TABLE 134.1 Biologic Features of Herpesviruses That Infect Humans

VIRUS	SUBFAMILY[a]	GENOME SIZE (kbp)	RECEPTOR(S)	SITES OF LATENCY
Human Virus				
HSV-1 (HHV-1)	Alpha	152	Nectin-1, nectin-2 TNFRSF14, 3-OS-HS	Sensory and cranial nerve ganglia
HSV-2 (HHV-2)	Alpha	152	Nectin-1, nectin-2 TNFRSF14	Sensory and cranial nerve ganglia
Varicella-zoster virus (HHV-3)	Alpha	125		Sensory and cranial nerve ganglia
Cytomegalovirus (HHV-5)	Beta	229	PDGFR α, EGFR Integrin $\alpha_2\beta_1$, $\alpha_6\beta_1$, $\alpha_v\beta_3$	Monocytes, macrophages, $CD34^+$ cells
HHV-6	Beta	165	CD46, CD134	$CD34^+$ cells, monocytes, macrophages
HHV-7	Beta	145		CD4 cells
Epstein-Barr virus (HHV-4)	Gamma	172	CD21, CD35, EphA2, MHC class II Integrins $\alpha_v\beta_6$, $\alpha_v\beta_8$	Memory B cells
Kaposi sarcoma–associated herpesvirus (HHV-8)	Gamma	165	Integrin $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_1$, DC-SIGN, EphA2	B cells
Simian Virus				
Herpes B virus (Macacine herpesvirus 1)	Alpha	150	Nectin-1	Sensory and cranial nerve ganglia

[a]Alpha, Beta, and Gamma refer to subfamilies Alphaherpesvirinae, Betaherpesvirinae, and Gammaherpesvirinae, respectively.
DC-SIGN, Dendritic cell–specific ICAM-3–grabbing nonintegrin; *EGFR,* epidermal growth factor receptor; *EphA2,* ephrin receptor tyrosine kinase A2; *HHV,* human herpesvirus; *HSV,* herpes simplex virus; *MHC,* major histocompatibility complex; *PDGFR,* platelet-derived growth factor receptor; *3-OS-HS,* 3-*O* sulfated heparan sulfate; *TNFRSFI4,* tumor necrosis factor receptor superfamily, member 14.
Modified from Straus SE. Introduction to herpesviridae. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. *6th ed. Philadelphia: Churchill Livingstone; 2005:1756–1762.*

nuclear antigen 1 protein, which allows viral episomes to partition to dividing latently infected B cells.[8] EBV and KSHV encode a number of latency proteins expressed in different types of virus-associated malignancies. Herpesvirus genomes exist in a circular, episomal form during latency in specific cell types. HHV-6 is an exception; up to 1% of healthy persons have HHV-6 integrated in their chromosomes.[9]

Several mechanisms have been proposed for maintaining latency in herpesviruses. These include expression of viral microRNAs during latency that inhibit expression of immediate-early viral genes[10,11] and methylation of histone proteins associated with lytic genes, which results in compaction of chromatin and silencing of the lytic genes.[12,13] In addition, certain viral and cellular proteins, which are normally in the nucleus of cells undergoing herpesvirus replication, may be sequestered to the cytoplasm during latency so that the viral proteins cannot activate gene expression.[14]

Latent viral genomes can reactivate to produce infectious virus. Reactivation can be stimulated in some virus-infected cells by radiation, trauma to nerves (in the case of the Alphaherpesvirinae), hyperthermia,[15] or hypoxia.[16] Reactivation is more common in immunosuppressed or immunocompromised hosts that have impaired T-cell immunity. For example, in the absence of antiviral prophylaxis, 50% or more of seropositive transplant recipients reactivate HSV, EBV, HHV-6, and HHV-7. Stress can also lead to reactivation; CMV reactivation occurs in 33% of seropositive immunocompetent patients in intensive care units.[17] Reactivation allows the virus to be transmitted to other individuals, thereby perpetuating virus infection over time to other generations.

PATHOGENESIS

Many herpesviruses, such as HSV, EBV, CMV, HHV-6, and HHV-7, are shed from the oral mucosa without symptoms despite the presence of neutralizing antibody and virus-specific T cells.[18] It is during asymptomatic shedding, rather than during symptomatic disease, that most viruses are transmitted from person to person. In contrast, VZV is only transmitted when patients have varicella or zoster.

Symptomatic disease due to some herpesviruses is associated with lytic virus replication, resulting in skin lesions due to HSV or VZV or visceral lesions due to HSV, VZV, or CMV. Other diseases, such as erythema multiforme associated with HSV or hemolytic anemia associated with CMV or EBV, are due to the immune response to the virus. Most symptoms from infectious mononucleosis associated with EBV are due to the proliferation of T cells that respond to the infection rather than to lytic destruction of virus-infected B cells.

Most human encounters with herpesviruses are asymptomatic or induce very mild symptoms. Many persons infected with HSV-1 or HSV-2 are asymptomatic, and young children and infants infected with CMV and EBV are usually asymptomatic. In contrast, most persons infected with VZV present with chickenpox and most with HHV-6 have fever. Infections are rarely fatal except in highly immunocompromised persons. It is in the best interest of the virus for the host to survive so that the infection can be transmitted to others. Whereas some herpesviruses (e.g., HSV, VZV, CMV, HHV-6) infect a wide range of cells in the body, others (e.g., EBV, HHV-7, KSHV) have a more narrow host range. Most herpesviruses spread in the blood. VZV, EBV, HHV-7, and KHSV disseminate in the bloodstream by lymphocytes, and CMV and HHV-6 by monocytes; HSV viremia has been reported in some persons with primary genital infection and in severely immunocompromised persons.

EPIDEMIOLOGY

Nearly all adults are infected with HSV-1, VZV, EBV, HHV-6, and HHV-7 (Table 134.2). Fifteen percent to 25% of adults in the United States are infected with HSV-2, 40% to 70% are infected with CMV, and less than 3% are infected with KSHV. Rates of HSV-1, HSV-2, CMV, EBV, and KSHV are higher in developing countries than in the United States.

Herpesviruses are usually spread by direct contact because the enveloped viruses do not survive long in the environment; VZV is the exception and is spread by airborne transmission. HSV, EBV, CMV, and HHV-6 are spread by infected saliva; HHV-7 and KSHV are also likely spread by saliva. Sexual contact results in spread of HSV, CMV, KSHV, and perhaps EBV. Intrauterine infection with HSV, VZV, and CMV can occur; most infants infected with HSV acquire the infection at the time of delivery. CMV, EBV, and KSHV have been transmitted by organ transplantation, and CMV and EBV have been spread by blood transfusion.

CLINICAL SYNDROMES

Several herpesviruses cause similar clinical syndromes, including vesicular skin lesions, retinitis, hepatitis, encephalitis, and mononucleosis;

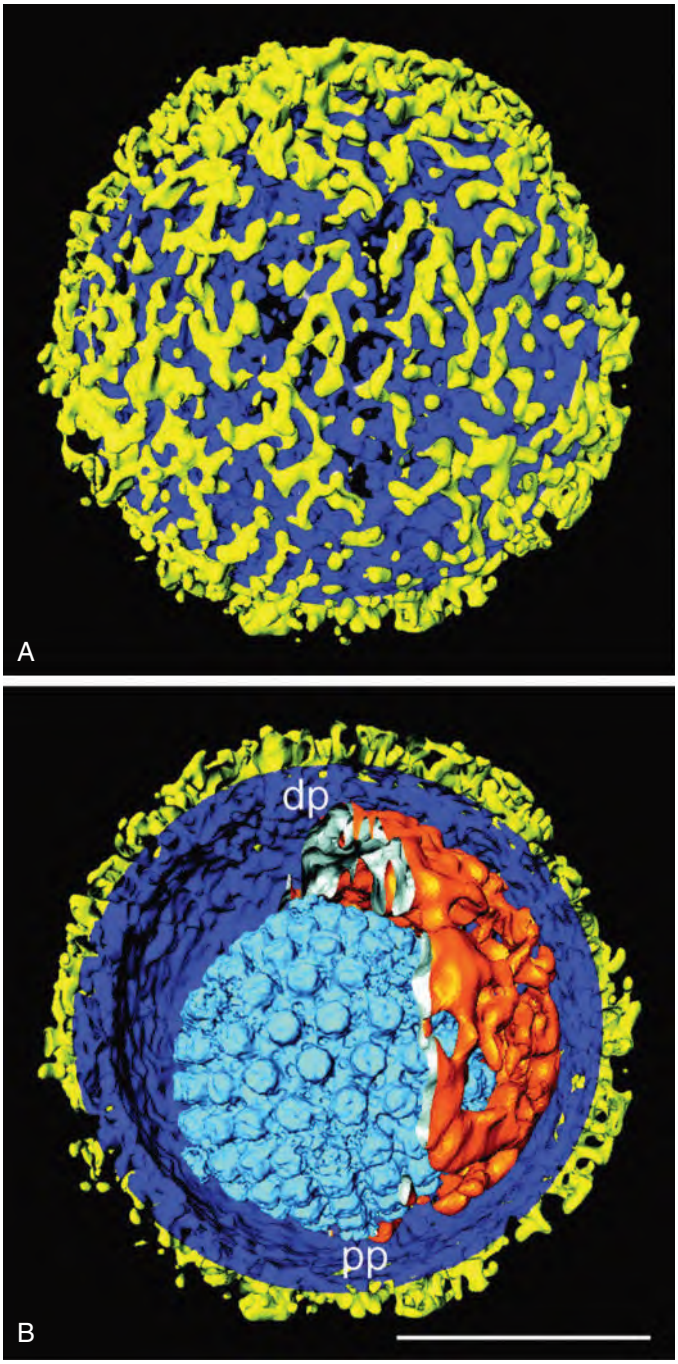

FIG. 134.1 Structure of a herpes simplex virus virion based on cryoelectron tomography. (A) The outer surface of the virion shows viral glycoproteins *(yellow)* embedded in the viral membrane *(blue).* (B) The interior of the virion shows the viral nucleocapsid *(light blue)* surrounded by the protein tegument *(orange),* which is inside the viral envelope *(blue and yellow). dp,* Distal pole; *pp,* proximal pole. Scale bar = 100 nm. *(From Grünewald K, Desai P, Winkler DC, et al. Three-dimensional structure of herpes simplex virus from cryo-electron tomography.* Science. *2003;302:1396–1398, with permission.)*

virus-specific diagnostic tests are needed to distinguish the virus that causes a particular syndrome (Table 134.3; see also Table 134.2).

Herpesviruses cause more severe disease in persons with impaired cellular, but not with impaired humoral, immunity (see Table 134.2). Patients with impaired T-cell immunity, such as organ transplant recipients receiving immunosuppression therapy, hematopoietic cell transplant recipients, patients with acquired immunodeficiency syndrome (AIDS), or patients with congenital T-cell or natural killer (NK) cell deficiencies, have more severe herpesvirus infections.[19,20] Patients infected with human immunodeficiency virus (HIV) and low CD4 cell counts often have severe herpesvirus infections. Persistent erosive mucocutaneous oral or anogenital HSV infections may occur, and resistance to acyclovir is not uncommon. VZV can cause verrucous skin lesions or small vessel central nervous system vasculitis or radiculopathy in patients with AIDS. CMV can cause encephalitis, retinitis, colitis, or radiculopathy; however, pneumonitis is rare in patients with AIDS. EBV is associated with central nervous system lymphomas or non-Hodgkin lymphoma, whereas KSHV is associated with Kaposi sarcoma, primary effusion lymphoma, and Castleman disease in patients with AIDS. Interestingly, HHV-6 and HHV-7 rarely cause disease in patients with AIDS. Infection with HSV-2 increases the rate of transmission and infection with HIV.[21]

IMMUNITY

Humoral immunity contributes to protection from primary infection with herpesviruses. Antibody acquired transplacentally protects neonates from HSV, VZV, and CMV; infection of neonates can cause severe disease when mothers develop primary infection and lack virus-specific antibody near the time of birth. VZV and CMV infection during fetal development is associated with fetal growth restriction and birth defects. Antibody to VZV (varicella-zoster immune globulin) or CMV (CMV hyperimmune globulin) reduces the severity of primary disease in immunocompromised persons. Antibodies have numerous activities than can inhibit infection; these including neutralization of infection, antibody-dependent cellular cytotoxicity, complement-mediated cellular cytotoxicity, and antibody-dependent cellular phagocytosis. Most herpesviruses spread in the body from cell to cell rather than as free virions; therefore the effect of antibody is limited once infection is well established.

The observation that patients with hypogammaglobulinemia are not at risk for developing severe herpesvirus infections, whereas those with impaired cellular immunity can have life-threatening disease, indicates the important role of cellular immunity in controlling the severity of herpesvirus disease. Numerous virus epitopes are recognized by $CD4^+$ and $CD8^+$ T cells, and few appear to be dominant in HSV and CMV infection.[22,23] $CD4^+$ T cells produce cytokines that are critical for controlling virus infection, especially interferon-γ and tumor necrosis factor-α. $CD8^+$ T cells can kill virus-infected cells, and in some cells can induce cleavage of viral proteins to prevent virus replication without killing the cells. Cellular immunity is critical for controlling the severity of acute infection and reducing virus reactivation.

