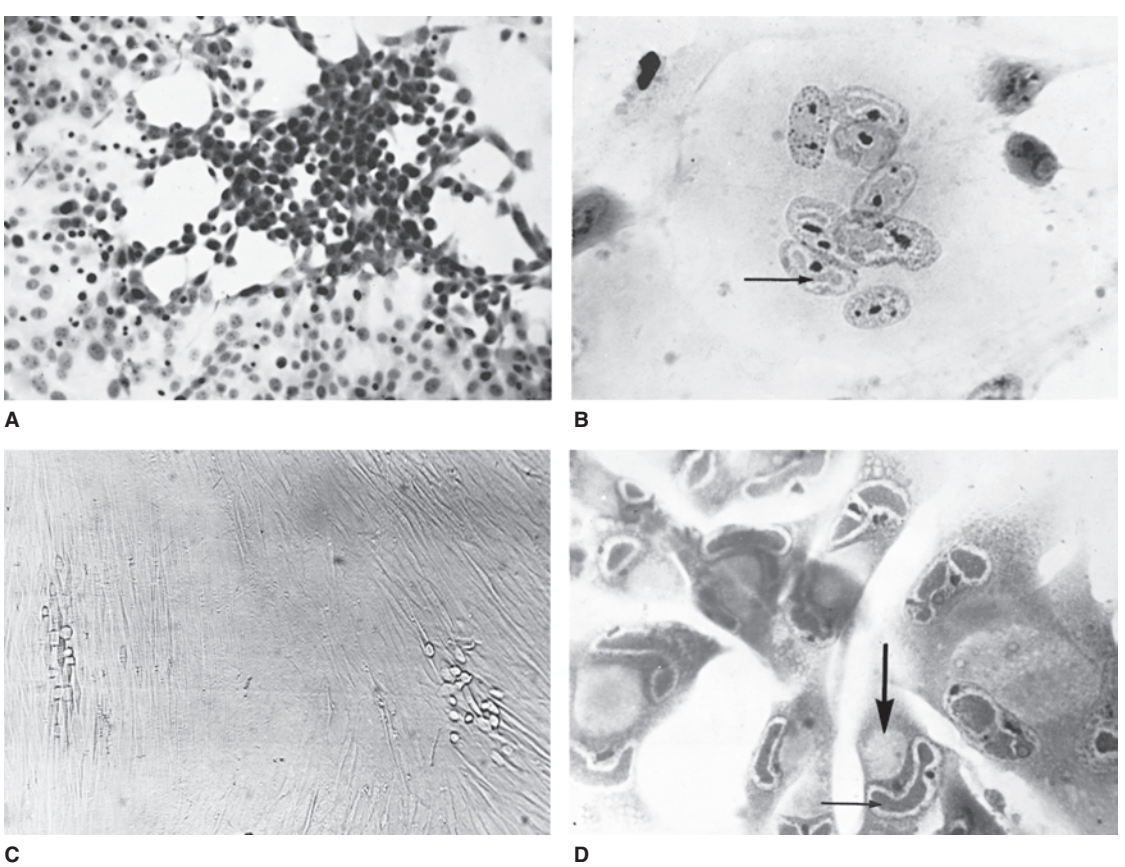


FIGURE 33-3 Cytopathic effects induced by herpesviruses. **A:** Herpes simplex virus in HEp-2 cells (hematoxylin and eosin stain, 57×), with early focus of swollen, rounded cells. **B:** Varicella-zoster virus in human kidney cells (hematoxylin and eosin stain, 228×), with multinucleated giant cell containing acidophilic intranuclear inclusions (arrow). **C:** Cytomegalovirus in human fibroblasts (unstained, 35×) with two foci of slowly developing cytopathic effect. **D:** Cytomegalovirus in human fibroblasts (hematoxylin and eosin stain, 228×), showing giant cells with acidophilic inclusions in the nuclei (*small arrow*) and cytoplasm (*large arrow*), the latter being characteristically large and round. (Courtesy of I Jack; reproduced from White DO, Fenner FJ: *Medical Virology*, 3rd ed. Academic Press, 1986.)

Upon reactivation, the virus causes zoster (shingles). Adults who are infected for the first time with varicella-zoster virus are apt to develop serious viral pneumonia.

CMV replicates in epithelial cells of the respiratory tract, salivary glands, and kidneys and persists in lymphocytes. It causes an infectious mononucleosis (heterophil-negative). In newborns, cytomegalic inclusion disease may occur. CMV is an important cause of congenital defects and mental retardation.

HHV-6 infects T lymphocytes. It is typically acquired in early infancy and causes exanthem subitum (roseola infantum). HHV-7, also a T-lymphotropic virus, has not yet been linked to any specific disease.

EBV replicates in epithelial cells of the oropharynx and parotid gland and establishes latent infections in lymphocytes. It causes infectious mononucleosis and is the cause of human lymphoproliferative disorders, especially in immunocompromised patients. HHV-8 appears to be associated with the development of Kaposi sarcoma, a vascular tumor that is common in patients with AIDS.

Herpes B virus of macaque monkeys can infect humans. Such infections are rare, but those that occur usually result in severe neurologic disease and are frequently fatal.

Human herpesviruses are frequently reactivated in immunosuppressed patients (eg, transplant recipients, cancer patients) and may cause severe disease, such as pneumonia or lymphomas.

Herpesviruses have been linked with malignant diseases in humans and lower animals: EBV with Burkitt lymphoma of African children, with nasopharyngeal carcinoma, and with other lymphomas; KSHV with Kaposi sarcoma; Marek disease virus with a lymphoma of chickens; and a number of primate herpesviruses with reticulum cell sarcomas and lymphomas in monkeys.

HERPESVIRUS INFECTIONS IN HUMANS

HERPES SIMPLEX VIRUSES

HSV are extremely widespread in the human population. They exhibit a broad host range, being able to replicate in many types of cells and to infect many different animals. They grow rapidly and are highly cytolytic. The HSVs are responsible for a spectrum of diseases, ranging from gingivostomatitis to keratoconjunctivitis, encephalitis, genital disease, and infections of newborns. The HSVs establish latent infections in nerve cells; recurrences are common.

Properties of the Viruses

There are two distinct HSV, types 1 and 2 (HSV-1 and HSV-2) (Table 33-3). Their genomes are similar in organization and exhibit substantial sequence homology. However, they can be distinguished by sequence analysis or by restriction enzyme analysis of viral DNA. The two viruses cross-react serologically, but some unique proteins exist for each type. They differ in their mode of transmission. Whereas HSV-1 is spread by contact, usually involving infected saliva, HSV-2 is transmitted sexually or from a maternal genital infection to a newborn. This results in different clinical features of human infections.

The HSV growth cycle proceeds rapidly, requiring 8–16 hours for completion. The HSV genome is large (~150 kbp) and can encode at least 70 polypeptides; the functions of many of the proteins in replication or latency are not known. At least eight viral glycoproteins are among the viral late gene products. One (gD) is the most potent inducer of neutralizing antibodies. Glycoprotein C is a complement (C3b)-binding protein, and gE is an Fc receptor, binding to the Fc portion of immunoglobulin G (IgG). Glycoprotein G is type specific and allows for antigenic discrimination between HSV-1 (gG-1) and HSV-2 (gG-2).

Pathogenesis and Pathology

A. Pathology

Because HSV causes cytolytic infections, pathologic changes are due to necrosis of infected cells together with the inflammatory response. Lesions induced in the skin and mucous membranes by HSV-1 and HSV-2 are the same and resemble those of varicella-zoster virus. Changes induced by HSV are similar for primary and recurrent infections but vary in degree, reflecting the extent of viral cytopathology.

Characteristic histopathologic changes include ballooning of infected cells, production of Cowdry type A intranuclear inclusion bodies, margination of chromatin, and formation of multinucleated giant cells. Cell fusion provides an efficient method for cell-to-cell spread of HSV, even in the presence of neutralizing antibody.

B. Primary Infection

HSV is transmitted by contact of a susceptible person with an individual excreting virus. The virus must encounter mucosal surfaces or broken skin for an infection to be initiated (unbroken skin is resistant). HSV-1 infections are usually limited to the oropharynx, and the virus is spread by respiratory droplets or by direct contact with infected saliva. HSV-2 is usually transmitted by genital routes. Viral replication occurs first at the site of infection. Virus then invades local nerve endings and is transported by retrograde axonal flow to dorsal root ganglia, where, after further replication, latency is established. Whereas oropharyngeal HSV-1 infections result in latent infections in the trigeminal ganglia, genital HSV-2 infections lead to latently infected sacral ganglia. Viremia is more common during primary HSV-2 infections than during HSV-1 infections.

Primary HSV infections are usually mild; in fact, most are asymptomatic. Only rarely does systemic disease develop. Widespread organ involvement can result when an

TABLE 33-3 Comparison of Herpes Simplex Virus Types 1 and 2

Characteristics	HSV-1	HSV-2
Biochemical		
Viral DNA base composition (G + C) (%)	67	69
Buoyant density of DNA (g/cm^3)	1.726	1.728
Buoyant density of virions (g/cm^3)	1.271	1.267
Homology between viral DNAs (%)	~50	~50
Biologic		
Animal vectors or reservoirs	None	None
Site of latency	Trigeminal ganglia	Sacral ganglia
Epidemiologic		
Age of primary infection	Young children	Young adults
Transmission	Contact (often saliva)	Sexual
Clinical		
Primary infection:		
Gingivostomatitis	+	–
Pharyngotonsillitis	+	–
Keratoconjunctivitis	+	–
Neonatal infections	±	+
Recurrent infection:		
Cold sores, fever blisters	+	–
Keratitis	+	–
Primary or recurrent infection:		
Cutaneous herpes		
Skin above the waist	+	±
Skin below the waist	±	+
Hands or arms	+	+
Herpetic whitlow	+	+
Eczema herpeticum	+	–
Genital herpes	±	+
Herpes encephalitis	+	–
Herpes meningitis	±	+

Modified with permission from Oxman MN: Herpes stomatitis. In Braude AI, Davis CE, Fierer J (editors). *Infectious Diseases and Medical Microbiology*, 2nd ed. Saunders, 1986:752.

immunocompromised host is not able to limit viral replication and viremia ensues.

C. Latent Infection

Virus resides in latently infected ganglia in a nonreplicating state; only a very few viral genes are expressed. Viral persistence in latently infected ganglia lasts for the lifetime of the host. No virus can be recovered between recurrences at or near the usual site of recurrent lesions. Provocative stimuli can reactivate virus from the latent state, including axonal injury, fever, physical or emotional stress, and exposure to ultraviolet light. The virus follows axons back to the peripheral site, and replication proceeds at the skin or mucous membranes. Spontaneous reactivations occur despite HSV-specific humoral and cellular immunity in the host. However, this immunity limits local viral replication, so that recurrent

infections are less extensive and less severe. Many recurrences are asymptomatic, reflected only by viral shedding in secretions. When symptomatic, episodes of recurrent HSV-1 infection are usually manifested as cold sores (fever blisters) near the lip. More than 80% of the human population harbor HSV-1 in a latent form, but only a small portion experience recurrences. It is not known why some individuals have reactivations and others do not.

Clinical Findings

HSV-1 and HSV-2 may cause many clinical entities, and the infections may be primary or recurrent (see Table 33-3). Primary infections occur in persons without antibodies and in most individuals are clinically inapparent but result in antibody production and establishment of latent infections in sensory ganglia. Recurrent lesions are common.

A. Oropharyngeal Disease

Primary HSV-1 infections are usually asymptomatic. Symptomatic disease occurs most frequently in small children (1–5 years of age) and involves the buccal and gingival mucosa of the mouth (Figure 33-4A). The incubation period is short (~3–5 days, with a range of 2–12 days), and clinical illness lasts 2–3 weeks. Symptoms include fever, sore throat, vesicular and ulcerative lesions, gingivostomatitis, and malaise. Gingivitis (swollen, tender gums) is the most striking and common lesion. Primary infections in adults commonly cause pharyngitis and tonsillitis. Localized lymphadenopathy may occur.

Recurrent disease is characterized by a cluster of vesicles most commonly localized at the border of the lip (Figure 33-4B). Intense pain occurs at the outset but fades over 4–5 days. Lesions progress through the pustular and crusting stages, and healing without scarring is usually complete in 8–10 days. The lesions may recur, repeatedly and at various intervals, in the same location. The frequency of recurrences varies widely among individuals. Many recurrences of oral shedding are asymptomatic and of short duration (24 hours).

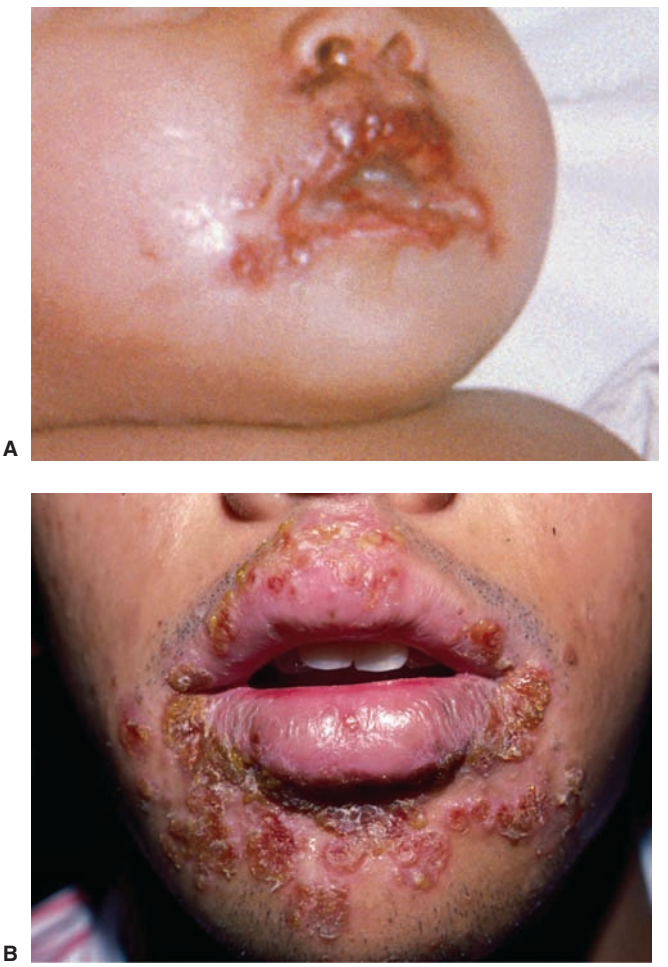


FIGURE 33-4 **A:** Primary herpes simplex gingivostomatitis. (Courtesy of JD Millar. Source: Centers for Disease Control and Prevention, Public Health Image Library, ID# 2902, 2008). **B:** Recurrent herpes simplex labialis. (Used with permission from Berger TG, Dept Dermatology, UCSF. Reproduced from McPhee SJ, Papadakis MA [editors]: *Current Medical Diagnosis & Treatment,* 48th ed. McGraw-Hill, 2009.)

B. Keratoconjunctivitis

HSV-1 infections may occur in the eye, producing severe keratoconjunctivitis. Recurrent lesions of the eye are common and appear as dendritic keratitis or corneal ulcers or as vesicles on the eyelids. With recurrent keratitis, there may be progressive involvement of the corneal stroma, with permanent opacification and blindness. HSV-1 infections are second only to trauma as a cause of corneal blindness in the United States.

C. Genital Herpes

Genital disease is usually caused by HSV-2, although HSV-1 can also cause clinical episodes of genital herpes. Primary genital herpes infections can be severe, with illness lasting about 3 weeks. Genital herpes is characterized by vesiculoulcerative lesions of the penis of the male or of the cervix, vulva, vagina, and perineum of the female. The lesions are very painful and may be associated with fever, malaise, dysuria, and inguinal lymphadenopathy. Complications include extragenital lesions (~20% of cases) and aseptic meningitis (~10% of cases). Viral excretion persists for about 3 weeks.

Because of the antigenic cross-reactivity between HSV-1 and HSV-2, preexisting immunity provides some protection against heterotypic infection. An initial HSV-2 infection in a person already immune to HSV-1 tends to be less severe.

Recurrences of genital herpetic infections are common and tend to be mild. A limited number of vesicles appear and heal in about 10 days. Virus is shed for only a few days. Some recurrences are asymptomatic with anogenital shedding lasting less than 24 hours. Whether a recurrence is symptomatic or asymptomatic, a person shedding virus can transmit the infection to sexual partners.

D. Skin Infections

Intact skin is resistant to HSV, so cutaneous HSV infections are uncommon in healthy persons. Localized lesions caused by HSV-1 or HSV-2 may occur in abrasions that become contaminated with the virus (traumatic herpes). These lesions are seen on the fingers of dentists and hospital personnel (herpetic whitlow) and on the bodies of wrestlers (herpes gladiatorum or mat herpes).

Cutaneous infections are often severe and life threatening when they occur in individuals with disorders of the skin, such as eczema or burns, that permit extensive local viral replication and spread. Eczema herpeticum is a primary infection, usually with HSV-1, in a person with chronic eczema. In rare instances, the illness may be fatal.

E. Encephalitis

A severe form of encephalitis may be produced by herpesvirus. HSV-1 infections are considered the most common cause of sporadic, fatal encephalitis in the United States. The disease carries a high mortality rate, and those who survive often have residual neurologic defects. About half of patients with HSV encephalitis appear to have primary infections, and the rest appear to have recurrent infection.

F. Neonatal Herpes

HSV infection of the newborn may be acquired in utero, during birth, or after birth. The mother is the most common source of infection in all cases. Neonatal herpes is estimated to occur in about 1 in 5000 deliveries per year. The newborn infant seems to be unable to limit the replication and spread of HSV and has a propensity to develop severe disease.

The most common route of infection (~75% of cases) is for HSV to be transmitted to a newborn during birth by contact with herpetic lesions in the birth canal. To avoid infection, delivery by cesarean section has been used in pregnant women with genital herpes lesions. However, many fewer cases of neonatal HSV infection occur than cases of recurrent genital herpes, even when the virus is present at term.

Neonatal herpes can be acquired postnatally by exposure to either HSV-1 or HSV-2. Sources of infection include family members and hospital personnel who are shedding virus. About 75% of neonatal herpes infections are caused by HSV-2. There do not appear to be any differences between the nature and severity of neonatal herpes in premature or full-term infants, in infections caused by HSV-1 or HSV-2, or in disease when virus is acquired during delivery or postpartum.

Neonatal herpes infections are almost always symptomatic. The overall mortality rate of untreated disease is 50%. Babies with neonatal herpes exhibit three categories of disease: (1) lesions localized to the skin, eye, and mouth; (2) encephalitis with or without localized skin involvement; and (3) disseminated disease involving multiple organs, including the central nervous system. The worst prognosis (~80% mortality rate) applies to infants with disseminated infection, many of whom develop encephalitis. The cause of death of babies with disseminated disease is usually viral pneumonitis or intravascular coagulopathy. Many survivors of severe infections are left with permanent neurologic impairment.

G. Infections in Immunocompromised Hosts

Immunocompromised patients are at increased risk of developing severe HSV infections. These include patients immunosuppressed by disease or therapy (especially those with deficient cellular immunity) and individuals with malnutrition. Renal, cardiac, and bone marrow transplant recipients are at particular risk for severe herpes infections. Patients with hematologic malignancies and patients with AIDS have more frequent and more severe HSV infections. Herpes lesions may spread and involve the respiratory tract, esophagus, and intestinal mucosa. Malnourished children are prone to fatal disseminated HSV infections. In most cases, the disease reflects reactivation of latent HSV infection.

Immunity

Many newborns acquire passively transferred maternal antibodies. These antibodies are lost during the first 6 months of life, and the period of greatest susceptibility to primary herpes infection occurs between ages 6 months and 2 years. Transplacentally acquired antibodies from the mother are not totally protective against infection of newborns, but they seem to ameliorate infection if not prevent it. HSV-1 antibodies begin to appear in the population in early childhood; by adolescence, they are present in most persons. Antibodies to HSV-2 rise during the age of adolescence and sexual activity.

During primary infections, IgM antibodies appear transiently and are followed by IgG and IgA antibodies that persist for long periods. The more severe the primary infection or the more frequent the recurrences, the greater the level of antibody response. However, the pattern of antibody response has not correlated with the frequency of disease recurrence. Cell-mediated immunity and nonspecific host factors (natural killer cells, interferon) are important in controlling both primary and recurrent HSV infections.

After recovery from a primary infection (inapparent, mild, or severe), the virus is carried in a latent state in the presence of antibodies. These antibodies do not prevent reinfection or reactivation of latent virus but may modify subsequent disease.

Laboratory Diagnosis

A. Polymerase Chain Reaction

Polymerase chain reaction (PCR) assays can be used to detect virus and are sensitive and specific. PCR amplification of viral DNA from cerebrospinal fluid has replaced viral isolation from brain tissue obtained by biopsy or at postmortem examination as the standard assay for specific diagnosis of HSV infections of the central nervous system.

B. Isolation and Identification of Virus

Virus isolation remains the definitive diagnostic approach. Virus may be isolated from herpetic lesions and may also be found in throat washings, cerebrospinal fluid, and stool, both during primary infection and during asymptomatic periods. Therefore, the isolation of HSV is not in itself sufficient evidence to indicate that the virus is the causative agent of a disease under investigation.

Inoculation of tissue cultures is used for viral isolation. HSV is easy to cultivate, and cytopathic effects usually occur in only 2–3 days. The agent is then identified by neutralization test or immunofluorescence staining with specific antiserum. Typing of HSV isolates may be done using monoclonal antibody or by restriction endonuclease analysis of viral DNA but is only useful for epidemiologic studies.

C. Cytopathology

A rapid cytologic method is to stain scrapings obtained from the base of a vesicle (eg, with Giemsa's stain); the presence of multinucleated giant cells indicates that herpesvirus (HSV-1, HSV-2, or varicella-zoster) is present, distinguishing lesions from those caused by coxsackieviruses and nonviral entities.

D. Serology

Antibodies appear in 4–7 days after infection and reach a peak in 2–4 weeks. They persist with minor fluctuations for the life of the host. Detection methods available include neutralization, immunofluorescence, and enzyme-linked immunosorbent assay.

The diagnostic value of serologic assays is limited by the multiple antigens shared by HSV-1 and HSV-2. There may also be some heterotypic anamnestic responses to varicella-zoster virus in persons infected with HSV and vice versa. The use of HSV type-specific antibodies, available in some research laboratories, allows more meaningful serologic tests.