Patients with mutations in genes in the innate immunity pathway important for interferon signaling, such as *TLR3, UNC93B1, IRF3, TRAF3, TICAM1,* and *TBK1,* have an increased likelihood to develop HSV encephalitis.[24] Mutations in genes important for T-cell function, including *SH2D1A*, *BIRC4, ITK, CD27, CD70*, and *MAGT1,*[25,26] can result in severe EBV disease, and mutations in *STIM1* can result in severe KSHV disease.[27] Mutations in other genes important for cellular immunity, including *PIK3CD, PIK3R1, GATA2*, *IKBKG*, *IFN-γR1, IL2Rγ, FCGR3A,* and *DOCK8,* can result in severe infections with multiple herpesviruses.[20] Patients with NK cell defects are especially prone to severe herpesvirus infections.[28] Polymorphisms in *HLA* genes are associated with symptomatic HSV[29] or EBV infection,[30] whereas polymorphisms in *TLR2*[31] or *IL10*[32] are associated with increased severity of HSV or EBV infection, respectively.

Herpesviruses encode numerous genes that inhibit cellular immune mechanisms.[33–35] EBV and KSHV encode homologues of the antiapoptotic protein BCL2, whereas HSV, CMV, and HHV-6 encode other proteins that inhibit apoptosis. Many herpesviruses encode proteins that inhibit recognition of infected cells by $CD4^+$ and $CD8^+$ T and NK cells. HSV, EBV, and CMV encode proteins that inhibit the TAP protein that is required for processing major histocompatibility complex (MHC) class I molecules, and KSHV encodes proteins that enhance endocytosis of MHC class I molecules from the cell surface. HSV, EBV, and CMV also encode proteins that inhibit MHC class II, and CMV and KSHV encode proteins that inhibit NK cells. HSV, VZV, EBV, CMV, and KSHV encode proteins that inhibit interferon. HSV encodes a glycoprotein (gE) that inhibits the activity of antibody, whereas HSV and KSHV encode proteins that inhibit complement. EBV and CMV encode interleukin (IL)-10 homologues, and KSHV encodes an IL-6 homologue. HHV-6 and HHV-8

TABLE 134.2 Features of Herpesvirus Infections and Seroepidemiology

VIRUS	PRIMARY INFECTION IN HEALTHY PERSONS	INFECTION IN IMMUNOCOMPROMISED PERSONS	SEROPREVALENCE (%)		
				HEALTHY ADULTS	
			HEALTHY CHILDREN	United States	Developing World
Herpes simplex virus 1	Gingivostomatitis Keratoconjunctivitis Cutaneous herpes Genital herpes	Gingivostomatitis Keratoconjunctivitis Cutaneous herpes Visceral infections	20–40	50–70	50–90
Herpes simplex virus 2	Genital herpes Cutaneous herpes Gingivostomatitis Aseptic meningitis Neonatal herpes	Genital herpes Cutaneous herpes Disseminated infection	0–5	15–25	20–60
Varicella-zoster virus	Varicella	Disseminated infection	50–75	85–95	50–80
Cytomegalovirus	Mononucleosis Hepatitis Congenital cytomegalic inclusion disease	Hepatitis Retinitis Other visceral infections	10–30	40–70	40–80
Epstein-Barr virus	Mononucleosis Hepatitis Encephalitis	Polyclonal and monoclonal lymphoproliferative syndromes Oral hairy leukoplakia	10–30	80–95	90–100
Human herpesvirus 6	Exanthem subitum Infantile fever and seizures Encephalitis	Fever and rash Encephalitis Bone marrow suppression	80–100	60–100	60–100
Human herpesvirus 7	Exanthem subitum Childhood fever and seizures Encephalitis	Encephalitis	40–80	60–100	40–100
Kaposi sarcoma–associated herpesvirus	Febrile exanthem Mononucleosis?	Kaposi sarcoma Castleman disease Primary effusion lymphoma	<3	<3	10–60
Herpes B virus	Mucocutaneous lesions Encephalitis	Not reported	0	0	0

Modified from Straus SE. Introduction to herpesviridae. In: Mandell GL, Bennett EJ, Dolin R, eds. Principles and Practice of Infectious Diseases. *6th ed. Philadelphia: Churchill Livingstone; 2005:1756–1762.*

TABLE 134.3 Clinical Syndromes Associated With Human Herpesviruses

SYNDROME	HSV-1	HSV-2	VZV	CMV	EBV	HHV-6	HHV-7	KSHV	HERPES B VIRUS
Gingivostomatitis	+	+	–	–	–	–	–	–	–
Genital lesions	+	+	–	–	–	–	–	–	–
Keratoconjunctivitis	+	+	+	–	–	–	–	–	–
Cutaneous lesions	+	+	+	–	–	–	–	+	+
Neonatal infection	+	+	+	+	–	–	–	–	–
Retinitis	+	+	+	+	–	–	–	–	–
Esophagitis	+	+	+	+	–	–	–	–	–
Pneumonitis	+	+	+	+	+	+	–	–	–
Hepatitis	+	+	+	+	+	+	–	–	–
Meningitis	–	+	+	–	–	+	–	–	–
Encephalitis	+	+	+	+	+	+	+	–	+
Myelitis	+	+	+	+	+	+/–	–	–	+
Mononucleosis	–	–	–	+	+	+	–	+?	–
Hemolytic anemia	–	–	+	+	+	–	–	–	–
Leukopenia	–	–	+	+	+	+	–	–	–
Thrombocytopenia	–	–	+	+	+	+	–	–	–

CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *HHV,* human herpesvirus; *HSV,* herpes simplex virus; *KSHV,* Kaposi sarcoma–associated herpesvirus; *VZV,* varicella-zoster virus. *Modified from Straus SE. Introduction to herpesviridae. In: Mandell GL, Bennett JE, Dolin R, eds.* Principles and Practice of Infectious Diseases. *6th ed. Philadelphia: Churchill Livingstone; 2005:1756–1762.*

encode chemokines, and CMV, EBV, HHV-6, HHV-7, and KSHV encode chemokine receptor homologues.[36] Herpesviruses also express microRNAs that contribute to immune evasion.[37,38] Many herpesviruses activate the inflammasome, a complex of proteins that in turn activate IL-1β and IL-18, which have antiviral activities; these same viruses often encode proteins that inhibit the inflammasome.[39,40] Together these immune evasion proteins allow the virus to avoid destruction by the host immune system.

ONCOGENESIS

Two human herpesviruses, EBV and KSHV, are oncogenic in humans, whereas the other human herpesviruses are not associated with cancer.[41] Oncogenic viruses must be maintained in cells and be transmitted to progeny cells. Oncogenic viruses express a limited set of viral proteins during latency to avoid detection by the immune system and to provide functions needed to immortalize the cell. EBV and KSHV encode proteins that activate cellular gene expression and B-cell signaling pathways. EBV LMP-1 functions as an oncogene and mimics the activity of CD40 to activate nuclear factor kappa B and signal transducers and activators of transcription (STATs), whereas KSHV encodes several proteins (e.g., K1, K12, ORF74) with transforming activity. EBV is associated with B-cell malignancies including Hodgkin disease, non-Hodgkin lymphoma, and Burkitt lymphoma, as well as epithelial cell cancers such as gastric carcinoma and nasopharyngeal carcinoma. Similarly, KSHV is associated with Kaposi sarcoma (an endothelial cell cancer) and two B-cell malignancies—primary effusion lymphoma and Castleman disease.

DIAGNOSIS

Most primary herpesvirus infections, such as herpes gingivitis, genital herpes, varicella, and roseola, are diagnosed by their clinical symptoms. Serology is useful for confirming acute or previous infection. Type-specific serologies are available for HSV-1 and HSV-2, either of which can cause oral or genital disease.

Polymerase chain reaction (PCR) assay is the standard test for detection of HSV, EBV, CMV, or HHV-6 encephalitis; culture of virus from the cerebrospinal fluid is much less likely to be positive.[42] Intrathecal synthesis of antibody to VZV is more sensitive for diagnosis of VZV encephalitis than is PCR assay.[43] PCR assay of cerebrospinal fluid is also useful for the diagnosis of HSV meningitis and can be an important clue for EBV central nervous system lymphoma in highly immunocompromised patients. Quantification of CMV and EBV DNA in the blood is useful for monitoring the risk for disease due to these viruses and for response to therapy in transplant recipients. Culture of herpesviruses is much less sensitive than the PCR assay but is useful for analysis of drug-resistant virus. Because asymptomatic shedding is common for most herpesviruses, a positive culture does not necessarily indicate that the virus is causing disease. Direct fluorescent antibody testing is useful for detection of VZV in skin lesions.

Lytic replication of herpesviruses causes characteristic intranuclear inclusions in tissues. CMV and HHV-6 cause both intranuclear and cytoplasmic inclusions, whereas HSV and VZV result in only intranuclear inclusions (Fig. 134.2). Immunohistochemistry with monoclonal antibodies can be used to identify specific viruses in tissues.

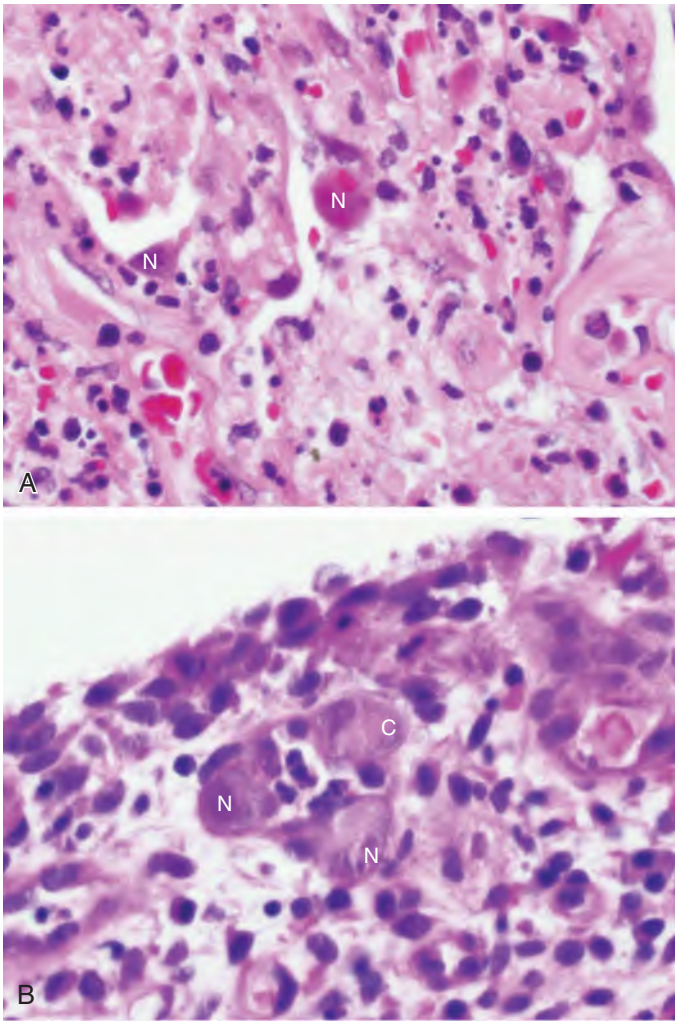

FIG. 134.2 (A) Intranuclear inclusions in cells infected with herpes simplex virus. (B) Intranuclear and cytoplasmic inclusions in cells infected with cytomegalovirus. *C,* Cytoplasmic; *N,* intranuclear. *(Courtesy David Kleiner, Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD.)*

THERAPY

Nearly all US Food and Drug Administration–approved oral or intravenous antiviral agents for herpesvirus infections act at the same step of virus replication; they inhibit the viral DNA polymerase.[44] Some antiviral agents are phosphorylated by the HSV or VZV thymidine kinase (acyclovir, penciclovir) or CMV UL97 protein kinase (ganciclovir), whereas other antiviral drugs do not require phosphorylation by viral proteins (foscarnet, cidofovir). In general, foscarnet and cidofovir are more toxic to cells because they are active in both infected and uninfected cells. Valacyclovir, valganciclovir, and famciclovir are prodrugs that are converted to their active form (i.e., acyclovir, ganciclovir, penciclovir, respectively) by cellular enzymes. Brincidovir, which is under development, has activity against most, if not all, of the herpesviruses and is a lipid conjugated form of cidofovir without significant renal toxicity.[45] In 2017, letermovir, a viral terminase inhibitor important for viral DNA cleavage and packaging,[46] was approved for prophylaxis of CMV in hematopoietic cell transplant recipients. Other drugs under development that act at steps other than the viral DNA polymerase include maribavir for CMV,[47] which inhibits the viral protein kinase UL97; pritelivir, a helicase-primase inhibitor for HSV [48]; and amenamevir, a helicase-primase inhibitor for HSV and VZV[49] (see Chapter 46).