Epidemiology

HSV are worldwide in distribution. No animal reservoirs or vectors are involved with the human viruses. Transmission is by contact with infected secretions. The epidemiology of HSV-1 and HSV-2 differs.

HSV-1 is probably more constantly present in humans than any other virus. Primary infection occurs early in life and is usually asymptomatic; occasionally, it produces oropharyngeal disease (gingivostomatitis in young children, pharyngitis in young adults). Antibodies develop, but the virus is not eliminated from the body; a carrier state is established that lasts throughout life and is punctuated by transient recurrent attacks of herpes.

The highest incidence of HSV-1 infection occurs among children 6 months to 3 years of age. By adulthood, 70–90% of persons have type 1 antibodies. There is a high rate of geographic variation in seroprevalence. Middle-class individuals in developed countries acquire antibodies later in life than those in lower socioeconomic populations. Presumably, this reflects more crowded living conditions and poorer hygiene among the latter. The virus is spread by direct contact with infected saliva or through utensils contaminated with the saliva of a virus shedder. The source of infection for children is usually an adult with a symptomatic herpetic lesion or with asymptomatic viral shedding in saliva.

The frequency of recurrent HSV-1 infections varies widely among individuals. At any given time, 1–5% of normal adults are excreting virus, often in the absence of clinical symptoms.

HSV-2 is usually acquired as a sexually transmitted disease, so antibodies to this virus are seldom found before puberty. It is estimated that there are about 40–60 million infected individuals in the United States. Antibody prevalence studies have been complicated by the cross-reactivity between HSV types 1 and 2. Surveys using type-specific glycoprotein antigens recently determined that 17% of adults in the United States possess HSV-2 antibodies, with seroprevalence higher among women than men, higher among blacks than whites, and age related, reaching 56% in blacks ages 30–49 years.

Reactivation and asymptomatic shedding occurs with both HSV-1 and HSV-2. PCR-based studies showed frequent subclinical reactivations in immunocompetent hosts that often lasted less than 12 hours. Both symptomatic and asymptomatic infections provide a reservoir of virus for transmission to susceptible persons. Studies have estimated that transmission of genital herpes in more than 50% of cases resulted from sexual contact in the absence of lesions or symptoms.

Maternal genital HSV infections pose risks to both the mother and the fetus. Rarely, pregnant women may develop disseminated disease after primary infection, with a high mortality rate. Primary infection before 20 weeks of gestation has been associated with spontaneous abortion. The fetus may acquire infection as a result of viral shedding from recurrent lesions in the mother's birth canal at the time of delivery. Estimates of the frequency of cervical shedding of virus among pregnant women vary widely.

Genital HSV infections increase acquisition of human immunodeficiency virus (HIV) type 1 infections because the ulcerative lesions are openings in the mucosal surface.

Treatment, Prevention, and Control

Several antiviral drugs have proved effective against HSV infections, including acyclovir, valacyclovir, and vidarabine (see Chapter 30). All are inhibitors of viral DNA synthesis. Acyclovir, a nucleoside analog, is monophosphorylated by the HSV thymidine kinase and is then converted to the triphosphate form by cellular kinases. The acyclovir triphosphate is efficiently incorporated into viral DNA by the HSV polymerase, where it then prevents chain elongation. The drugs may suppress clinical manifestations, shorten time to healing, and reduce recurrences of genital herpes. However, HSV remains latent in sensory ganglia. Drug-resistant virus strains may emerge.

Newborns and persons with eczema should be protected from exposure to persons with active herpetic lesions.

Patients with genital herpes should be counseled that asymptomatic shedding is frequent and that the risk of transmission can be reduced by antiviral therapy and condom usage.

Experimental vaccines of various types are being developed. One approach is to use purified glycoprotein antigens found in the viral envelope, expressed in a recombinant system. Such vaccines might be helpful for the prevention of primary infections. A promising recombinant HSV-2 glycoprotein vaccine failed to prevent herpesvirus infections in a large clinical trial in 2010.

VARICELLA-ZOSTER VIRUS

Varicella (chickenpox) is a mild, highly contagious disease, chiefly of children, characterized clinically by a generalized vesicular eruption of the skin and mucous membranes. The disease may be severe in adults and in immunocompromised individuals.

Zoster (shingles) is a sporadic, incapacitating disease of elderly or immunocompromised individuals that is characterized by pain and a rash limited in distribution to the skin innervated by a single sensory ganglion. The lesions are similar to those of varicella.

Both diseases are caused by the same virus. Whereas varicella is the acute disease that follows primary contact with the virus, zoster is the response of the partially immune host to reactivation of varicella virus present in latent form in neurons in sensory ganglia.

Properties of the Virus

Varicella-zoster virus is morphologically identical to HSV. It has no animal reservoir. The virus propagates in cultures of human embryonic tissue and produces typical intranuclear inclusion bodies (see Figure 33-3B). Cytopathic changes are more focal and spread much more slowly than those induced by HSV. Infectious virus remains strongly cell associated, and serial propagation is more easily accomplished by passage of infected cells than of tissue culture fluids.

The same virus causes chickenpox and zoster. Viral isolates from the vesicles of chickenpox or zoster patients exhibit no significant genetic variation. Inoculation of zoster vesicle fluid into children produces chickenpox.

Pathogenesis and Pathology

A. Varicella

The route of infection is the mucosa of the upper respiratory tract or the conjunctiva (Figure 33-5). After initial replication

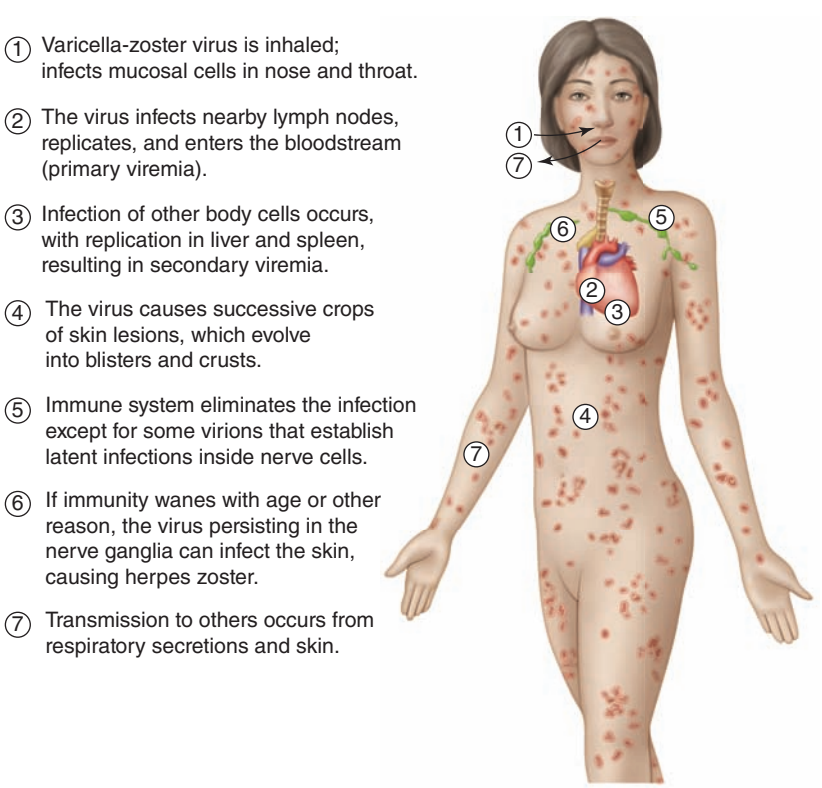


FIGURE 33-5 The pathogenesis of primary infection with varicella-zoster virus. The incubation period lasts from 10 to 21 days. Secondary viremia results in the transport of virus to skin and respiratory mucosal sites, where replication in epidermal cells causes the characteristic rash (chickenpox). Varicella-zoster virus-specific immunity is required to terminate viral replication. The virus gains access to cells of the trigeminal and dorsal root ganglia during primary infection and establishes latency. (Reproduced with permission from Nester EW, Anderson DG, Roberts CE Jr, Nester MT [editors]: *Microbiology: A Human Perspective,* 6th ed. McGraw-Hill, 2009, p. 548. © The McGraw-Hill Companies, Inc.)

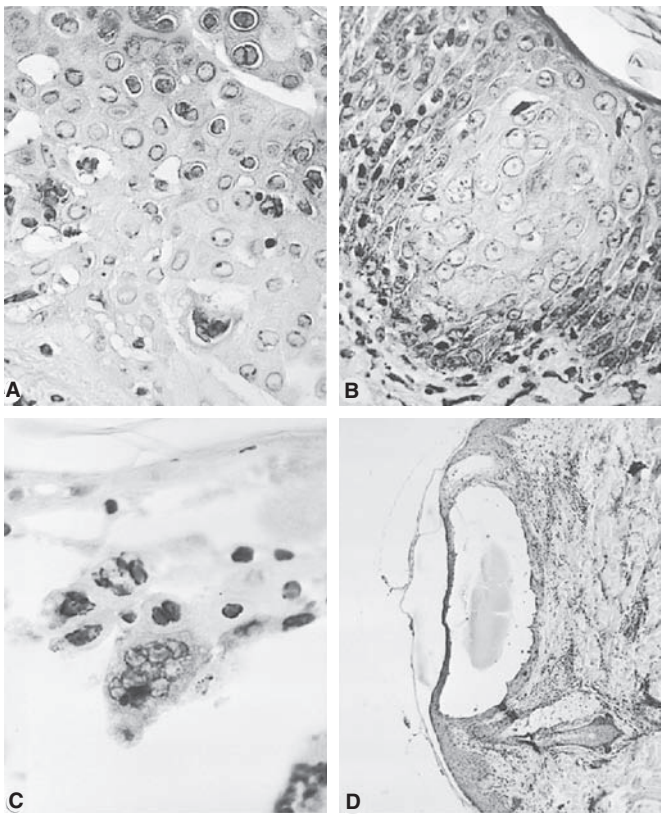


FIGURE 33-6 Characteristic histologic changes of varicella-zoster virus infection. Punch biopsies of varicella-zoster virus vesicles were fixed and stained with hematoxylin and eosin. **A:** Early infection showing "balloon degeneration" of cells with basophilic nuclei and marginated chromatin (reduced from 480×). **B:** Later infection showing eosinophilic intranuclear inclusions surrounded by wide clear zones (reduced from 480×). **C:** Multinucleated giant cell in the roof of a varicella vesicle (reduced from 480×). **D:** Low-power view of an early vesicle showing separation of the epidermis (acantholysis), dermal edema, and mononuclear cell infiltration (reduced from 40×). (Reproduced with permission from Gelb LD: Varicella-zoster virus. In Fields BN, Knipe DM [editors-in-chief]. *Virology*, 2nd ed. Raven Press, 1990.)

in regional lymph nodes, primary viremia spreads virus and leads to replication in the liver and spleen. Secondary viremia involving infected mononuclear cells transports virus to the skin, where the typical rash develops. Swelling of epithelial cells, ballooning degeneration, and the accumulation of tissue fluids result in vesicle formation (Figure 33-6).

Varicella-zoster virus replication and spread are limited by host humoral and cellular immune responses. Interferon is likely involved also. It has been shown that a varicella-zoster virus-encoded protein, ORF61, antagonizes the β-interferon pathway. This presumably contributes to the pathogenesis of viral infection.

B. Zoster

The skin lesions of zoster are histopathologically identical to those of varicella. There is also an acute inflammation of the sensory nerves and ganglia. Often only a single ganglion may be involved. As a rule, the distribution of lesions in the skin corresponds closely to the areas of innervation from an individual dorsal root ganglion.

It is not clear what triggers reactivation of latent varicella-zoster virus infections in ganglia. It is believed that waning immunity allows viral replication to occur in a ganglion, causing intense inflammation and pain. Virus travels down the nerve to the skin and induces vesicle formation. Cell-mediated immunity is probably the most important host defense in containment of varicella-zoster virus. Reactivations are sporadic and recur infrequently.

Clinical Findings

A. Varicella

Subclinical varicella is unusual. The incubation period of typical disease is 10–21 days. Malaise and fever are the earliest symptoms, soon followed by the rash, first on the trunk and then on the face, the limbs, and the buccal and pharyngeal mucosa in the mouth. Successive fresh vesicles appear in crops, so that all stages of macules, papules, vesicles, and crusts may be seen at one time (Figure 33-7). The rash lasts about 5 days, and most children develop several hundred skin lesions.

Complications are rare in normal children, and the mortality rate is very low. Encephalitis does occur in rare cases and can be life threatening. Survivors of varicella encephalitis may be left with permanent sequelae. In neonatal varicella, the infection is contracted from the mother just before or after birth but without sufficient immune response to modify the disease. Virus is often widely disseminated and may prove fatal.

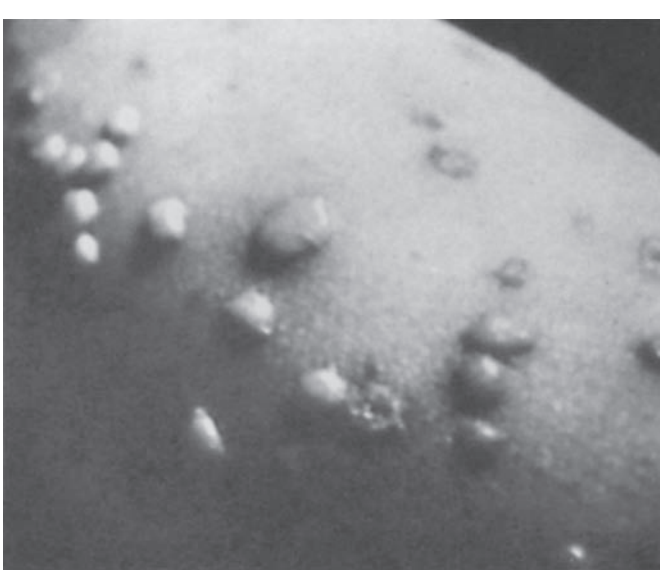


FIGURE 33-7 Multiple stages or "crops" of varicella skin lesions. (Reproduced with permission from Gelb LD: Varicella-zoster virus. In Fields BN, Knipe DM [editors-in-chief]. *Virology*, 2nd ed. Raven Press, 1990.)

Cases of congenital varicella syndrome after maternal cases of chickenpox during pregnancy have been described.

Varicella pneumonia is rare in healthy children but is the most common complication in neonates, adults, and immunocompromised patients. It is responsible for many varicella-related deaths.

Immunocompromised patients are at increased risk of complications of varicella, including those with malignancies, organ transplants, or HIV infection and those receiving high doses of corticosteroids. Disseminated intravascular coagulation may occur that is rapidly fatal. Children with leukemia are especially prone to developing severe, disseminated varicella-zoster virus disease.

B. Zoster

Zoster usually occurs in persons immunocompromised as a result of disease, therapy, or aging, but it occasionally develops in healthy young adults. It usually starts with severe pain in the area of skin or mucosa supplied by one or more groups of sensory nerves and ganglia. Within a few days after onset, a crop of vesicles appears over the skin supplied by the affected nerves. The trunk, head, and neck are most commonly affected (Figure 33-8), with the ophthalmic division of the trigeminal nerve involved in 10–15% of cases. The most common complication of zoster in elderly adults is postherpetic neuralgia—protracted pain that may continue for months. It is especially common after ophthalmic zoster. Visceral disease, especially pneumonia, is responsible for deaths that occur in immunosuppressed patients with zoster (<1% of patients).

Varicella zoster central nervous system disease, most frequently meningitis, often presents without a typical zoster rash.

Immunity

Varicella and zoster viruses are identical, the two diseases being the result of differing host responses. Previous infection with varicella is believed to confer lifelong immunity to varicella. Antibodies induced by varicella vaccine persist for at least 20 years. Zoster occurs in the presence of neutralizing antibody to varicella.

Increases in varicella antibody titer may occur in persons with HSV infections.

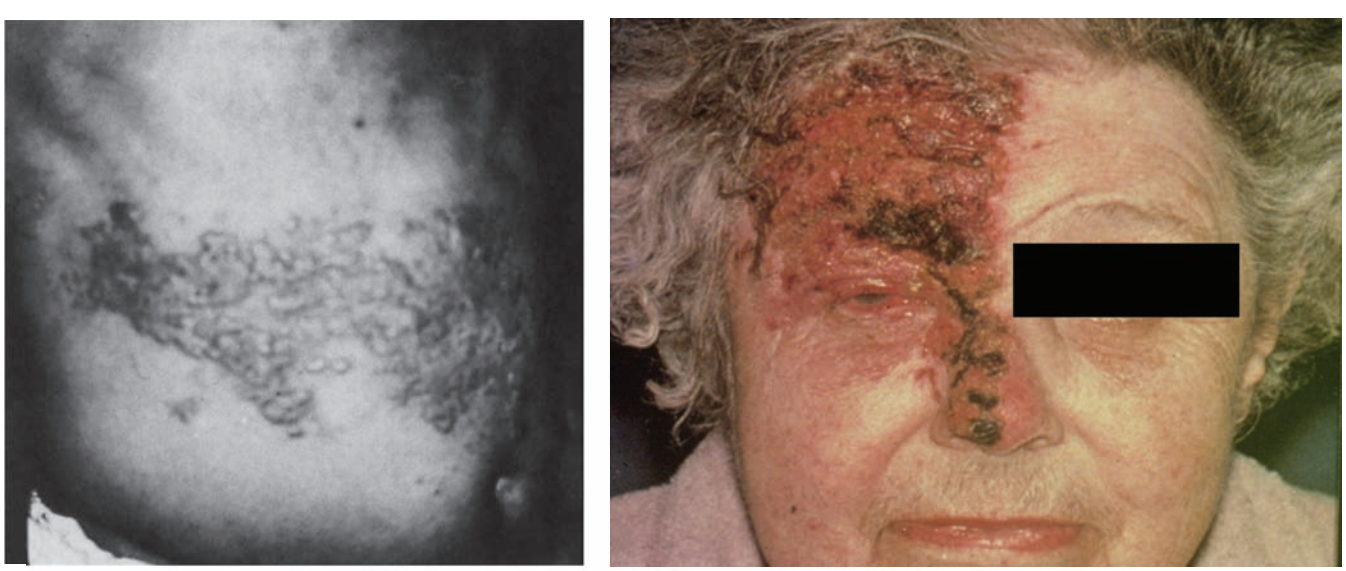
The development of varicella-zoster virus-specific cell-mediated immunity is important in recovery from both varicella and zoster. Appearance of local interferon may also contribute to recovery.

Varicella-zoster virus, similar to other herpesviruses, encodes means of evading host immune responses. For example, it downregulates major histocompatibility complex class I and II antigen expression and the β-interferon pathway.

Laboratory Diagnosis

Rapid diagnostic procedures are clinically useful for varicella-zoster virus. PCR assays are preferred for sensitivity, specificity, and rapidity. Varicella-zoster virus DNA can be detected in saliva in many patients, including those with zoster without rash. Viral DNA can be detected in vesicle fluid, skin scrapings, and biopsy material.

In stained smears of scrapings or swabs of the base of vesicles (Tzanck smear), multinucleated giant cells are seen (see Figure 33-6). These are absent in nonherpetic vesicles. Intracellular viral antigens can be demonstrated by immunofluorescence staining of similar smears. Herpesviruses can be



A B

FIGURE 33-8 **A:** Herpes zoster in the distribution of thoracic nerves. (Courtesy of AA Gershon.) **B:** Herpes zoster ophthalmicus. (Courtesy MN Oxman, University of California, San Diego. Reproduced from Prevention of herpes zoster. Recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR Morb Mortal Wkly Rep* 2008;57[RR-5]:1.)

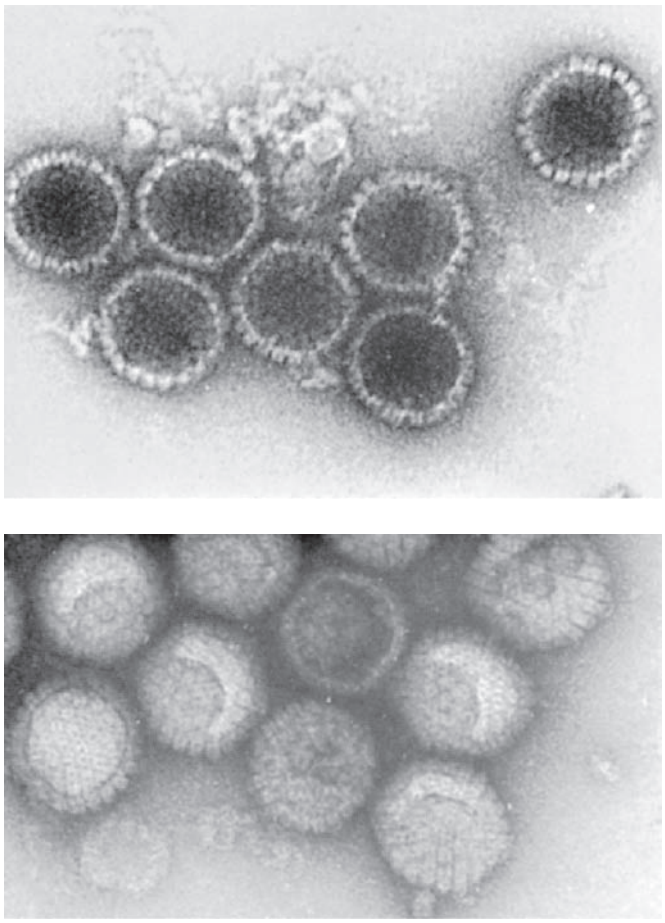


FIGURE 33-9 **Top:** Herpesvirus particles from human vesicle fluid stained with uranyl acetate to show DNA core (140,000×). **Bottom:** Virions stained to show protein capsomeres of the virus coat (140,000×). Note: Different herpesviruses cannot be distinguished by electron microscopy. (Courtesy of KO Smith and JL Melnick.)

differentiated from poxviruses by the morphologic appearance of particles in vesicular fluids examined by electron microscopy (Figure 33-9).

Virus can be isolated from vesicle fluid early in the course of illness using cultures of human cells in 3–7 days. Varicella-zoster virus in vesicle fluid is very labile, and cell cultures should be inoculated promptly.

A rise in specific antibody titer can be detected in the patient's serum by various tests, including fluorescent antibody and enzyme immunoassay. The choice of assay to use depends on the purpose of the test and the laboratory facilities available. Cell-mediated immunity is important but is difficult to demonstrate.

Epidemiology

Varicella and zoster occur worldwide. Varicella (chickenpox) is highly communicable and is a common epidemic disease of childhood (most cases occur in children younger than 10 years of age). Adult cases do occur. It is much more common in winter and spring than in summer in temperate climates. Zoster occurs sporadically, chiefly in adults and without seasonal prevalence. About 10–20% of adults will experience at least one zoster attack during their lifetime, usually after the age of 50 years.