Resistance of HSV, VZV, or CMV to antiviral drugs usually only occurs in highly immunocompromised persons and is usually due to mutations in the HSV or VZV thymidine kinase or CMV protein kinase; foscarnet or, less often, cidofovir is used to treat drug-resistant HSV, VZV, or CMV. Resistance to the latter two agents can occur due to mutations in the viral DNA polymerase. Antiviral therapy has not been proven to be clinically effective for HHV-6, HHV-7, and KSHV. Antiviral therapy is not beneficial for reducing symptoms of EBV disease, with the exception of oral hairy leukoplakia. Corticosteroids are occasionally used to treat severe manifestations of EBV, which are due to the T-cell proliferative response to the virus rather than to lytic replication in B cells.

Currently available antiviral agents inhibit lytic replication, not latent replication, and therefore do not affect the latent reservoir of viral DNA. One approach that has been suggested to reduce the latent reservoir of herpesvirus DNA is to activate lytic replication in latently infected cells (e.g., using a histone deacetylase inhibitor) and then treat with an inhibitor of lytic replication (acyclovir or ganciclovir). This approach has been used in vitro[50] and in a small number of patients with

EBV-positive lymphomas.[51] Another approach is to infuse human leukocyte antigen–matched cytotoxic T cells to destroy latently EBV-, CMV-, or HHV-6–infected cells.[52]

PREVENTION

Varicella-zoster immune globulin is used to decrease the severity of disease in immunocompromised persons exposed to chickenpox or shingles, and CMV immune globulin is used to decrease disease in organ transplant recipients at high risk for CMV disease. Hyperimmune globulin was not shown to prevent congenital CMV in one study[53]; additional trials are ongoing. Acyclovir reduces recurrences of HSV and severity of varicella in uninfected immunocompromised persons exposed to VZV; ganciclovir or foscarnet reduces the risk for CMV disease in transplant recipients who often have virus reactivation. While CMV can reactivate in patients with acute disease in the intensive care unit, a study of ganciclovir to reduce CMV reactivation disease in CMV-seropositive adults with critical illnesses did not support its use for prophylaxis.[54]

Currently licensed vaccines are only available for VZV to prevent varicella and zoster.[55] The live-attenuated vaccines differ only in the titer of the vaccine virus used; the live shingles vaccine is approximately 14 times the titer of the varicella vaccine. Both vaccines induce humoral and cellular immunity. The varicella vaccine reduces the risk and severity of varicella, but does not prevent infection. In 2017, a glycoprotein subunit vaccine was licensed to prevent zoster, and is particularly effective in the elderly.[56] Vaccine-induced antibody is the correlate of protection against varicella, while VZV-specific CD4 T cells correlate with protection from zoster; the correlate of protection against other herpesviruses in not well understood. Live-attenuated vaccines are not likely options for EBV and KSHV, which contain oncogenes and other genes that induce lymphocyte proliferation. Candidate vaccines for herpesviruses that are farthest along in clinical trials are subunit vaccines. Although a glycoprotein D vaccine for genital herpes failed to show efficacy for protection against genital herpes infection in women,[57] additional vaccines are under development.[58] A glycoprotein B vaccine for CMV reduced infection in healthy women[59,60] and reduced virus reactivation in a subset of organ transplant recipients in phase II trials.[61] A CMV DNA vaccine reduced virus reactivation in hematopoietic stem cell transplant recipients[62] but was unsuccessful in a phase 3 trial. Additional CMV vaccines are in clinical trials and under development.[63] A glycoprotein gp350 vaccine reduced the rate of EBV infectious mononucleosis, but did not prevent asymptomatic infection, in healthy young adults.[64]

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The complete reference list is available online at Expert Consult.

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135 Herpes Simplex Virus

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SHORT VIEW SUMMARY

Definition

- Herpes simplex virus (HSV) is a human alphaherpesvirus of two types, HSV-1 and HSV-2.
- Both types cause common infections in otherwise healthy children and adults, with varied clinical manifestations that are generally more severe in patients with immunosuppression.

Epidemiology

- HSV-1 and HSV-2 have a worldwide distribution and have no known animal reservoirs.
- HSV-1 is acquired more frequently and earlier than HSV-2. Approximately 3.7 billion adults have antibodies to HSV-1 by their 40s.
- HSV-2 seroprevalence correlates with onset of sexual activity and is consistently higher in women than men.
- Global incidence of HSV-2 has been estimated at 19.2 million new cases per year.
- HSV-2 increases risk of HIV-1 acquisition and transmission.

Microbiology

- HSV is an enveloped virus that is 160 nm in diameter and has a linear, double-stranded DNA genome.
- HSV-1 and HSV-2 have approximately 50% homology, and homologous sequences are distributed throughout the genome map.
- HSV infection occurs through attachment to cells via ubiquitous receptors, reflecting a wide tissue range of infections in the host including sensory neurons, which allow lifelong latency.
- Viral replication occurs through nuclear and cytoplasmic phases including attachment, fusion, DNA replication, capsid formation, and egress.
- Latency occurs within neural ganglia and is associated with transcription of only a limited number of virus-encoded RNAs.

Clinical Manifestations

- HSV has been isolated from nearly all visceral and mucosal sites. Clinical manifestations depend on the anatomic site, antigenic type (1 or 2) of the virus, and age and immune status of the host.
- Initial (primary) infections are usually more severe than recurrent ones, but reactivation of latent infection can result in frequent clinical manifestations.
- Orofacial infection (gingivostomatitis and pharyngitis) is the most frequent initial clinical manifestation of HSV-1 infection. Recurrent lesions on the vermilion border of the lip (herpes labialis) are the most frequent manifestation of latent infection.
- Clinical aspects of primary genital infections by HSV-1 or HSV-2 are similar, but recurrences are more frequent with HSV-2. Complications include aseptic meningitis, transverse myelitis, and sacral radiculopathy. Extragenital lesions may occur during the course of primary genital infection.
- HSV can cause vision-threatening eye infections such as keratitis and retinitis.
- Herpes simplex encephalitis is the most commonly identified cause of acute, sporadic viral encephalitis in the United States. Magnetic resonance imaging is the neuroimaging technique of choice, and lumbar puncture is diagnostic.
- Esophagitis, pulmonary infections, hepatitis, and overwhelming disseminated disease may be caused by HSV, most commonly in immunocompromised patients. Severe skin infections can be seen in patients with eczema.
- Neonatal infections may occur through contact with HSV-infected secretions. Infants younger than 6 weeks have the highest frequency of visual and central nervous system involvement.

Diagnosis

- Clinical criteria are used for consideration of the diagnosis of HSV infection, but laboratory tests are needed to confirm the diagnosis.
- Diagnosis can be made by detection of HSV DNA by polymerase chain reaction assay in lesion scrapings, fluids, or tissue. Viral isolation in tissue culture is three to four times less sensitive than DNA molecular techniques.
- Serology is diagnostic of established infection. Western blot most accurately discriminates HSV-1 and HSV-2 infections.

Therapy

- Acyclovir, valacyclovir, or famciclovir is used to treat mucocutaneous and visceral infections (see Table 135.3).
- Primary or recurrent genital infections may be treated to limit duration of symptoms. Individuals with frequent recurrences may be treated with suppressive therapy.
- Herpes simplex encephalitis and meningitis are treated with high-dose acyclovir (10 mg/kg intravenously every 8 hours for 14–21 days).
- Acyclovir-resistant HSV strains can be treated with foscarnet or cidofovir.

Prevention

- There is currently no licensed vaccine to prevent either HSV-1 or HSV-2.

Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) produce a wide variety of illnesses including mucocutaneous infections, infections of the central nervous system (CNS), and occasional infections of visceral organs; some of these conditions may be life threatening. HSV-2 is biologically and epidemiologically linked to increased acquisition and transmission of human immunodeficiency virus type 1 (HIV-1) infection. Effective chemotherapy for HSV infection is available but does not appear to alter the effects of recent or prior HSV-2 infection on HIV acquisition or transmission.

The word "herpes" (from the Greek, "to creep") has been used in medicine since antiquity. Cold sores (herpes febrilis) were described by the Roman physician Herodotus in AD 100.[1] Genital herpes was first described by John Astruc, physician to the king of France in 1736: the first English translation of his treatise on venereal disease appeared in 1754.[2,3] Transmission of infection in orolabial lesions was documented in the late 19th century. Experimental transfer of disease to rabbits was accomplished in the early 20th century, and HSV was grown in vitro in 1925.[4,5] In the 1960s, Nahmias and Dowdle[6] reported two antigenic types of HSV with different sites of viral recovery.

DESCRIPTION OF VIRUS

Microbiology Virus Structure

The eight known human herpesviruses (HHVs) are divided by genomic and biologic behavior into three groups: alphaherpesviruses

(HSV-1, HSV-2, and varicella-zoster virus [VZV]), betaherpesviruses (cytomegalovirus [CMV], HHV-6, and HHV-7), and gammaherpesviruses (Epstein-Barr virus and Kaposi sarcoma–associated herpesvirus, or HHV-8). Herpesviruses share morphologic traits including an internal core containing double-stranded DNA, an icosahedral capsid with 162 capsomers, an amorphous material surrounding the capsid called a tegument, a lipid envelope with surface viral glycoproteins, and an overall diameter of about 160 nm.[7] Despite these similarities, the biologic and epidemiologic features of each of the herpesviruses are different. Although HSV-1 and HSV-2 are the two most closely related herpesviruses, the two agents are serologically and genetically distinct.[6]

The genome of HSV is a linear, double-stranded DNA molecule (molecular weight approximately 1×10^8 kDa) that encodes about 90 transcriptional units, 84 of which appear to encode proteins. Sequences from both terminal ends of the genome repeat in an inverted fashion, dividing the genome into two unique components.[8] The overall sequence homology between HSV-1 and HSV-2 is about 50%,[9] with homologous sequences distributed over the entire genome map. Most polypeptides specified by one viral type are antigenically related to polypeptides of the other viral type. Many type-specific regions unique to HSV-1 and HSV-2 proteins do exist, however, and some appear to be important in evading host immunity. Interspecies recombinants of HSV-1 and HSV-2 are widely circulated despite divergence of these viruses 6 to 8 million years ago.[10,11]

HSV is genomically stable, and restriction endonuclease or sequence analysis of viral DNA can distinguish between the two subtypes and among strains of each subtype.[12,13] Isolates from epidemiologically related sources, such as sexual partners, mother-infant pairs, or victims of a common-source outbreak, are often nearly identical.[14–17] The variability of clinical strains of HSV-1 and HSV-2 is such that HSV isolates obtained from two individuals can be differentiated,[18] and superinfection within a single person can be identified using nucleotide sequencing.[19] Globally, nucleotide and protein identity among strains is high, with a maximum nucleotide divergence of 0.4% and approximately 90% protein identity.[20,21]

The degree of sequence diversity across the globe is only partially characterized,[11,20,22,23] but whole-genome sequencing has been extended more recently to a variety of clinical isolates.[24] Although hot spots of sequence variability are increasingly being identified in specific genes,[21] the role of this variability in HSV pathogenesis is not understood at the present time.

Virus Replication

Viral replication has nuclear and cytoplasmic phases. The initial steps of replication include attachment and fusion between the viral envelope and cell membrane to liberate the nucleocapsid into the cytoplasm of the cell. The initial attachment to the cell membrane involves the interactions of viral glycoproteins C and B with cellular heparan sulfate.[25,26] Subsequently, viral glycoprotein D binds to cellular coreceptors that belong to the tumor necrosis factor receptor family of proteins, the immunoglobulin superfamily (nectin family), or both.[27] The ubiquity of these receptors underscores the wide host range of herpesviruses, and their presence on sensory neurons implicates them in development of neuronal infection and latency.[28,29]

After attachment, the deenveloped tegument capsid structure is transported to nuclear pores where viral DNA is released into the nucleus. The virion envelope fuses with the host cell membrane and releases several functional proteins. The virion host shutoff protein shuts off synthesis (by increasing cellular RNA degradation), whereas VP16 turns on transcription of immediate early (IE) genes of HSV replication,[30] some of which are important determinants of neurovirulence in animal models. Others are required for synthesis of a subsequent polypeptide group, the β or early polypeptides. Many β-proteins are regulatory proteins and enzymes required for DNA replication including the targets (such as viral DNA polymerase and DNA helicase) of most antiviral drugs in current use or development.[31] Transcription of the viral genome, replication of viral DNA, and assembly of capsids take place in the nucleus.[32] The late (γ) class of HSV genes, which are structural and assist with viral egress, requires viral DNA replication for expression. DNA replication takes place in a "rolling circle" pattern similar to a roll of toilet paper. Specific viral genes "clip" the end of the viral DNA into the procapsid.