A live attenuated varicella vaccine is available. In the prevaccine era, varicella caused about 4 million illnesses, 11,000 hospitalizations, and 100 deaths annually in the United States. Since the vaccine was introduced in 1995, there has been a steady decline in the incidence of varicella diseases; however, varicella outbreaks continue to occur among school children because some children are unvaccinated and a single dose of the vaccine is 80–85% effective in vaccinated persons.

Varicella spreads readily by airborne droplets and by direct contact. A varicella patient is probably infectious (capable of transmitting the disease) from shortly before the appearance of rash to the first few days of rash. Contact infection is less common in zoster, perhaps because the virus is absent from the upper respiratory tract in typical cases. Zoster patients can be the source of varicella in susceptible children, perhaps because viral DNA is often present in their saliva. Varicella-zoster virus DNA has been detected using a PCR amplification method in air samples from hospital rooms of patients with active varicella (82%) and zoster (70%) infections.

Treatment

Varicella in normal children is a mild disease and requires no treatment. Neonates and immunocompromised patients with severe infections should be treated.

γ-Globulin of high varicella-zoster virus antibody titer (varicella-zoster immune globulin) can be used to prevent the development of the illness in patients exposed to varicella who are at high risk of developing severe disease. It has no therapeutic value after varicella has started. Standard immune globulin is without value because of its low titer of varicella antibodies.

The manufacturer of the only United States-licensed varicella-zoster immune globulin discontinued its production in 2004; however, in 2006, a new investigational (not licensed) product became available. It can be requested for patients at increased risk for severe disease.

Several antiviral compounds provide effective therapy for varicella, including acyclovir, valacyclovir, famciclovir, and foscarnet. Acyclovir can prevent the development of systemic disease in varicella-infected immunosuppressed patients and can halt the progression of zoster in adults. Acyclovir does not appear to prevent postherpetic neuralgia.

Prevention and Control

A live attenuated varicella vaccine was approved in 1995 for general use in the United States. A similar vaccine has been used successfully in Japan for about 30 years. A single dose

of the vaccine is highly effective at inducing protection from varicella in children (80–85% effective) but less so in adults (70%). The vaccine is about 95% effective in preventing severe disease. About 5% of individuals develop a mild vaccine-associated rash 1 month after immunization. In 2006, two doses of the vaccine were recommended for children, and that schedule is reportedly more than 98% effective in preventing varicella disease. Transmission of the vaccine virus is rare but can occur when the vaccinee has a rash. The duration of protective immunity induced by the vaccine is unknown but is probably long term. Varicella infections can occur in vaccinated persons, but they are usually mild illnesses.

A zoster (shingles) vaccine was licensed in the United States in 2006. It is a 14 times more potent version of the varicella vaccine. It has been shown to be effective in older adults at reducing both the frequency of outbreaks of zoster and the severity of disease that does occur. The zoster vaccine is recommended for those with chronic medical conditions and for persons older than 60 years of age.

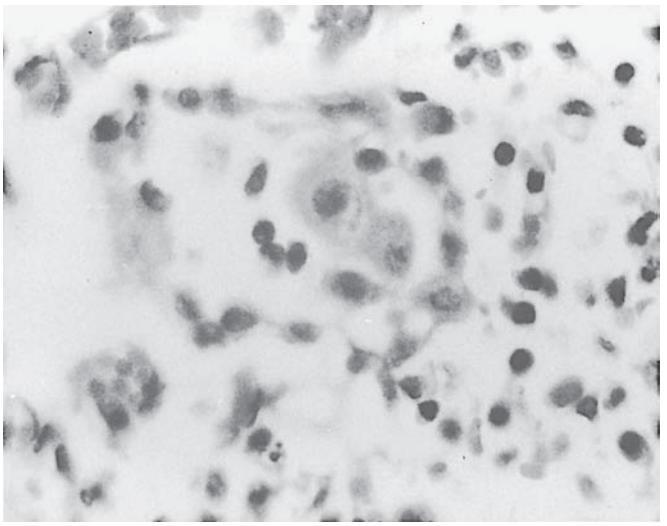


FIGURE 33-10 Massively enlarged "cytomegalic" cells typical of cytomegalovirus infection present in the lung of a premature infant who died of disseminated cytomegalovirus disease. (Courtesy of GJ Demmler.)

CYTOMEGALOVIRUS

CMVs are ubiquitous herpesviruses that are common causes of human disease. CMVs are the agents of the most common congenital infection.

Cytomegalic inclusion disease is a generalized infection of infants caused by intrauterine or early postnatal infection with the CMVs. The name for the classic cytomegalic inclusion disease derives from the propensity for massive enlargement of CMV-infected cells. CMV poses an important public health problem because of its high frequency of congenital infections, which may lead to severe congenital anomalies. Inapparent infection is common during childhood and adolescence. Severe CMV infections are frequently found in adults who are immunosuppressed.

Properties of the Virus

CMV has the largest genetic content of the human herpesviruses. Its DNA genome (240 kbp) is significantly larger than that of HSV. Only a few of the many proteins encoded by the virus (~200) have been characterized. One, a cell surface glycoprotein, acts as an Fc receptor that can nonspecifically bind the Fc portion of immunoglobulins. This may help infected cells evade immune elimination by providing a protective coating of irrelevant host immunoglobulins.

The major immediate-early promoter-enhancer of CMV is one of the strongest known enhancers because of the concentration of binding sites for cellular transcription factors. It is used experimentally to support high-level expression of foreign genes.

Many genetically different strains of CMV are circulating in the human population. The strains are sufficiently related antigenically, however, so that strain antigenic differences are probably not important determinants in human disease.

CMVs are very species specific and cell type specific. All attempts to infect animals with human CMV have failed. A number of animal CMVs exist, all of them species specific.

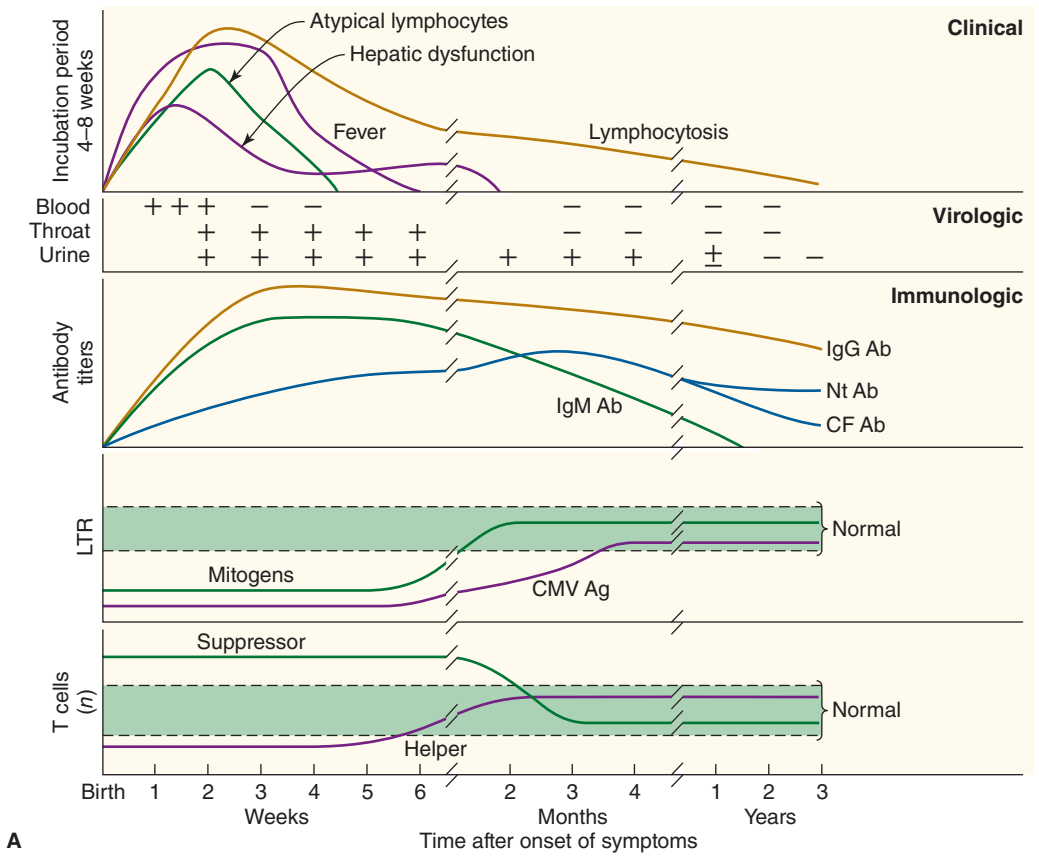
Human CMV replicates in vitro only in human fibroblasts, although the virus is often isolated from epithelial cells of the host. CMV replicates very slowly in cultured cells, with growth proceeding more slowly than that of HSV or varicella-zoster virus. Very little virus becomes cell free; infection is spread primarily from cell to cell. It may take several weeks for an entire monolayer of cultured cells to become involved.

CMV produces a characteristic cytopathic effect (see Figure 33-3C). Perinuclear cytoplasmic inclusions form in addition to the intranuclear inclusions typical of herpesviruses. Multinucleated cells are seen. Many affected cells become greatly enlarged. Inclusion-bearing cytomegalic cells can be found in samples from infected individuals (Figure 33-10).

Pathogenesis and Pathology

A. Normal Hosts

CMV may be transmitted from person to person in several different ways, all requiring close contact with virus-bearing material. There is a 4- to 8-week incubation period in normal older children and adults after viral exposure. The virus causes a systemic infection; it has been isolated from lung, liver, esophagus, colon, kidneys, monocytes, and T and B lymphocytes. The disease is an infectious mononucleosis-like syndrome, although most CMV infections are subclinical. Similar to all herpesviruses, CMV establishes lifelong latent infections. Virus can be shed intermittently from the pharynx and in the urine for months to years after primary infection (Figure 33-11). Prolonged CMV infection of the kidney does