After nucleocapsids are assembled in the nucleus, envelopment occurs as the nucleocapsids bud through the inner nuclear membrane into the perinuclear space. In some cells, viral replication in the nucleus forms type A basophilic Feulgen-positive bodies that contain viral DNA and eosinophilic inclusion bodies that are devoid of viral nucleic acid or protein and represent a "scar" of infection. Virions are then transported through the endoplasmic reticulum and Golgi apparatus to the cell surface. The entire viral production cycle takes 4 to 6 hours, and an infected cell survives for 16 to 20 hours. HSV is cytopathic to cells that harbor the full cycle of HSV replication.[33]

Molecular Features of Latency

Some neuronal cells survive HSV infection and continue normal cellular functions but maintain viral genomes in a repressed state termed *latency*.[34,35] Latency is associated with transcription of only a limited number of virus-encoded RNAs.[36,37] The molecular mechanisms by which latency is established, maintained, and altered are incompletely understood. Subsequent activation of the viral genome may occur, resulting in the normal pattern of regulated viral gene expression, replication, and release of HSV, although without apparent damage to the infected neuron. The release of virions from the latently infected neuron to the peripheral endings (neurites) follows a complex process of anterograde transport through neuronal axons.[38,39] Subsequent viral entry into epithelial cells can result in viral replication; this entire process is termed *reactivation*.[40,41]

Although infectious virus typically cannot be cultured from sensory or autonomic nervous system ganglia dissected from cadavers, maintenance and growth of the neural cells in tissue culture results in production of infectious virions (explantation) and in subsequent permissive infection of susceptible cells (cocultivation).[42,43] HSV replication was first detected in neurons during reactivation in vitro, which suggested that the neuron harbors latent virus in vivo.[36] Viral DNA and RNA have since been found in neural tissue in the absence of infectious virus.[37] Individual neurons infected with multiple strains of virus have been documented in severely immunosuppressed patients[44] and more recently in immunocompetent individuals,[45] suggesting that the ganglia can be reseeded with HSV throughout chronic infection or reinfection, or both, through exogenous contact with new strains due to incomplete immunity.

Three noncoding RNA latency-associated transcripts (LATs) are the only transcripts in abundance in the nuclei of latently infected neurons.[36,46,47] In both trigeminal and dorsal root ganglia, LATs appear to maintain, rather than establish, latency.[48] LAT transcript abundance and low genome copy number correlate with subnuclear positioning of HSV genomes around the centromere.[49] Chromatization of HSV DNA appears to play a vital role in silencing expression of lytic replication genes.[50,51] Although certain viral transcripts are known to be necessary for reactivation from latency, the molecular mechanisms of HSV latency are not fully understood, and strategies to interrupt or maintain latency in neurons are in developmental stages.[52] Latency-competent deletion mutants of the LAT genomic region have reduced reactivation efficiency.[46,53] In addition, substitution of HSV-1 LAT for HSV-2 LAT induces an HSV-1 reactivation pattern.[48]

HSV-1 LATs promote the survival of acutely infected neurons perhaps by inhibiting apoptotic pathways.[54,55] LAT-derived microRNA is highly expressed during latency and appears to silence expression of the key neurovirulence factor infected cell protein 34.5 (ICP34.5)[56] and prevent expression of ICP0, an IE protein vital to HSV reactivation, through antisense binding of messenger RNA (mRNA). However, exit from latency appears to correlate with derepression of all, rather than just a small cluster of, HSV replication genes.[57] Evidence suggests that latency is not bimodally defined from lytic infection: specifically, there is evidence of cell-to-cell spread within ganglia following primary infection and expression of lytic genes during latency.[58,59] Thus within a single ganglion, HSV-infected neurons may vary significantly across a spectrum varying from deep latency to full lytic reactivation.

Dynamics of Herpes Simplex Virus Latency and Reactivation

Although latency is the predominant viral state on a per-neuron basis, the high frequency of oral and genital tract reactivation for HSV-1 and HSV-2 suggests that the virus is rarely quiescent within the entire biomass of ganglionic tissue.[60,61] Experimental data suggest that HSV-2 is frequently and nearly continually shed into genital mucosa. Mathematical models of HSV-2 reactivation predict that viral release from the ganglia occurs in a nearly continuous drip,[60] whereas only a single HSV particle from neurons is necessary to spark viral replication in genital epithelial cells.[60] Studies employing microdissection plus real-time polymerase chain reaction (PCR) of individual neurons from cadaveric trigeminal ganglia explants revealed that many more neurons (2%–10%) harbor HSV than would be predicted by in situ hybridization studies for LAT.[62,63] Moreover, viral copy number is highly variable among neurons, with extremely high levels in certain neurons.[62,63] HSV DNA copy numbers are similar in LAT-positive and LAT-negative neurons, adding uncertainty to the role that LATs play in preventing reactivation. In mice, IE, early, and late transcripts are abundant within latently infected ganglia, again suggesting a highly dynamic state among HSV-infected neurons, with some exhibiting deep latency and others showing evidence of lytic reactivation.[64]

EPIDEMIOLOGY

HSVs have a worldwide distribution and are found in the most remote human populations. There are no known animal vectors for HSV-1 or HSV-2, and although experimental animals are easily infected, humans appear to be the only natural reservoir. HSV-1 resulted from ancient codivergence with *Homo sapiens* from chimps, whereas HSV-2 was transmitted across species to a precursor of modern humans roughly 1.4 to 3 million years ago.[11,65] Multiple HSV-1 gene fragments, many of ancient origin, have been detected in whole HSV-2 genomes, suggesting frequent coinfection and genetic recombination.[66]

Herpes infection is the predominant cause of genital ulcers throughout the world. This is due to an overall decrease in *Treponema pallidum* and chancroid infections in most populations,[67] increase in PCR usage for HSV detection, and increase in HSV-2 reactivation frequency among individuals coinfected with HSV and HIV, rather than an increase in worldwide HSV prevalence.

Herpes Simplex Virus Type 1

Infection with HSV-1 is acquired more frequently and earlier than infection with HSV-2. More than 90% of adults have antibodies to HSV-1 by their 40s. Prevalence of antibody to HSV-1 increases with age and demonstrates an inverse correlation with socioeconomic status. In post–World War II era Western populations, 80% to 100% of middle-aged adults of lower socioeconomic status had antibodies to HSV-1 compared with only 30% to 50% of adults in higher socioeconomic groups.[68–70] Serosurveys continue to show a decline in the age-specific prevalence rates for HSV-1 infection in both the United States and globally, although socioeconomic class distinctions remain.[71] However, in much of Asia and Africa, HSV-1 infection is nearly universal and is acquired early in childhood (Fig. 135.1). Although primary HSV-1 and HSV-2 are clinically indistinguishable, in the United States, genital HSV-1 is now more common in whites, whereas primary genital HSV-2 remains more common in blacks.[72] HSV-1 now accounts for approximately 140 million cases of genital herpes.[70] This increased frequency of sexually acquired HSV-1 infections as well as an increased proportion of neonatal HSV cases due to HSV-1 may be accounted for by the decrease in HSV-1 acquisition in childhood.[73–75]

Herpes Simplex Virus Type 2

Antibodies to HSV-2 start to appear during puberty and correlate with initiation of sexual activity.[71,76] Widespread use of serologic testing has provided a detailed characterization of a worldwide HSV-2 pandemic over the past 2 decades (Fig. 135.2).[71,77,78] Global HSV-2 prevalence is estimated at 11.3% (417 million people) among individuals 15 to 49 years of age, with 19.2 million new infections in 2012.[79] Surveys generally indicate very high levels of infection in Africa, although risk varies within each country according to sex and region.[80] Seroprevalence is

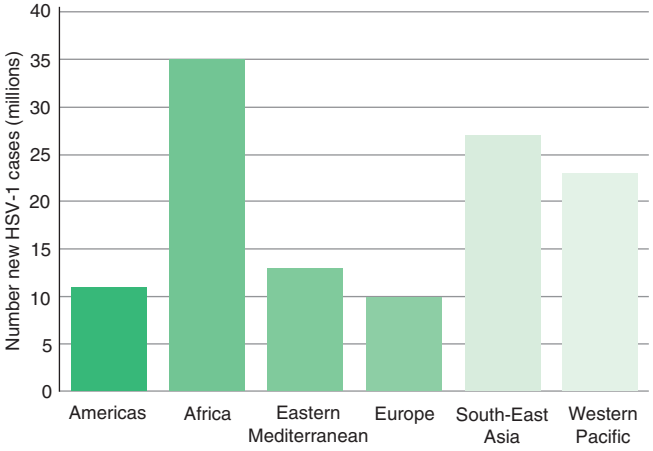
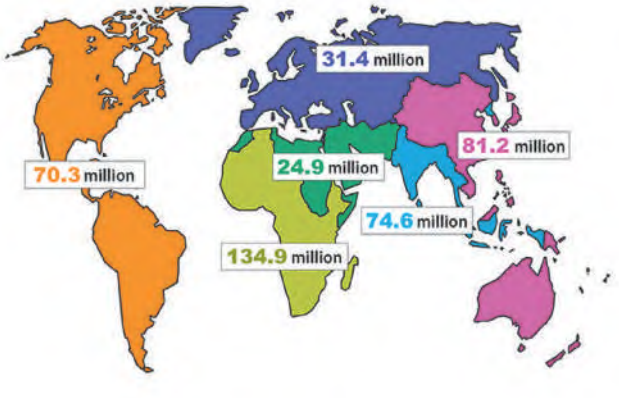


FIG. 135.1 Global seroincidence of herpes simplex virus type 1 *(HSV-1)* infection. *(From Looker KJ, Magaret AS, May MT, et al. Global and regional estimates of prevalent and incident herpes simplex virus type 1 infections in 2012.* PLoS One. *2015;10:e0140765.)*



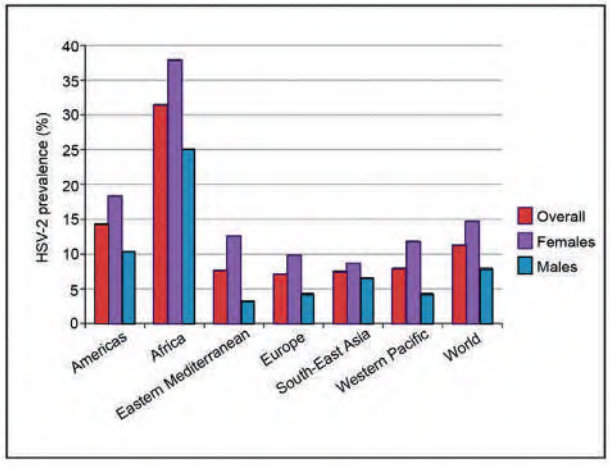


FIG. 135.2 Global herpes simplex virus type 2 *(HSV-2)* prevalence by geographic region. *(From Looker KJ, Magaret AS, Turner KM, et al. Global estimates of prevalent and incident herpes simplex virus type 2 infections in 2012.* PLoS One. *2015;10:e114989.)*

lower in Europe, Australia, Latin America, and Asia, although it remains highly dependent on the risk of the group being evaluated. In the United States, nationwide surveys showed an increase in HSV-2 seroprevalence from 16.4% to 21.7% of adults between 1979 and 1991, with a decrease to 16% from 2005 to 2010.[71,77,81] The cumulative lifetime incidence of HSV-2 is 25% in white women, 20% in white men, 80% in black women, and 60% in black men. The higher rates of HSV-2 among African Americans may reflect patterns of sexual networking rather than differences in high-risk individual behavior.[82]

Although global incidence decreases with age (Fig. 135.3), local incidence of HSV-2 infection is often difficult to estimate owing to the common nature of asymptomatic seroconversion, attenuation of symptoms due to prior HSV-1 infection, location of lesions in nonvisible locations (e.g., perianal), and differential access to health care and diagnostics. For instance, among HSV-seronegative women in the control arm of an HSV-2 vaccine trial, only half of seroconversions were clinically symptomatic.[83] Nevertheless, data are accumulating and vary between populations based on risk characteristics and geography. Vaccine and condom prevention studies conducted in serodiscordant American couples document HSV-2 seroincidence levels between 6.7 and 8.6 infections per 100 person-years for women and 1.5 to 3.7 per 100 person-years for men.[84–86] Seroincidence in several cohorts of high-risk urban youth was 11.7 cases per 100 person-years.[87] In African populations characterized by high preexisting HSV-2 seroprevalence, seroincidence was 1.8 to 12.9 per 100 person-years, with higher acquisition rates among persons infected with HIV-1 and seronegative women in a monogamous relationship with a seropositive man.[88–90] Among adolescent cohorts in sub-Saharan Africa, incidence exceeding 20 per 100 person-years has been reported,[91,92] although far lower rates have been noted in certain regions.[93]

Herpes Simplex Virus Type 2 Risk Factors

HSV-2 prevalence in a population is defined by geographic region, sex, sexual habits, and study population. Prevalence of HSV-2 in women is consistently higher than in men (see Figs. 135.2 and 135.3).[68,69,75,78,79] HSV-2 infection exceeds 80% among HIV-infected individuals, individuals recruited from sexually transmitted disease clinics, and men who have sex with men (MSM).[94,95] HSV-2 antibody levels are closely related to the lifetime number of sexual partners, age of sexual debut, and history of other sexually transmitted diseases.[96,97] HSV-2 infection is nearly universal among female sex workers with many exposures, suggesting a genetic phenotype of complete protection is rare.[98]