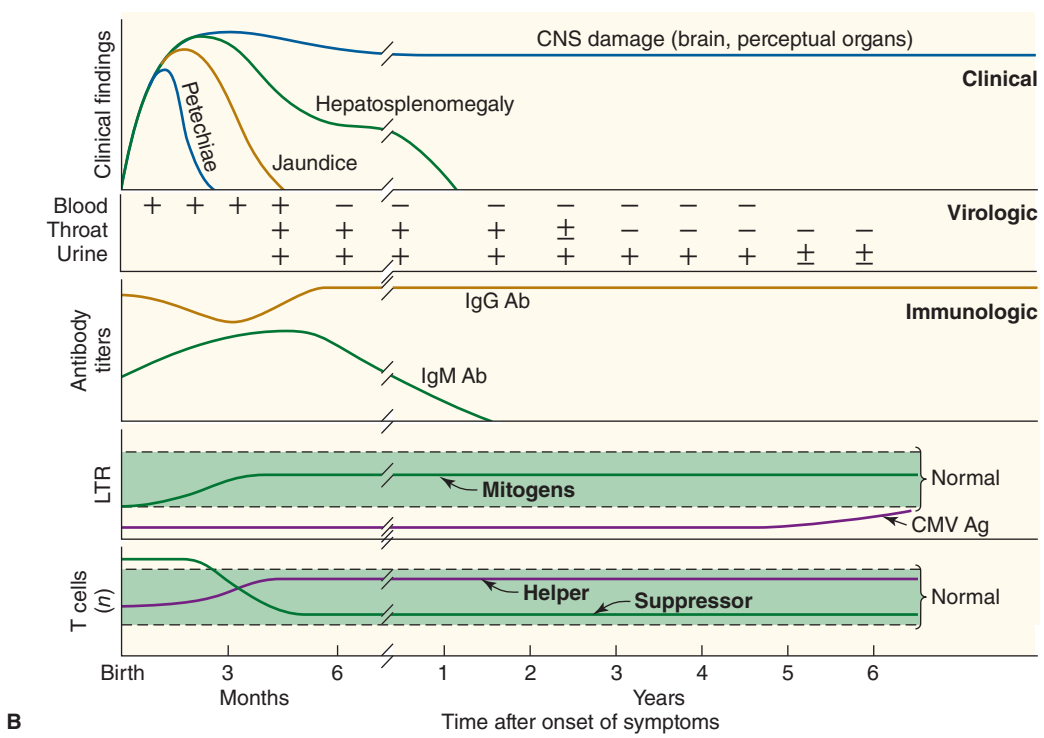


FIGURE 33-11 Clinical, virologic, and immunologic features of cytomegalovirus infection in normal individuals (**A**) and in congenitally infected infants (**B**). Ab, antibody; Ag, antigen; CF, complement fixing; CMV, cytomegalovirus; CNS, central nervous system; Ig, immunoglobulin; LTR, lymphocyte transformation response; Nt, neutralizing. (Reproduced with permission from Alford CA, Britt WJ: Cytomegalovirus. In Fields BN, Knipe DM [editors-in-chief]. *Virology*, 2nd ed. Raven Press, 1990.)

not seem to be deleterious in normal persons. Salivary gland involvement is common and is probably chronic.

Cell-mediated immunity is depressed with primary infections (Figure 33-11), and this may contribute to the persistence of viral infection. It may take several months for cellular responses to recover.

B. Immunosuppressed Hosts

Primary CMV infections in immunosuppressed hosts are much more severe than in normal hosts. Individuals at greatest risk for CMV disease are those receiving organ transplants, those with malignant tumors who are receiving chemotherapy, and those with AIDS. Viral excretion is increased and prolonged, and the infection is more apt to become disseminated. Pneumonia is the most common complication.

The host immune response presumably maintains CMV in a latent state in seropositive individuals. Reactivated infections are associated with disease much more often in immunocompromised patients than in normal hosts. Although usually less severe, reactivated infections may be as virulent as primary infections.

C. Congenital and Perinatal Infections

Fetal and newborn infections with CMV may be severe (Figure 33-12). About 1% of live births annually in the United States have congenital CMV infections, and about 5–10% of those will develop cytomegalic inclusion disease. A high percentage of babies with this disease will exhibit developmental defects and mental retardation.

The virus can be transmitted in utero with both primary and reactivated maternal infections. About one-third of pregnant women with primary infection transmit the virus. Generalized cytomegalic inclusion disease results most often from primary maternal infections. There is no evidence that gestational age at the time of maternal infection affects expression of disease in the fetus. Intrauterine transmission occurs in about 1% of seropositive women. Fetal damage seldom results from these reactivated maternal infections; the infection of the infant remains subclinical though chronic (see Figure 33-11).

CMV can also be acquired by the infant from exposure to virus in the mother's genital tract during delivery and from maternal breast milk. In these cases, the infants usually have received some maternal antibody, and the perinatally acquired CMV infections tend to be subclinical. Transfusion-acquired CMV infections in newborns vary, depending on the amount of virus received and the serologic status of the blood donor. Whether CMV is acquired in utero or perinatally, a more chronic infection results—with respect to viral excretion—than when the virus is acquired later in life (see Figure 33-11).

High-throughput sequencing was used for a genome-wide analysis of CMV in congenitally infected infants. A complex mixture of genome types was found, with more intrahost variability than expected for a DNA virus.

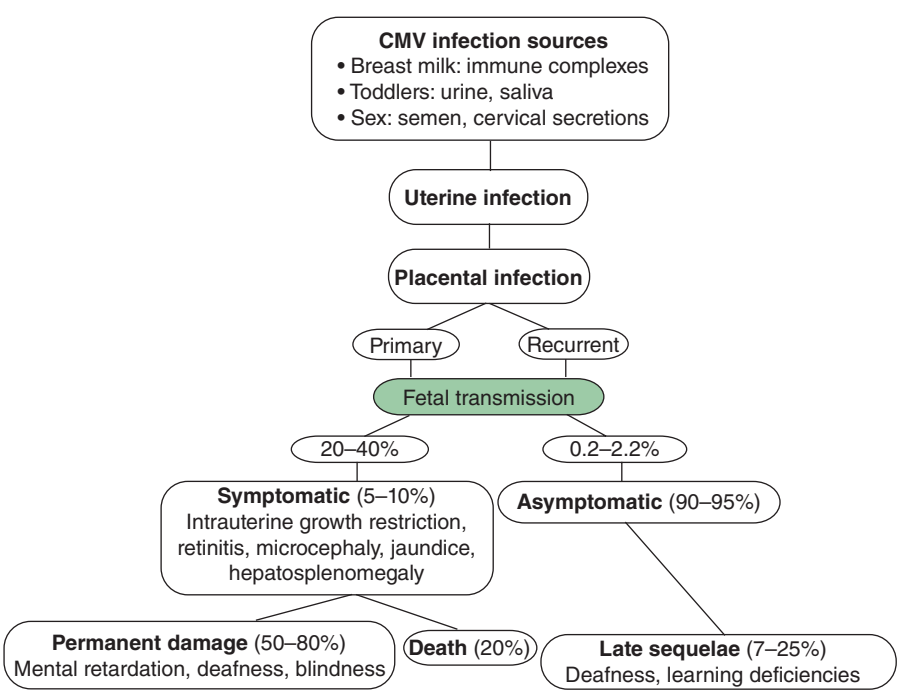


FIGURE 33-12 Congenital infections by cytomegalovirus and birth defects in symptomatic and asymptomatic children. Cytomegalovirus is the most common intrauterine infection associated with congenital defects. (Reproduced with permission from Pereira L, Maidji E, McDonagh S, Tabata T: Insights into viral transmission at the uterine-placental interface. *Trends Microbiol* 2005;13:164–174. Copyright Elsevier.)

Clinical Findings

A. Normal Hosts

Primary CMV infection of older children and adults is usually asymptomatic but occasionally causes a spontaneous infectious mononucleosis syndrome. CMV is estimated to cause 20–50% of heterophil-negative (non-EBV) mononucleosis cases.

CMV mononucleosis is a mild disease, and complications are rare. Subclinical hepatitis is common. In children younger than 7 years old, hepatosplenomegaly is frequently observed.

An association has been observed between the presence of CMV and restenosis after coronary angioplasty. It is speculated that the virus may be contributing to the proliferation of smooth muscle cells, leading to restenosis.

B. Immunocompromised Hosts

Both morbidity and mortality rates are increased with primary and recurrent CMV infections in immunocompromised individuals. Pneumonia is a frequent complication. Interstitial pneumonitis caused by CMV occurs in 10–20% of bone marrow transplant recipients. Virus-associated leukopenia is common in solid organ transplant recipients; also seen are obliterative bronchiolitis in lung transplants, graft atherosclerosis after heart transplantation, and CMV-related rejection of renal allografts. CMV often causes disseminated disease in untreated AIDS patients; gastroenteritis and chorioretinitis are common problems, the latter often leading to progressive blindness.

C. Congenital and Perinatal Infections

Congenital infection may result in death of the fetus in utero (see Figure 33-12). Cytomegalic inclusion disease of newborns is characterized by involvement of the central nervous system and the reticuloendothelial system. Clinical features include intrauterine growth retardation, jaundice, hepatosplenomegaly, thrombocytopenia, microcephaly, and retinitis. Mortality rates are about 20%. The majority of survivors develop significant central nervous system defects within 2 years; severe hearing loss, ocular abnormalities, and mental retardation are common. About 10% of infants with subclinical congenital CMV infection develop deafness. It has been estimated that one in every 1000 infants born in the United States is seriously retarded as a result of congenital CMV infection.

Many women infected previously with CMV show reactivation and begin to excrete the virus from the cervix during pregnancy. At the time of delivery through the infected birth canal, infants may become infected, although they possess high titers of maternal antibody acquired transplacentally. These infants begin to shed virus at about 8–12 weeks of age. They continue to excrete the virus for several years but remain healthy.

Acquired infection with CMV is common and usually inapparent. The virus is shed in the saliva and urine of infected individuals for weeks or months. CMV may be a cause of isolated pneumonia in infants younger than 6 months of age.

Immunity

Antibodies to CMV in human sera in the United States increase with age, from about 40% in teenagers to more than 80% in those more than 60 years old. Reactivation of latent infection occurs in the presence of humoral immunity. The presence of antibody in breast milk does not prevent transmission of infection to breastfeeding infants. Maternal antibody protects more against development of serious disease in the infant than viral transmission.

Laboratory Diagnosis

A. Polymerase Chain Reaction and Antigen Detection Assays

PCR assays have replaced virus isolation for routine detection of CMV infections. Cell culture methods of viral isolation are too slow to be useful in guiding therapy, particularly in immunosuppressed patients. The PCR assays are designed to detect replicating virus, not latent viral genomes. Blood and urine are most commonly tested. PCR assays can provide viral load data, which appears to be important in predicting CMV disease. Monoclonal antibodies against viral antigens can be used to detect virus-positive leukocytes from patients.

B. Isolation of Virus

Human fibroblasts are used for virus isolation attempts. The virus can be recovered most readily from throat washings and urine. In cultures, 2–3 weeks are usually needed for the appearance of cytologic changes, consisting of small foci of swollen, translucent cells with large intranuclear inclusions (see Figure 33-3C and D). The virus stays cell associated.

C. Serology

Many types of assays can detect CMV IgG antibodies, indicative of past infection (and the potential to undergo reactivation). Detection of viral IgM antibodies suggests a current infection. Serologic assays are not informative for immunocompromised patients. Furthermore, serologic techniques cannot distinguish strain differences among clinical isolates.

Epidemiology

CMV is endemic in all parts of the world; epidemics are unknown. It is present throughout the year, with no seasonal variation seen in infection rates.

The prevalence of infection varies with socioeconomic status, living conditions, and hygienic practices. Antibody prevalence may be moderate (40–70%) in adults in high socioeconomic groups in developed countries—in contrast to a prevalence of 90% in children and adults in developing nations and in low socioeconomic groups in developed countries.

New infections are almost always asymptomatic. After infection, virus is shed from multiple sites. Viral shedding may continue for years, often intermittently, as latent virus becomes reactivated. Thus, exposures to CMV are widespread and common.

Humans are the only known host for CMV. Transmission requires close person-to-person contact. Virus may be shed in urine, saliva, semen, breast milk, and cervical secretions and is carried in circulating white blood cells. Oral and respiratory spread are probably the dominant routes of CMV transmission. CMV can be transmitted by blood transfusion. Estimated risk varies widely but is about 1–5% per unit of whole blood. Seronegative solid organ transplantation recipients are at risk because a seropositive organ transmits the virus in 60–80% of cases.