Cofactors for genital HSV-2 acquisition risk at the level of an individual are well defined from prospective trials. Despite equivalent shedding rates,[99] women are consistently at higher risk for HSV-2 acquisition than men. Possible explanations include greater mucosal surface area, higher likelihood of asymptomatic ulcers (which may facilitate transmission) in men, or high-risk placement within sexual networks. It is uncertain whether past HSV-1 infection reduces HSV-2 infection risk. However, people with prior HSV-1 infection are three times as likely to acquire HSV-2 subclinically.[83] Overall, one-third of source partners within serodiscordant couples deny a history of genital lesions.[100]

In contrast to bacterial sexually transmitted diseases, HSV-2 is commonly transmitted within long-term couples rather than casual sexual relationships. Longitudinal studies of such couples showed transmission rates ranging from 3% to 12% per year.[86,101] Although incidence of transmission within serodiscordant couples is relatively low in clinical trials, the median time to transmission within discordant couples in natural history cohorts is 3 months,[102] with a median number of only 40 sex acts before transmission, or an approximate 3.5% per-coital risk.[86]

Knowledge of a long-term partner's HSV-2–positive status decreases transmission incidence by 50%, highlighting the importance of formal diagnosis and disclosure of infection.[86,102] Consistent condom use decreases HSV acquisition among women, and chemoprophylaxis of the source partner decreases transmission by roughly 50%.[86,101] Circumcision decreases both HIV-1 and HSV-2 acquisition risk in men[103–105] but does not appear to impact transmission rates of HSV-2 to female partners.[106]

TRANSMISSION

Transmission of HSV most frequently occurs through close contact with a person who is repeatedly shedding virus at a peripheral site, at a mucosal surface, or in genital or oral secretions.[107–109] In 1921, Lipschutz[5] inoculated material from genital herpetic lesions into the skin of humans, eliciting clinical infection within 48 to 72 hours in six persons and within 24 days in one case. It is now understood that infection occurs by inoculation of virus onto susceptible mucosal surfaces (e.g., oropharynx, cervix, conjunctivae) or through small cracks in the skin. Because HSV is readily inactivated at room temperature and by

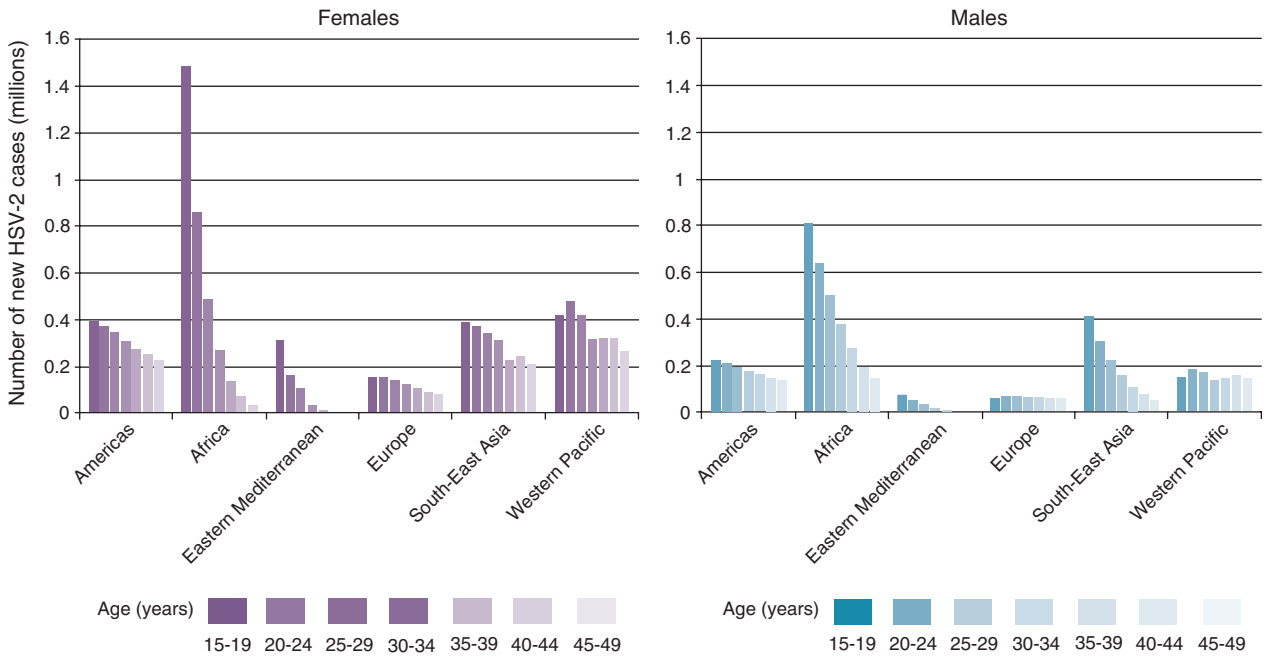


FIG. 135.3 Estimated herpes simplex virus type 2 *(HSV-2)* incidence by sex, age, and geographic region. *(From Looker KJ, Magaret AS, Turner KM, et al. Global estimates of prevalent and incident herpes simplex virus type 2 infections in 2012.* PLoS One. *2015;10:e114989.)*

drying, aerosol and fomitic spread are unusual. Transmission of HSV-1 from orogenital contact is increasingly recognized, perhaps because of reduction in age-specific prevalence of HSV-1 at the time of sexual debut.[110] Spread of HSV-1 infection from oral secretions to other skin areas is a hazard of certain occupations (e.g., dentists, respiratory care unit personnel), and laboratory-acquired and nosocomial outbreaks in hospital or nursery personnel have been reported.[111] Herpes gladiatorum outbreaks among wrestlers are well recognized.[112] Transmission of HSV can occur in infants born to mothers excreting HSV at delivery.[113] Anal and perianal infections with HSV-1 or HSV-2 are common among sexually active populations of MSM.[114] Most cases occur within 5 days of contact, highlighting the short incubation period of primary infection.

Precise virologic determinants of transmission likelihood are poorly understood. For HIV infection, a clear relationship between genital and plasma HIV viral load and per-coital risk for HIV transmission is established.[115,116] However, because genital HSV-2 levels fluctuate extremely rapidly over hours both on and off therapy,[117,118] the precise degree to which source partner viral load during sex impacts likelihood of transmission is unknown.[119] Nevertheless, modeling suggests that a certain viral load threshold influences sexual transmission.[120]

Subclinical or asymptomatic shedding of HSV in oral and genital secretions is a hallmark of infection,[99,107,121] both in immune competent and immunocompromised persons,[122] and transmission occurs more commonly during asymptomatic shedding.[100,123] Prolonged asymptomatic shedding episodes lasting several days are well described, even among immunocompetent patients taking daily antiviral therapy.[99,118] Frequency of symptomatic recurrences poorly predicted likelihood of transmission in a prospective trial, again highlighting the high transmission risk for asymptomatic shedding.[124]

Frequency of detectable shedding is markedly heterogeneous among individuals seropositive for HSV-2, likely influencing the variability in reported per-coital transmission rates.[121] DNA polymerase inhibitors that decrease frequency of asymptomatic shedding as well as peak HSV-2 titers during recurrence also decrease transmission within serodiscordant couples.[101]

PATHOGENESIS

Primary Infection

Exposure to HSV at mucosal surfaces or abraded skin permits entry of the virus and initiation of its replication in cells of the epidermis and dermis.[125] Initial HSV infection is often subclinical, without apparent lesions. In animal models and human subjects, both clinical acquisition and subclinical acquisition are associated with sufficient viral replication to permit infection of either sensory or autonomic nerve endings, with the subsequent potential for lifelong reactivation.[37,61,125,126] After traversing the neuroepithelial gap and entering into the neuronal cell, the virus or nucleocapsid is transported intraaxonally to the nerve cell bodies in ganglia.[127] For HSV-1 infection, trigeminal ganglia are most commonly infected, although extension to the inferior and superior cervical ganglia also occurs.[34,35] With genital infection, sacral nerve root ganglia (S2 to S5) are most commonly affected.[40] Autonomic ganglia also appear to be infected, albeit clinical manifestations of such infections are relatively uncommon.[128] In humans, the interval from inoculation of virus in peripheral tissue to spread to the ganglia is unknown.

High-level viral replication occurs in ganglia and contiguous neural tissue during primary infection, although lytic transcripts also are detectable during and between reactivations in mouse and guinea pig models.[58,125,126,129] After initial inoculation of the neural ganglion, virus spreads to other mucosal skin surfaces by centrifugal migration of infectious virions through peripheral sensory nerves. This mode of spread explains the characteristic development of new lesions distant from the initial crop of vesicles in patients with primary genital or orolabial HSV infection, the large surface area over which these vesicles may be visualized, and the recovery of virus from neural tissue distant from neurons innervating the inoculation site.[130] Contiguous spread of virus also likely occurs via autoinoculation.[117] Viremia is present during approximately 25% of primary HSV-2 infections, and its presence may affect the natural history of HSV-2 disease in terms of site, severity, and frequency of reactivation.[131]

During primary HSV-2 infection, a local resident T-cell population has yet to be established in mucosa or ganglia. Therefore innate immune cells and antigen presenting cells represent early immune responders in biopsies of active lesions and are likely to be critical in eliminating infected cells during first exposure to the virus.[132]

Ganglionic Cell–Mediated Immunity

After resolution of primary disease, viral DNA is present in 2% to 11% of ganglion cells in the anatomic region of initial infection.[62] Therefore many neurons may contribute to reactivation, the frequency and severity of which may be influenced by host T-cell responses at the ganglion level as well as the previously described molecular features of latency. Although it is unknown whether reactivating stimuli transiently suppress these immune cells or independently upregulate transcription of lytic genes, or both, it is well documented that $CD8^+$ T cells juxtapose to HSV-1 latently infected neurons in human trigeminal ganglia.[133] These activated cells are reactive to a broad array of early and late HSV antigens.[134] In murine models, resident $CD8^+$ lymphocytes and lymphocyte-derived cytokines appear to be important in preventing infectious virions from being transported down the length of the axon for release in the basal layer of the epidermis[135–137] and can block reactivation both with interferon-γ release[138] and granzyme B degradation of IE protein ICP4.[139] In addition, in animal models, the latent viral load in the entire biomass of ganglia correlates positively with number of neurons infected and rate of reactivation but inversely with number of $CD8^+$ T cells present.[140,141] Glutamine, which promotes proliferation of activated T cells, decreased ganglionic HSV-2 reactivation in a murine system.[142]

Mucosal Cell–Mediated Immunity

Studies involving genital mucosal responses to HSV-2 infection indicate that viral-host interactions in the mucosa dictate clinical expression of disease. Histologic examinations reveal that herpetic lesions consist of a thin-walled vesicle or ulceration in the basal region; multinucleated infected cells that may include intranuclear inclusion bodies; necrosis; and an acute inflammatory infection including neutrophils, natural killer (NK) cells, B cells, and T cells.[132] A distinct subset of HSV-2–specific $CD8^+$ T cells that persist in genital skin conduct immune surveillance directed at containing virus at the point of release into the epithelium and are first responders capable of controlling HSV-2 and aborting clinical lesions.[143,144] Once virus reaches the dermal-epidermal junction, there are two possible outcomes: subclinical shedding or recurrence defined clinically by a skin blister and ulceration (Fig. 135.4).

Host effector cell density at the precise site of viral release into the genital/oral mucosa appears to be the main influence in dictating clinical and subclinical expression of disease.[145] These cells were shown to lack chemokine-receptor expression required for lymphocyte egress, express gene signatures of T-cell activation and antiviral activity, and produce cytolytic granules during virologic quiescent time periods.[143,146] $CD8^+$ memory T-cell trafficking into genital mucosa is temporally associated with clearance of virus from genital lesions,[147,148] and $CD8^+$ T-cell density at the specific site of infection is likely a key predictor of the extent of viral spread and potential.[149] Low levels of plasma HSV-specific $CD8^+$ cytotoxic T-lymphocyte precursors, rather than low $CD4^+$ lymphocyte counts, predict frequent and severe HSV-2 recurrences in untreated as well as treated HIV-1–infected patients.[150,151] HSV-2–specific $CD8^+$ and $CD4^+$ T cells appear to persist for many years in genital skin previously involved in an HSV-2 reactivation.[143,149,152] Heterogeneous spatial density of $CD8^+$ T-cell levels across the mucosa is a likely explanation for persistent breakthrough shedding.[143,149,153]

Innate Host Factors Impacting Pathogenesis and Disease Severity

Herpesviruses are evolutionarily ancient, infect a broad range of hosts, and have developed complex mechanisms for immune system evasion. Both HSV-1 and HSV-2 encode proteins that are directed at subverting innate and acquired responses.[154,155] ICP47 inhibits the transporter activity protein–mediated transport of viral peptides to the endoplasmic reticulum/Golgi apparatus; this prevents HSV peptide presentation by major histocompatibility class I molecules needed for $CD8^+$ cytotoxic

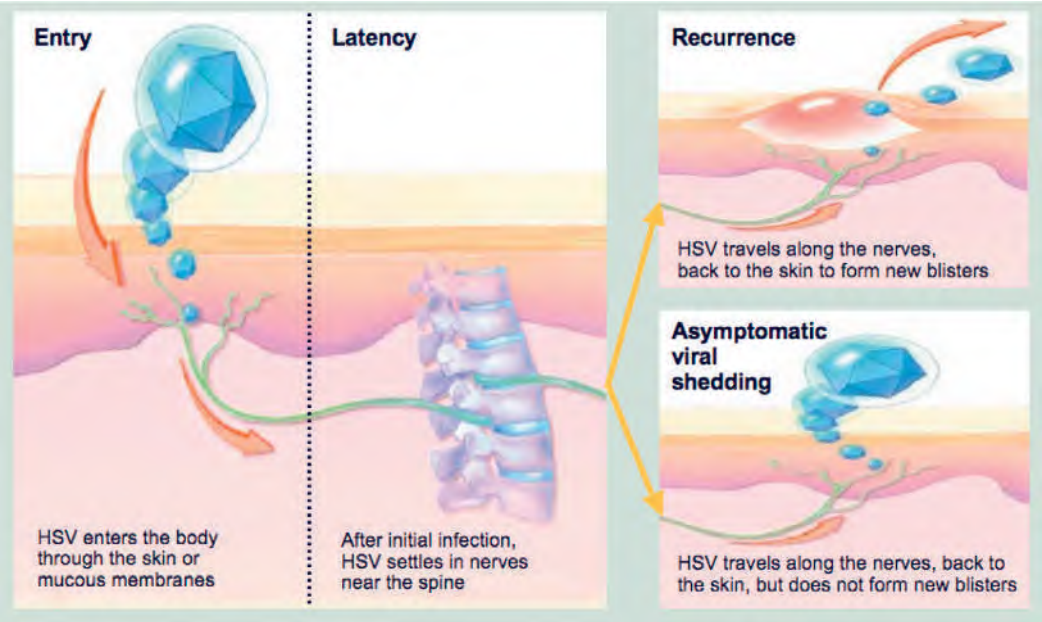


FIG. 135.4 **Schemata of herpes simplex virus *(HSV)* recurrence and asymptomatic viral shedding.**

T-cell responses to HSV.[155,156] The virion host shutoff protein rapidly degrades host and viral mRNA on host cell infection, which suppresses the interferon α/β antiviral innate response.[157] HSV glycoprotein J inhibits cytotoxic T-lymphocyte–induced apoptosis of infected cells and results in increased viral replication.[158,159] The antiviral function of several interferon-stimulated gene products is counteracted by HSV proteins, including ICP34.5, ICP0, and US11.[160,161]

Defects in innate immunity are associated with severe HSV-1 and HSV-2 infections. Fatal severe HSV-1 infections occur in individuals with innate immunity defects in NK cells and plasmacytoid dendritic cells.[162,163] Specific deficiencies in effective innate function involving the nuclear factor kappa B regulator,[164] Toll-like receptor (TLR)-3,[165] and TLR signaling protein UNC-93B[166] all are associated with familial and childhood HSV encephalitis. These mutations are rarely associated with severe cases of other infections.[167]

The innate immune response impacts the overall course of genital herpes as well. Defects in interferon receptors in mice promote enhanced infection.[168] TLR-2 polymorphisms are associated with increased HSV-2 shedding and recurrence rate,[169] and a randomized clinical trial found that a topically applied TLR-7 and TLR-8 agonist resulted in decreases in shedding.[170] Similarly, variation at the apolipoprotein E allele is associated with increased shedding.[171] Most host genetic determinants of frequency and severity of reactivation remain unidentified.

Cell-Mediated Host Factors Impacting Pathogenesis and Disease Severity

The role of the innate immune response is often not clearly differentiated from acquired immunity. Interferons that are influenced by innate cells (plasmacytoid dendritic cells, NK-T cells, and NK cells) may alter the balance of the Th1/Th2 response to HSV-2 and trigger similar transcription pathways in innate and acquired immune cells. Dendritic cells infiltrate genital lesions along with $CD4^+$ lymphocytes, and differences in antigen presentation may be factors in viral clearance.[172–175]

Animal models suggest that multiple cell populations including NK cells, macrophages, various T lymphocytes, and lymphokines generated by these cells play a role in host defense against HSV infection.[176,177] Experimental ablation of lymphocytes indicated that T cells play a major role in viral containment and prevention of lethal disseminated disease, although antibodies also help reduce viral titer in neural tissue.[178] In animals, passive transfer of primed lymphocytes confers protection against rechallenge.[176] Maximal protection usually requires the activation of multiple T-cell subpopulations including cytotoxic T cells and T cells responsible for delayed hypersensitivity.[179,180] In humans, serious systemic manifestations of disease can occur in patients with T-cell immunodeficiency resulting from HIV, organ transplant, chemotherapy, or certain inherited disorders.[181–183]

There is an evolving appreciation of the complexity of the cellular immune response to HSV-2. The impressive natural breadth and structure of the HSV-directed T-cell repertoire in regard to HSV target antigens is increasingly defined.[184,185] The compartmentalization of the acquired response is also better understood: responses in the neural ganglia, CNS, and mucosal sites all may play different roles.[137,144] Biopsy specimens of human herpetic lesions show that the predominant infiltrating cell is initially the $CD4^+$ lymphocyte,[132,186] displaying activation markers such as interleukin-2 receptor, dopamine receptor, and intercellular adhesion molecule-1 and secreting large amounts of γ-interferons.[187] In animal models of primary HSV infection, $CD4^+$ T cells release specific cytokines (CXCL-9 and CXCL-10), which are critical for subsequent $CD8^+$ T-cell function and infiltration.[188] This dense infiltrate of HSV-specific $CD8^+$ T cells as well as the number of circulating HSV-specific $CD4^+$ T cells is associated with clearance of HSV-2 from genital lesions, and these cells are disproportionately represented in the mucosa compared with the serum.[150,189] Persistence of ganglionic $CD8^+$ T cells in murine models is associated with experimental containment of reactivation.[140] However, plasma levels and the functionality of these cells or dendritic cells have, to date, not correlated with lesion or shedding rate, again pointing to the prominence of mucosal viral-host interactions in influencing disease expression.[190]

Some aspects of HSV disease may be related to cell-mediated immunopathologic events. In experimental animals, stromal keratitis associated with HSV-1 infection is precipitated by HSV-specific T cells. Molecular cross-reactivity between the HSV proteins and cellular proteins did not appear to play a role in this phenomenon in one study.[191] Thus the underlying mechanism of this immunopathologic syndrome has not been identified. The role of immunopathogenesis in oral and genital lesions is also unknown.

Humoral Host Factors Impacting Pathogenesis and Disease Severity

Agammaglobulinemic patients appear to handle HSV infection normally. However, neonatal HSV is more likely to occur in vaginally delivered infants when the mother has primary rather than recurrent infection, because placental antibodies are generated after primary infection and increase in avidity over time.[192–194] These data suggest cellular immunity is required for viral clearance, whereas antibodies may be required for

reducing acquisition. These factors must be considered in the design of immunotherapeutics versus prophylactic vaccines.

During natural infection, antibodies are broadly generated against tegument, capsid, and other nonessential viral glycoproteins, although the importance of antibody response magnitude, breadth, tissue compartment specificity, and subclass is not defined for HSV infection.[178] Surface viral glycoproteins necessary for attachment also participate as antigens that are recognized by antibodies mediating neutralization and immune-mediated cytolysis (antibody-dependent cell-mediated cytotoxicity).[195] Monoclonal antibodies specific for each of the known viral glycoproteins confer experimental protection against subsequent neurologic disease or ganglionic latency.[196] In an ex vivo model of human reactivation, adequate neutralizing antibody concentrations prevented the successful transmission of HSV from dorsal root ganglion neurons to keratinocytes, despite successful anterograde transport of fully assembled particles down the length of the sensory neuron.[197] Effector functionality of antibodies appears to be a key component of protection in animal studies.[198–200] Although several vaccines have shown promise in animal vaccine studies, evaluation of these vaccines in humans has been slow.[84,85] Interestingly, immunization with a glycoprotein deletion strain (ΔgD-2) conferred protection against lethal challenge in an animal model.[27]

SPECTRUM OF DISEASES CAUSED BY HERPES SIMPLEX VIRUS

HSV has been isolated from nearly all visceral and mucocutaneous sites, but clinical manifestations and infection course depend on the anatomic site involved, antigenic type of the virus, and age and immune status of the host. Presentations vary from subclinical mucosal shedding to overwhelming sepsis or encephalitis. First episodes of HSV disease, especially primary infections, are frequently accompanied by systemic signs and symptoms, involve both mucosal and extramucosal sites, have a higher complication rate, and have a longer duration of symptoms and viral shedding from lesions.[201,202] Conversely, asymptomatic primary infection is also common. Both viral subtypes can cause genital and orofacial infections, and infections caused by the two subtypes are clinically indistinguishable. However, the frequency of reactivation is influenced by anatomic site and virus type.[203]

OROFACIAL HERPES SIMPLEX VIRUS INFECTION

Gingivostomatitis and pharyngitis are the most frequent clinical manifestations of first-episode HSV-1 infection,[204,205] usually result from primary infection, and are most commonly seen in children and young adults.[206,207] Clinical signs and symptoms, which include malaise, myalgias, inability to eat, irritability, and cervical adenopathy, last 3 to 14 days. Lesions may involve the hard and soft palate, gingiva, tongue, lip, and face (Fig. 135.5). HSV-1 and HSV-2 infection of the pharynx usually results in exudative or ulcerative lesions of the posterior pharynx, tonsillar pillars, or both. Lesions of the tongue, buccal mucosa, or gingiva occur later in the course in one-third of cases. Fever lasts 2 to 7 days. It can be difficult to clinically differentiate HSV pharyngitis from bacterial pharyngitis, *Mycoplasma pneumoniae* infections, and pharyngeal ulcerations of noninfectious causes (e.g., Stevens-Johnson syndrome). Recurrent herpes labialis is the most frequent clinical manifestation of reactivation. No substantial evidence suggests that reactivation of orolabial HSV infection is associated with symptomatic recurrent pharyngitis. Release of HSV from the trigeminal ganglia may be associated with asymptomatic salivary virus excretion, intraoral mucosal ulcerations, or herpetic ulcerations on the vermilion border of the lip or external facial skin. About 50% to 70% of seropositive patients undergoing trigeminal nerve root decompression and 10% to 15% of seropositive patients undergoing dental extraction develop orolabial HSV disease a median of 3 days after these procedures.[208,209]

In immunosuppressed patients, infection may extend into mucosal and deep cutaneous layers. Friability, necrosis, bleeding, severe pain, and inability to eat or drink may result.[210] The lesions of HSV mucositis are similar to oral lesions caused by cytotoxic drug therapy, trauma, or fungal or bacterial infection.[211] Persistent and disabling ulcerative HSV infections are common in patients with acquired immunodeficiency syndrome (AIDS).[212] HSV and *Candida* infections often occur concurrently. Systemic acyclovir therapy reduces the frequency of clinical reactivation, speeds the rate of healing, and relieves the pain of mucosal HSV infections in immunosuppressed patients.[210,211] Patients with atopic eczema or burns may acquire severe orofacial HSV infections (eczema herpeticum), which may rapidly involve extensive areas of skin with occasional systemic dissemination.[213] Extensive eczema herpeticum typically resolves promptly with delivery of intravenous acyclovir.[214]

FIG. 135.5 Primary herpes simplex virus gingivostomatitis in a child extending to involve the cheek, chin, and periocular skin.

Erythema multiforme is also associated with HSV infections, and evidence suggests that HSV infection is the precipitating event in about 75% of cases of cutaneous erythema multiforme.[215] HSV antigen is often present in circulatory immune complexes and skin lesion biopsy samples from these patients.[216] Patients with severe HSV-associated erythema multiforme are candidates for chronic suppressive oral antiviral therapy.[217]

Complications of Oral Herpes Simplex Virus Type 1

HSV-1 and VZV are implicated as common causes of Bell palsy (facial paralysis of the mandibular portion of the facial nerve).[218] HSV DNA was found in ganglionic fluid in a high percentage of patients undergoing decompressive surgery for Bell palsy, suggesting recent reactivation as the cause of disease.[219] Although one trial showed faster and more frequent resolution of facial paralyses with the prompt use of antiviral therapy directed at HSV-1 or VZV, more recent data on antiviral therapy for Bell palsy suggest no benefit, perhaps related to the delayed timing of initiation of therapy. Corticosteroids are a mainstay of therapy and correlate with improved short-term and long-term resolution of symptoms (a common regimen is prednisone, 60–80 mg/day for 7 days).[220–222] There is no consensus on use of antiviral agents plus corticosteroids versus corticosteroids alone for the treatment of Bell palsy.