Intrauterine infection may produce serious disease in newborns. About 1% of infants born in the United States are infected with CMV. The majority have subclinical but chronic infections; 5–10% have cytomegalic inclusion disease with attendant developmental defects and high mortality. Congenital infections, whether subclinical or clinically apparent, result in chronic infections, with viral shedding detectable for years. Many more infants become infected with CMV in the first months of life, often from infected breast milk or by nursery spread. Most of these infections are subclinical but are usually chronic, with persistent viral shedding.

Many women of child-bearing age in the United States remain at risk for primary CMV infection during pregnancy. Transmission in utero occurs in about 40% of primary infections of mothers. Such primary maternal infections during pregnancy are responsible for most cases of cytomegalic inclusion disease. Infants and children with subclinical CMV infections are the major source of exposure. Other congenital infections are caused by reactivations of latent maternal infections. Transmission in utero from such reactivations is uncommon (~1%).

CMV infections are markedly increased in immunosuppressed populations; transplant recipients often develop infections, most of which are caused by reactivations of their own latent virus.

Treatment and Control

Drug treatments of CMV infections have shown some encouraging results. Ganciclovir, a nucleoside structurally related to acyclovir, has been used successfully to treat life-threatening CMV infections in immunosuppressed patients. The severity of CMV retinitis, esophagitis, and colitis is reduced by ganciclovir. In addition, early treatment with ganciclovir reduces the incidence of CMV pneumonia in bone marrow allograft recipients. Ganciclovir also controls progressive hearing loss in neonates with congenital infections. Foscarnet, an analog of inorganic pyrophosphate, is recommended for treatment of CMV retinitis. Acyclovir and valacyclovir have shown some benefits in bone marrow and renal transplant patients.

Specific control measures are not available to prevent CMV spread. Isolation of newborns with generalized cytomegalic inclusion disease from other newborns is advisable.

Screening of transplant donors and recipients for CMV antibody may prevent some transmissions of primary CMV. The CMV-seronegative transplant recipient population represents a high-risk group for CMV infections. Seronegative liver transplant recipients who commenced antiviral valganciclovir prophylaxis immediately after transplant had better outcomes than recipients for whom prophylaxis was delayed. Administration of human IgG prepared from plasma pools obtained from healthy persons with high titers of CMV antibodies (CMV immune globulin) has given discordant results in tests to decrease the incidence of viral infections in transplant recipients. CMV immune globulin is in limited supply.

The use of blood from seronegative donors has been recommended when infants will require multiple transfusions. This approach would eliminate transfusion-acquired CMV infections, but it is difficult to implement.

Both live and recombinant CMV vaccines are under development.

EPSTEIN-BARR VIRUS

EBV is a ubiquitous herpesvirus that is the causative agent of acute infectious mononucleosis and is associated with nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin and non-Hodgkin lymphomas, other lymphoproliferative disorders in immunodeficient individuals, and gastric carcinoma.

Properties of the Virus

The EBV DNA genome contains about 172 kbp, has a G + C content of 59%, and encodes about 100 genes. There are two major strains of EBV, types A and B.

A. Biology of Epstein-Barr Virus

The major target cell for EBV is the B lymphocyte. When human B lymphocytes are infected with EBV, continuous cell lines can be established, indicating that cells have been immortalized by the virus. Very few of the immortalized cells produce infectious virus. Laboratory studies of EBV are hampered by the lack of a fully permissive cell system able to propagate the virus.

EBV initiates infection of B cells by binding to the viral receptor, which is the receptor for the C3d component of complement (CR2 or CD21). EBV directly enters a latent state in the lymphocyte without undergoing a period of complete viral replication. The hallmarks of latency are viral persistence, restricted virus expression, and the potential for reactivation and lytic replication.

The efficiency of B-cell immortalization by EBV is quite high. When virus binds to the cell surface, cells are activated to enter the cell cycle. Subsequently, a limited repertoire of EBV genes are expressed, and the cells are able

to proliferate indefinitely. The linear EBV genome forms a circle and is amplified during the cell cycle S phase; the majority of viral DNA in the immortalized cells exists as circular episomes.

EBV-immortalized B lymphocytes express differentiated functions, such as secretion of immunoglobulin. B-cell activation products (eg, CD23) are also expressed. Several patterns of latent viral gene expression are recognized based on the spectrum of proteins and transcripts expressed. These include EBV nuclear antigens (EBNA1, 2, 3A-3C, LP), latent membrane proteins (LMP1, 2), and small untranslated RNAs (EBERs).

At any given time, very few cells (<10%) in an immortalized population release virus particles. Latency can be disrupted and the EBV genome activated to replicate in a cell by a variety of stimuli, including chemical inducing agents or cross-linking cell surface immunoglobulin.

EBV can replicate in vivo in epithelial cells of the oropharynx, parotid gland, and uterine cervix; it is found in epithelial cells of some nasopharyngeal carcinomas. Although epithelial cells in vivo contain an EBV receptor, the receptor is lost from cultured cells.

EBV is associated with a number of lymphoproliferative disorders. Viral gene expression in these cells is limited and varies from only EBNA1 to the full complement of proteins found in latently infected B cells.

B. Viral Antigens

EBV antigens are divided into three classes based on the phase of the viral life cycle in which they are expressed: (1) Latent phase antigens are synthesized by latently infected cells. These include the EBNAs and the LMPs. Their expression reveals that an EBV genome is present. Only EBNA1, needed to maintain the viral DNA episomes, is invariably expressed; expression of the other latent phase antigens may be regulated in different cells. LMP1 mimics an activated growth factor receptor. (2) Early antigens are nonstructural proteins whose synthesis is not dependent on viral DNA replication. The expression of early antigens indicates the onset of productive viral replication. (3) Late antigens are the structural components of the viral capsid (viral capsid antigen) and viral envelope (glycoproteins). They are produced abundantly in cells undergoing productive viral infection.

C. Experimental Animal Infections

EBV is highly species specific for humans. However, cotton-top tamarins inoculated with EBV frequently develop fatal malignant lymphomas.

Pathogenesis and Pathology

A. Primary Infection

EBV is commonly transmitted by infected saliva and initiates infection in the oropharynx. Viral replication occurs in epithelial cells (or surface B lymphocytes) of the pharynx and salivary glands. Many people shed low levels of virus for weeks to months after infection. Infected B cells spread the infection from the oropharynx throughout the body. In normal individuals, most virus-infected cells are eliminated, but small numbers of latently infected lymphocytes persist for the lifetime of the host (one in 10^5–10^6 B cells).

Primary infections in children are usually subclinical, but if they occur in young adults, acute infectious mononucleosis often develops. Mononucleosis is a polyclonal stimulation of lymphocytes. EBV-infected B cells synthesize immunoglobulin. Autoantibodies are typical of the disease, with heterophil antibody that reacts with antigens on sheep erythrocytes the classic autoantibody.

B. Reactivation from Latency

Reactivations of EBV latent infections can occur, as evidenced by increased levels of virus in saliva and of DNA in blood cells. These are usually clinically silent. Immunosuppression is known to reactivate infection, sometimes with serious consequences.

Clinical Findings

Most primary infections in children are asymptomatic. In adolescents and young adults, the classic syndrome associated with primary infection is infectious mononucleosis (~50% of infections). EBV is also associated with several types of cancer.

A. Infectious Mononucleosis

After an incubation period of 30–50 days, symptoms of headache, fever, malaise, fatigue, and sore throat occur. Enlarged lymph nodes and spleen are characteristic. Some patients develop signs of hepatitis.

The typical illness is self-limited and lasts for 2–4 weeks. During the disease, there is an increase in the number of circulating white blood cells, with a predominance of lymphocytes. Many of these are large, atypical T lymphocytes. Low-grade fever and malaise may persist for weeks to months after acute illness. Complications are rare in normal hosts.

B. Cancer

EBV is associated with Burkitt lymphoma, nasopharyngeal carcinoma, Hodgkin and non-Hodgkin lymphomas, and gastric carcinoma. EBV-associated posttransplant lymphoproliferative disorders are a complication for immunodeficient patients. Sera from patients with Burkitt lymphoma or nasopharyngeal carcinoma contain elevated levels of antibody to virus-specific antigens, and the tumor tissues contain EBV DNA and express a limited number of viral genes.

Burkitt lymphoma is a tumor of the jaw in African children and young adults (see Chapter 43). Most African tumors (>90%) contain EBV DNA and express EBNA1 antigen. In other parts of the world, only about 20% of Burkitt lymphomas contain EBV DNA. It is speculated that EBV may be

involved at an early stage in Burkitt lymphoma by immortalizing B cells. Malaria, a recognized cofactor, may foster enlargement of the pool of EBV-infected cells. Finally, there are characteristic chromosome translocations that involve immunoglobulin genes and result in deregulation of expression of the c-*myc* proto-oncogene.

Nasopharyngeal carcinoma is a cancer of epithelial cells and is common in males of Chinese origin. EBV DNA is regularly found in nasopharyngeal carcinoma cells, and patients have high levels of antibody to EBV. EBNA1 and LMP1 are expressed. Genetic and environmental factors are believed to be important in the development of nasopharyngeal carcinoma.

Immunodeficient patients are susceptible to EBV-induced lymphoproliferative diseases that may be fatal. From 1% to 10% of transplant patients develop an EBV-associated lymphoproliferative disorder, often when experiencing a primary infection. Aggressive monoclonal B-cell lymphomas may develop.

AIDS patients are susceptible to EBV-associated lymphomas and oral hairy leukoplakia, a wart-like growth that develops on the tongue; it is an epithelial focus of EBV replication. Virtually all central nervous system non-Hodgkin lymphomas are associated with EBV, but fewer than 50% of systemic lymphomas are EBV positive. In addition, EBV is associated with classic Hodgkin disease, with the viral genome detected in the malignant Reed-Sternberg cells in up to 50% of cases.

Immunity

EBV infections elicit an intense immune response consisting of antibodies against many virus-specific proteins, a number of cell-mediated responses, and secretion of lymphokines. Cell-mediated immunity and cytotoxic T cells are important in limiting primary infections and controlling chronic infections.

Serologic testing to determine the pattern of specific antibodies to different classes of EBV antigens is the usual means of ascertaining a patient's status with regard to EBV infection.

Laboratory Diagnosis

A. Molecular Assays for Identification of Virus

Nucleic acid hybridization is the most sensitive means of detecting EBV in patient materials. EBER RNAs are abundantly expressed in both latently infected and lytically infected cells and provide a useful diagnostic target for detection of EBV-infected cells by hybridization. Viral antigens can be demonstrated directly in lymphoid tissues and in nasopharyngeal carcinomas. During the acute phase of infection, about 1% of circulating lymphocytes will contain EBV markers; after recovery from infection, about one in 1 million B lymphocytes will carry the virus.

B. Isolation of Virus

EBV can be isolated from saliva, peripheral blood, or lymphoid tissue by immortalization of normal human lymphocytes, usually obtained from umbilical cord blood. This assay is laborious and time consuming (6–8 weeks), requires specialized facilities, and is seldom performed. It is also possible to culture "spontaneously transformed" B lymphocytes from virus-infected patients. Any recovered immortalizing agent is confirmed as EBV by detection of EBV DNA or virus-specific antigens in the immortalized lymphocytes.

EBV is present in the saliva of many immunosuppressed patients. Up to 20% of healthy adults will also yield virus-positive throat washings.