GENITAL HERPES SIMPLEX VIRUS INFECTION

First-episode primary genital herpes is associated with prolonged duration of symptoms, lesions (10–20 days), and viral shedding. This is particularly true for primary infection (i.e., HSV-1 and HSV-2 antibody negative), which is the case for about half of first-episode cases.[201] About 25% of patients with a first clinical episode of symptomatic genital herpes already have HSV-2 directed antibodies, suggesting asymptomatic acquisition occurred in the past.[223] First episodes of genital herpes caused by HSV-2 in patients who had prior HSV-1 infection are associated with less frequent systemic symptoms and faster healing than primary genital herpes, although rates of recurrence are the same.[201–203] The clinical courses of first-episode genital herpes caused by HSV-1 and HSV-2 are similar,[72,224] but frequency of subsequent recurrences in the first year after acquisition differ considerably: 55% and 90%, respectively.[203,224] Genital HSV-1 acquisition is rare after HSV-2 infection.[225] Prior oral HSV-1 infection appears to protect against genital HSV-1 infection, although the degree of this protection is unknown.

In 70% of women and 40% of men, first-episode genital herpes is accompanied by fever, headache, malaise, and myalgias. Pain, itching, dysuria, vaginal and urethral discharge, and tender inguinal lymphadenopathy are the predominant local symptoms and persist for several days after systemic symptoms. Local symptoms often peak between days 7 and 11 of detectable shedding, whereas inguinal tenderness can persist for several weeks. Widely spaced bilateral lesions of the external genitalia are characteristic on examination (Figs. 135.6 and 135.7). Lesions may be present in varying stages including vesicles, pustules, painful erythematous ulcers, crusting (on dry surfaces), or reepithelialization (mucosal surfaces). Multiple small ulcers often coalesce into one larger ulcer. If untreated, formation of new ulcers between days 4 and 10 of infection is common. The mean time from the onset of a primary genital HSV lesion to complete healing is 19.5 days for women and 16.5 days for men.[201,202]

Local Complications of Genital Herpes Simplex Virus Infection

The complications of genital herpes are related to local extension, spread to extragenital sites, or both.[113,226] Complications occur more frequently in women than in men.[201] A clear mucoid discharge and dysuria are present in first episodes of HSV infection in 83% of women and 44% of men. The severity of dysuria is often out of proportion to the urethral discharge seen on examination and the mild inflammation detected on urinalysis. HSV-2 cervicitis, when symptomatic, is notable for purulent or bloody vaginal discharge and can be difficult to clinically differentiate from *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection. When present on speculum examination, cervical ulceration or necrosis is specific for HSV-2 infection. HSV-2 is present on the cervix and urethra in more than 80% of women with first-episode infections and 20% of women with recurrent lesions (Fig. 135.8).[227,228] Traditional colposcopy and Pap test lack sensitivity for cervical HSV infection.[229] Moreover, HSV can be isolated from the urethra and urine of men and women without external genital lesions and from the urethra of 5% of women with dysuria-frequency syndrome.[228–230]

Occasionally, HSV genital tract disease is manifested by endometritis and salpingitis in women and prostatitis in men.[231,232] Both HSV-1 and HSV-2 can cause symptomatic or asymptomatic rectal and perianal infections. HSV proctitis is usually associated with rectal intercourse.[233,234] Symptoms include anorectal pain, anorectal discharge, tenesmus, and constipation. Sigmoidoscopy reveals ulcerative lesions of the distal 10 cm of the rectal mucosa. Rectal biopsy specimens show mucosal ulceration, necrosis, polymorphonuclear and lymphocytic infiltration of the lamina propria, and, occasionally, multinucleated intranuclear inclusion–bearing cells. External perianal lesions are present in only about one-half of cases.[233] Antiviral therapy speeds healing.[233–235] Perianal herpetic lesions are also found in immunosuppressed patients receiving cytotoxic therapy. Extensive perianal herpetic lesions, HSV proctitis, or both are common among HIV-infected patients.[212] Subclinical perianal shedding of HSV is detected both in heterosexual men and in women who report no rectal intercourse.[235,236] This phenomenon is due to the establishment of latency in the sacral dermatome from prior genital tract infection, with subsequent reactivation in epithelial cells in the perianal region.

FIG. 135.6 Primary genital herpes simplex virus type 2 infection of the vulva.

FIG. 135.7 Chancroidal herpes simplex virus lesion on penis. *(From Corey L. Herpes simplex virus infections. In: Mandell GL, series ed; Rein MF, ed.* Atlas of Infectious Diseases. Vol. V. Sexually Transmitted Diseases. *Philadelphia: Churchill Livingstone; 1996. Courtesy H.H. Handsfield, MD.)*

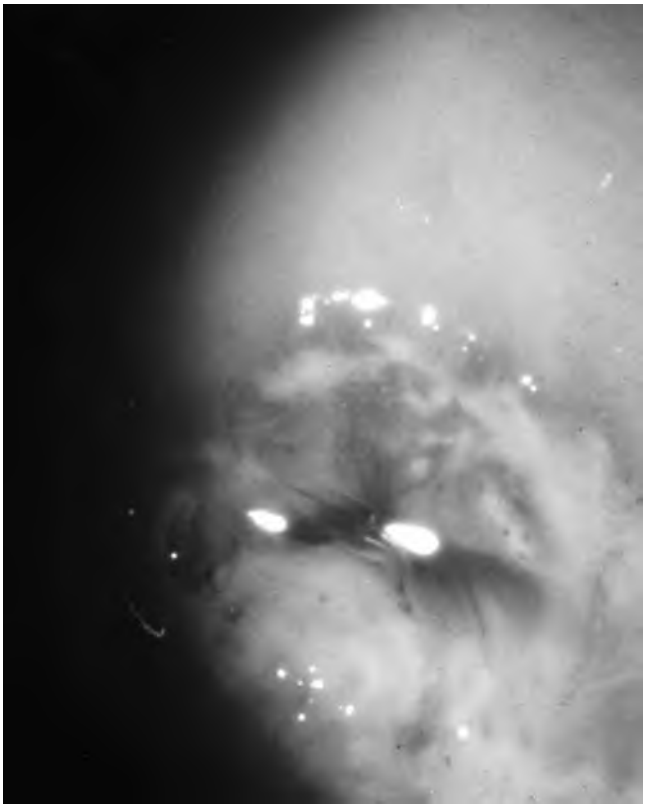


FIG. 135.8 Herpes simplex virus cervicitis. *(From Corey L. Herpes simplex virus infections. In: Mandell GL, series ed; Rein MF, ed.* Atlas of Infectious Diseases. Vol. V. Sexually Transmitted Diseases. *Philadelphia: Churchill Livingstone; 1996.)*

Aseptic Meningitis, Transverse Myelitis, and Sacral Radiculopathy

Both HSV-1 and HSV-2 have been isolated from cerebrospinal fluid (CSF), although overt viral meningitis is much more common with HSV-2.[237,238] In one series, 36% of women and 13% of men with primary genital HSV-2 infection had stiff neck, headache, and photophobia on two consecutive examinations.[201] Among these patients, hospitalization was necessary for 6.4% of women and 1.6% of men for aseptic meningitis. There was also a high frequency of CSF pleocytosis in patients without overt clinical evidence of meningeal irritation in a study of primary genital herpes in the early 1900s, suggesting that meningeal involvement may be quite common with primary genital herpes.[239]

Fever, headache, vomiting, photophobia, and nuchal rigidity are the predominant symptoms of HSV aseptic meningitis. Meningeal symptoms usually start 3 to 12 days after the onset of genital lesions. Symptoms generally reach a maximum 2 to 4 days into the illness and gradually recede without sequelae over 2 to 3 days. The CSF is usually clear, and opening pressures may be somewhat elevated. White blood cell counts in the CSF usually range from 10 to 1000 cells/mm.[3] The pleocytosis is predominantly lymphocytic in adults, although early in the course of disease and in neonates a predominantly polymorphonuclear response may be seen. The CSF glucose level is usually more than 50% of the blood glucose level, although hypoglycorrhachia has been reported.[240] The CSF protein is usually slightly elevated. In cases of aseptic meningitis, HSV may be isolated from the CSF, although HSV DNA detection by PCR assay is a considerably more sensitive diagnostic test and is now the mainstay for diagnosis.[238] The differential diagnosis of aseptic meningitis is broad, but the presence of both neurologic involvement and genital ulcerations narrows the possibilities to include sacral herpes zoster, Behçet syndrome, collagen vascular disease, inflammatory bowel disease, and porphyria. Although uncommon, aseptic meningitis may be the sole presenting sign of new HSV-2 acquisition. Use of systemic antiviral chemotherapy early in the course of primary genital herpes decreases subsequent development of aseptic meningitis. Controlled trials of intravenous acyclovir for established HSV meningitis have not been conducted. However, intravenous acyclovir, 10 mg/kg every 8 hours for 7 to 10 days, is recommended for hospitalized symptomatic patients.

Benign recurrent lymphocytic meningitis, or Mollaret meningitis, is characterized by recurrent episodes of meningitis lasting 3 to 7 days and resolving without neurologic sequelae.[241] Although the differential diagnosis for chronic meningitis is broad, HSV-2 is responsible for most recurrent cases.[242] In one small series of patients with meningitis during first-episode genital HSV-2 infection, 27% had possible symptomatic evidence of recurrent meningitis, and 10% had documented recurrent disease verified by HSV DNA in the CSF.[243] Prophylactic doses of acyclovir are often encouraged for patients with frequent recurrent meningitis.

Autonomic nervous system dysfunction can occur in association with genital HSV infection.[244,245] Manifestations include hyperesthesia or anesthesia of the perineum, lower back, or sacral regions; urinary retention; and constipation. This complication occurs more frequently in women than men but is sometimes present in men with HSV proctitis. Physical examination reveals a large bladder, decreased sacral sensation, and poor rectal and perineal sphincter tone. Impotence and absent bulbocavernous reflexes have been noted in men. CSF pleocytosis may be present in some patients. Electromyography usually reveals slowed nerve conduction velocities and fibrillation potentials in the affected area, and urinary cystometric examination shows a large atonic bladder. Most cases resolve within 4 to 8 weeks.

Transverse myelitis has also been reported in association with primary genital HSV infection.[246] Decreased deep tendon reflexes and muscle strength in the lower extremities as well as the previously described autonomic nervous system signs and symptoms are present. Residual neurologic dysfunction may occur. Whether autonomic nervous system and spinal cord dysfunction results from viral invasion of the CNS or an unusual immunologic response to infection is unknown.

Extragenital Lesions

Extragenital lesions commonly develop during the course of primary genital herpes and are more common in women than in men. Extragenital lesions are most frequently located in the buttock, groin, or thigh area, although the finger and eye can also be involved. Among patients with primary HSV-2, 9% develop extragenital lesions, most commonly on the buttocks. Among patients with primary genital HSV-1, 25% acquire extragenital lesions, most commonly in or around the mouth.[225] The distribution of lesions on the extremities or areas near the genital lesions and their typical occurrence 2 weeks into the course of disease suggest that most extragenital lesions develop by autoinoculation of virus or by viral reactivation in another part of the affected dermatome rather than viremic spread.[201,225] However, the common demonstration of plasma viremia during the course of primary HSV infection suggests that viremic spread may also be a factor.[131,247] Both HSV-1 and HSV-2 have been shown to be rare causes of pelvic inflammatory disease. Although this may represent dual infection with other sexually transmitted pathogens such as *N. gonorrhoeae* and *C. trachomatis,* extension of HSV infection into the uterine cavity with laparoscopic evidence of HSV-positive vesicular lesions on the fallopian tube has been reported.[231]

Disseminated Infection

Bloodborne dissemination as manifested by multiple vesicles over widespread areas of the thorax and extremities occurs rarely in individuals with primary mucocutaneous herpes.[248,249] Cutaneous dissemination usually occurs early in the disease and is often associated with aseptic meningitis, hepatitis, or pneumonitis. Other rare complications of primary genital HSV-2 infection include monarticular arthritis,[250] thrombocytopenia,[251] adrenal necrosis,[252] and myoglobinuria.[253] Pregnancy may predispose to severe visceral dissemination of primary genital HSV disease.[254,255] Reactivation of genital HSV in immunosuppressed patients, especially patients with impaired cellular immune responses, can be associated with interstitial pneumonia, hepatitis, and meningitis, similar to the manifestations of disseminated infection of the neonate.[256,257]

Disseminated visceral infections in immunosuppressed and pregnant patients are associated with high mortality and should be treated immediately with systemic antiviral chemotherapy.