C. Serology

Common serologic procedures for detection of EBV antibodies include enzyme-linked immunosorbent assays, immunoblot assays, and indirect immunofluorescence tests using EBV-positive lymphoid cells.

The typical pattern of antibody responses to EBV-specific antigens after a primary infection is shown in Figure 33-13. Early in acute disease, a transient rise in IgM antibodies to viral capsid antigen occurs, replaced within weeks by IgG antibodies to this antigen, which persist for life. Slightly later, antibodies to the early antigen develop that persist for several months. Several weeks after acute infection, antibodies to EBNA and the membrane antigen arise and persist throughout life.

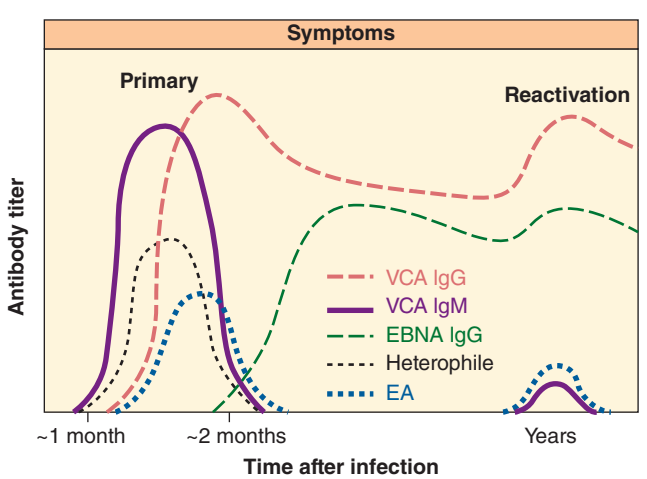


FIGURE 33-13 Typical pattern of antibody formation to Epstein-Barr virus (EBV)-specific antigens after a primary infection. Individuals with recent infection have immunoglobulin M (IgM) and IgG antibodies to the viral capsid antigen (VCA IgM, VCA IgG); only the IgG antibodies persist for years. Transient heterophil antibodies develop that can agglutinate sheep cells. Antibodies to early antigens (EA) develop in many patients and persist for several months. Several weeks after acute infection, antibodies to EBV nuclear antigens (EBNA) and membrane antigen appear and persist for life. (Reprinted from Gulley ML, Tang W: Laboratory assays for Epstein-Barr virus-related disease. *J Mol Diagnost* 2008;10:279–292 with permission from the American Society for Investigative Pathology and the Association for Molecular Pathology.)

The less-specific heterophil agglutination test may be used to diagnose EBV infections. In the course of infectious mononucleosis, most patients develop transient heterophil antibodies that agglutinate sheep cells. Commercially available spot tests are convenient. Accidental antigenic relationships provide for the specificity of this heterophil reaction.

Serologic tests for EBV antibodies require some interpretation. The presence of antibody of the IgM type to the viral capsid antigen is indicative of current infection. Antibody of the IgG type to the viral capsid antigen is a marker of past infection and indicates immunity. Early antigen antibodies are generally evidence of current viral infection, although such antibodies are often found in patients with Burkitt lymphoma or nasopharyngeal carcinoma. Antibodies to the EBNA antigens reveal past infection with EBV, although detection of a rise in anti-EBNA antibody suggests a primary infection. Not all persons develop antibody to EBNA.

Epidemiology

EBV is common in all parts of the world, with more than 90% of adults being seropositive. It is transmitted primarily by contact with oropharyngeal secretions. In developing areas, infections occur early in life; more than 90% of children are infected by age 6 years. These infections in early childhood usually occur without any recognizable disease. The inapparent infections result in permanent immunity to infectious mononucleosis. In industrialized nations, more than 50% of EBV infections are delayed until late adolescence and young adulthood. In almost half of cases, the infection is manifested by infectious mononucleosis. There are an estimated 100,000 cases of infectious mononucleosis annually in the United States.

Prevention, Treatment, and Control

There is no EBV vaccine available.

Acyclovir reduces EBV shedding from the oropharynx during the period of drug administration, but it does not affect the number of EBV-immortalized B cells. Acyclovir has no effect on the symptoms of mononucleosis and is of no proved benefit in the treatment of EBV-associated lymphomas in immunocompromised patients.

Adoptive transfer of EBV-reactive T cells shows promise as a treatment for EBV-related lymphoproliferative disease.

HUMAN HERPESVIRUS 6

The T-lymphotropic HHV-6 was first recognized in 1986. Initial isolations were made from cultures of peripheral blood mononuclear cells from patients with lymphoproliferative disorders.

Properties of the Virus

The viral DNA is about 160–170 kbp in size and has a mean composition of 43–44% (G + C). The genetic arrangement of the HHV-6 genome resembles that of human CMV.

HHV-6 appears to be unrelated antigenically to the other known human herpesviruses except for some limited cross-reactivity with HHV-7. Isolates of HHV-6 segregate into two closely related but distinct antigenic groups (designated A and B).

The virus grows well in CD4 T lymphocytes. Other cell types also support viral replication, including B cells and cells of glial, fibroblastoid, and megakaryocyte origin. Cells in the oropharynx must become infected because virus is present in saliva. It is not known which cells in the body become latently infected. Human CD46 is the cellular receptor for the virus.

Epidemiology and Clinical Findings

Seroepidemiologic studies using immunofluorescence tests for serum antibodies or PCR assays for viral DNA in saliva or blood cells have shown that HHV-6 is widespread in the population. It is estimated that more than 90% of children older than age 1 year and adults are virus positive.

Infections with HHV-6 typically occur in early childhood. This primary infection causes exanthem subitum (roseola infantum, or "sixth disease"), the mild common childhood disease characterized by a high fever and skin rash. The 6B variant appears to be the cause of this disease. The virus is associated with febrile seizures in children.

The mode of transmission of HHV-6 is presumed to be via oral secretions. The fact that it is a ubiquitous agent suggests that it must be shed into the environment from an infected carrier.

Infections persist for life. Reactivation appears to be common in transplant patients and during pregnancy. The consequences of reactivated infection remain to be determined. HHV-6 reactivation occurs in close to half of patients who undergo hematopoietic stem cell transplantation. Those reactivations occur soon after transplant and have been associated with delayed engraftment, central nervous system dysfunction, and increased mortality.

HUMAN HERPESVIRUS 7

A T-lymphotropic human herpesvirus, designated HHV-7, was first isolated in 1990 from activated T cells recovered from peripheral blood lymphocytes of a healthy individual.

HHV-7 is immunologically distinct from HHV-6, although they share about 50% homology at the DNA level.

HHV-7 appears to be a ubiquitous agent, with most infections occurring in childhood but later than the very early age of infection noted with HHV-6. Persistent infections are established in salivary glands, and the virus can be isolated from saliva of most individuals. In a longitudinal study of healthy adults, 75% of subjects excreted infectious virus in saliva one or more times during a 6-month observation period. Similar to HHV-6, primary infection with HHV-7 has been linked with roseola infantum in infants and young children. Any other disease associations of HHV-7 remain to be established.

HUMAN HERPESVIRUS 8

A new herpesvirus, designated HHV-8 and also called KSHV, was first detected in 1994 in Kaposi sarcoma specimens. KSHV is lymphotropic and is more closely related to EBV and herpesvirus saimiri than to other known herpesviruses. The KSHV genome (~165 kbp) contains numerous genes related to cellular regulatory genes involved in cell proliferation, apoptosis, and host responses (cyclin D, cytokines, chemokine receptor) that presumably contribute to viral pathogenesis. This molecular piracy of cell regulatory genes is a striking feature of the virus. KSHV is the cause of Kaposi sarcomas, vascular tumors of mixed cellular composition, and is involved in the pathogenesis of body cavity-based lymphomas occurring in AIDS patients and of multicentric Castleman disease.

KSHV is not as ubiquitous as other herpesviruses; about 5% of the general population in the United States and northern Europe have serologic evidence of KSHV infection. Contact with oral secretions is likely the most common route of transmission. The virus can also be transmitted sexually, vertically, by blood, and through organ transplants. Viral DNA has also been detected in breast milk samples in Africa. Infections are common in Africa (>50%) and are acquired early in life.

Viral DNA can be detected in patient specimens using PCR assays. Direct virus culture is difficult and impractical. Serologic assays are available to measure persistent antibody to KSHV using indirect immunofluorescence, Western blot, and enzyme-linked immunosorbent assay formats.

Foscarnet, famciclovir, ganciclovir, and cidofovir have activity against KSHV replication. The level of KSHV replication and rate of new Kaposi sarcomas are markedly reduced in HIV-positive patients on effective antiretroviral therapy, probably reflecting reconstituted immune surveillance against KSHV-infected cells.

B VIRUS

Herpes B virus of Old World monkeys is highly pathogenic for humans. Transmissibility of virus to humans is limited, but infections that do occur are associated with a high mortality rate (~60%). B virus disease of humans is an acute ascending myelitis and encephalomyelitis.

Properties of the Virus

B virus is a typical herpesvirus that is indigenous in macaques, Old World monkeys in Asia. B virus is enzootic in rhesus, cynomolgus, and other macaque monkeys (genus *Macaca*). It is designated cercopithecine herpesvirus 1, replacing the older name of *Herpes simiae*. Its genome organization is similar to that of HSV, with many genes arranged colinearly. Its genome is 75% G + C, the highest among herpesviruses. As with all herpesviruses, B virus establishes latent infections in infected hosts. The virus grows well in cultures of monkey kidney, rabbit kidney, and human cells with a short growth cycle. Cytopathic effects are similar to those of HSV.

Pathogenesis and Pathology

B virus infections seldom cause disease in rhesus monkeys. Vesicular lesions of the oropharynx may occur and resemble those induced in humans by HSV. Genital lesions also occur. Many rhesus monkeys carry latent B virus infections that may be reactivated by conditions of stress.

The virus is transmissible to other monkeys, rabbits, guinea pigs, rats, and mice. Rabbits routinely develop fatal infections after B virus inoculation.

B virus infections in humans usually result from a monkey bite, although infection by the respiratory route or ocular splash exposure is possible. The striking feature of B virus infections in humans is the very strong propensity to cause neurologic disease. Many survivors are left with neurologic impairment.

Epidemiology and Clinical Findings

B virus is transmitted by direct contact with virus or virus-containing material. Transmission occurs among *Macaca* monkeys, between monkeys and humans, and rarely from human to human. Virus may be present in saliva, conjunctival and vesicular fluids, genital areas, and feces of monkeys. Respiratory transmission can occur. Other sources of infection include direct contact with animal cages and with infected monkey cell cultures.

Infection in the natural host is rarely associated with obvious disease. Infections with B virus are very common in colonies of rhesus monkeys. Seroprevalence in adult animals is 70% or higher. Because latent infections may be reactivated, seropositive animals are reservoirs for transmission of B virus infections. The frequency of excretion of B virus by monkeys is probably no more than 3%.

Animal workers and persons handling macaque monkeys, including medical researchers, veterinarians, pet owners, and zoo workers, are at risk of acquiring B virus infection. Individuals having intimate contact with animal workers exposed to the monkeys are also at some risk.

Treatment and Control

There is no specific treatment after the clinical disease is manifest. However, treatment with acyclovir is recommended immediately after exposure. γ-Globulin has not proved to be effective treatment for human B virus infections. No vaccine is available.

The risk of B virus infections can be reduced by proper procedures in the laboratory and in the handling and management of macaque monkeys. This risk makes macaques unsuitable as pets.