Superinfection

Bacterial superinfection of genital herpes in immunocompetent patients is a rare complication. Pelvic cellulitis appears as an advancing erythema and swelling of the perineal area, and patients should receive systemic antimicrobial therapy. Fungal vaginitis is frequently encountered toward the end of genital herpes–associated symptoms and often leads to recurrence of pruritus and increased discharge; concurrent yeast infection occurs more frequently in women with genital herpes.[201] Bacterial vaginosis also appears to be more common in individuals seropositive for HSV-2.[258,259]

RECURRENT MUCOCUTANEOUS HERPES SIMPLEX VIRUS INFECTIONS

In contrast to first episodes of genital infection, the symptoms, signs, and anatomic sites of infection of recurrent genital or orolabial herpes are usually localized to a defined mucocutaneous site.[260,261] Local symptoms such as pain and itching are mild to moderate compared with first episodes of infection, and the duration of the episode is shorter. Lesions are usually confined to one side, and the involved area is on average one-tenth that of primary infection.[201,262] Recurrent orolabial HSV infection tends to be of shorter duration than genital HSV infection. Orolabial lesions usually pass through clinical stages of infection more rapidly, and the median time from onset of tingling to healing averages 5 days.[204]

Among immunocompetent individuals who acquire HSV-1 orally and genitally, HSV-1 reactivates more frequently in the oral region than in the genital region. Similarly, for HSV-2, reactivation in the genital region is 8 to 10 times more frequent than oral reactivation of HSV-2.[224,263] In experimental animal systems, both sacral and trigeminal ganglia contain latent virus, but reactivation differs according to the anatomic site of infection.[264] In a murine model, inserting the latency-associated transcripts of HSV-2 into an HSV-1 virus increased reactivation in sacral nerve root ganglia, indicating that viral factors influence site of reactivation.[47]

Both oral and genital HSV reactivations are frequently associated with prodromal symptoms, which occur in the absence of lesions in 20% of episodes.[260] Prodromal symptoms vary from a mild tingling sensation, occurring 0.5 to 48 hours before eruption, to shooting pains in the buttocks, legs, or hips 1 to 5 days before eruption. In many patients, the prodromal symptoms are the most bothersome part of the episode. HSV is present on mucosal surfaces more frequently during the prodrome, suggesting that viral reactivation is associated with these symptoms.[236,262] The severity and mean duration of pain are greater in women (5.9 days) compared with men (3.9 days), as is the likelihood of dysuria (27% vs. 9%), although dysuria is normally external, and isolation of HSV from the urethra is considerably less common than during the first HSV-2 episode. The mean duration of shedding (approximately 4 days in both sexes) is shorter than during primary infection but highly variable both between and within individuals over time.[265]

The diverse clinical spectrum of recurrent HSV infection is increasingly recognized. First, subclinical reactivation of virus on mucosal surfaces is common.[236] In addition, studies of both orolabial and genital ulcerative lesions have found a surprisingly high frequency of HSV isolated from "atypical" clinical syndromes (approximately 33%) including linear fissures or serpiginous ulcers without an erythematous base (see Fig. 135.7).[266] Even among experienced clinicians, false-positive and false-negative clinical diagnoses of genital herpes are common.[83,267,268] Therefore in the absence of a known HSV diagnosis, we recommend that all ulcerative lesions on the oral and genital mucosa be sampled for HSV.[269] A definitive etiologic diagnosis is best established by demonstration of viral nucleic acid or isolation of virus from the affected area. The detection of HSV-2 does not rule out coinfection with *Treponema pallidum* or *Haemophilus ducreyi,* which should be considered in the appropriate clinical and epidemiologic context.[268,270]

Importantly, although 80% of seroprevalent individuals deny genital lesions, the vast majority are not truly asymptomatic but have genital lesions that they do not recognize as herpetic. In several studies, seropositive women and men who were previously unaware of their diagnosis were educated regarding signs and symptoms of genital herpes. During follow-up periods of just a few months, 48% to 62% of these subjects developed classic recurrent lesions.[108,261,271] In one study, localized genital symptoms developed in an additional 25%.[108] The rate of subclinical shedding was the same among men and women with recognized and unrecognized genital HSV infection, although frequency and duration of recurrences were greater in subjects with previously recognized disease.

FREQUENCY OF REACTIVATION AND RECURRENCE

The major morbidity of genital HSV-2 infection is a result of the high frequency of reactivation.[272] Of patients who present with symptomatic first-episode genital HSV-2 infection, 90% experience clinical reactivation of infection, and 98% experience subclinical HSV-2 shedding in genital mucosa.[273–276] The median clinical recurrence rate is between four and five episodes per year, although there is great heterogeneity among patients: 20% of patients report more than 10 clinical recurrences during the year after primary infection.[203] Studies of recurrence rates of genital HSV-2 lesions show a steady but gradual decrease in recurrence rates over time. In one study, annual recurrences of genital herpes decreased from an average of 5 to 2 per year over a 5- to 8-year period. The decrease most commonly occurred 3 to 5 years after acquisition. However, there was again great variability, with 20% of patients reporting increased recurrences over time.[277] Both recurrence and asymptomatic shedding persist at high levels in most patients 10 years after initial infection.[278]

HSV-1 infection recurs much less frequently in the genital tract than HSV-2. Less than 5% of people with primary HSV-1 infection of the genital tract will have more than four lifetime recurrences.[224] Recurrence frequency is slightly higher for men and for people with prolonged duration of primary infection (>35 days).[203]

Subclinical Herpes Simplex Virus Type 2 Shedding

Subclinical or asymptomatic viral shedding is a critical concept for understanding the epidemiologic and transmission features of genital and orolabial HSV infections.[100,123,279,280] Previous studies indicated that two-thirds of mucosal HSV-1 or HSV-2 shedding episodes are subclinical.[236,273] Protocols with frequent swabbing for HSV-2 in the anogenital tract detect a high number of previously missed shedding episodes that last less than 6 hours, indicating that subclinical HSV episodes constitute more than three-fourths of the virologic reactivation in an individual (Fig. 135.9).[121,281] Shedding episodes of HSV may last from less than 2 hours to several days and, similar to clinical recurrences, occur most frequently after acquisition and then gradually decline to stable levels over a 1- to 2-year period. In women, the anatomic sites of asymptomatic shedding are often spatially dispersed across numerous genital sites[282,283] and include the cervix, vulva, anus, and urethra.[236] Anal reactivation is seen without a history of anal interactions, as the anal region has overlapping innervation with the vulvar area. In men, shedding occurs from the penile skin, urethra, anus, and occasionally semen.[276] Among MSM, perianal shedding is more common, whereas the converse is true for men who acquire HSV via heterosexual contact, suggesting that the site of initial inoculation and latency influence the subsequent pattern of reactivation. Similar patterns of subclinical reactivation occur in the oropharynx where frequent shedding correlates with frequent recurrence.

Subclinical reactivation can be detected by either culture or PCR. HSV DNA detection by PCR assay is three to four times more sensitive than viral isolation.[269] Studies of antiviral therapy have shown that long-term daily therapy reduces viral DNA detection by 70% to 95% (from 28% to 8% of days), indicating that HSV DNA as detected by PCR assay on mucosal surfaces represents the replicating form of the virus and hence is infectious.[273,284] Most sexual and maternal-fetal transmissions occur during episodes of subclinical shedding. Similarly, subclinical shedding can cause primary genital HSV-1 infections through orogenital sexual activity. Therefore counseling of patients with genital

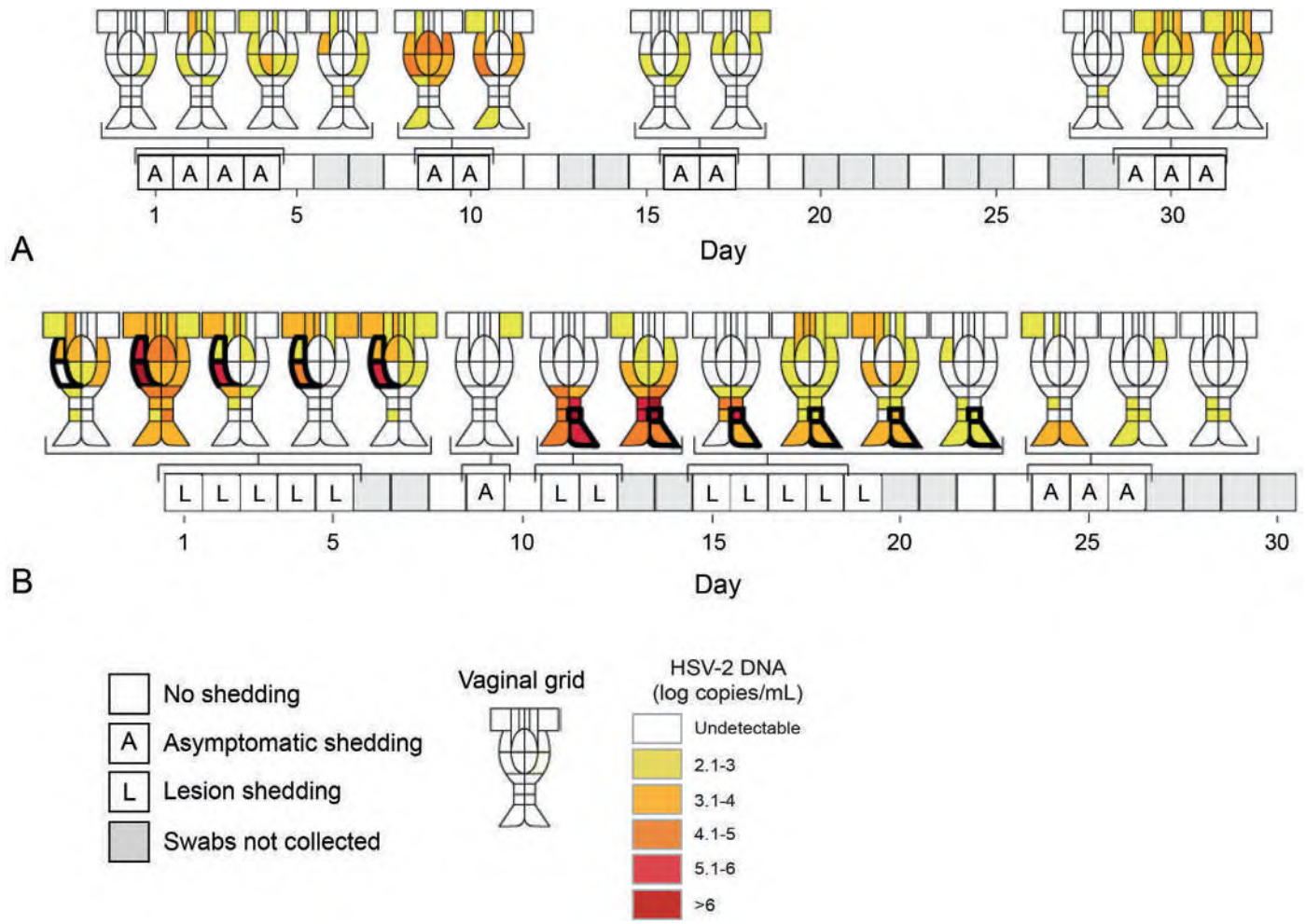


FIG. 135.9 Anatomic distribution of genital shedding in two women who had 22 genital samples collected over a 30-day period. The quantity of virus shed in each region is shown according to the heat map. (A) Widespread genital shedding in a woman with asymptomatic shedding. (B) Diffuse shedding in a woman with a symptomatic genital lesion on days 1 to 5, days 11 and 12, and days 15 to 19. The site of the lesion is highlighted in black. *(From Johnston C, Corey L. Current concepts for genital herpes simplex virus infection: diagnostics and pathogenesis of genital tract shedding.* Clin Microbiol Rev. *2016;29:149–161.)*

herpes needs to emphasize the potential for infectivity regardless of symptoms and provide appropriate strategies to decrease the risk to patients' sexual partners.

HERPETIC WHITLOW

Herpetic whitlow (HSV infection of the finger) may occur as a complication of primary oral or genital herpes by inoculation of virus through a break in the epidermal surface or by direct introduction of virus into the hand through occupational or some other type of exposure.[285] Before the increased use of gloves in health care settings, HSV-1 was most commonly isolated from herpetic infections of the hand. With the increasing prevalence of HSV-2, herpetic whitlow due to HSV-2 is encountered more frequently, and one survey found HSV-2 as the predominant causative agent.[225] Clinical signs and symptoms of herpetic whitlow include the abrupt onset of edema, erythema, and localized tenderness of the infected finger. Vesicular or pustular lesions of the fingertip can be difficult to distinguish from lesions of pyogenic bacterial infection. Fever, lymphadenitis, and epitrochlear and axillary lymphadenopathy are common. The infection may recur. Prompt diagnosis (to avoid unnecessary and potentially exacerbating surgical therapy or transmission) is essential. Antiviral chemotherapy to speed the healing process is recommended.

HERPES GLADIATORUM

HSV may infect almost any area of skin. Mucocutaneous HSV infections of the thorax, ears, face, and hands occur in outbreaks among wrestlers. Transmission of these infections is facilitated by trauma to the skin sustained during matches. Prompt diagnosis and therapy are required to contain the spread of this infection and reduce microepidemics among wrestling teams.[286]

EYE INFECTIONS

HSV infection of the eye is the most frequent cause of corneal blindness in the United States.[287,288] HSV keratitis commonly results from reactivation of latent, orally acquired, trigeminal ganglia–derived HSV-1. It arises with an acute onset of pain, blurring of vision, chemosis, conjunctivitis, and characteristic dendritic lesions of the cornea (Fig. 135.10). Use of topical glucocorticoids may exacerbate symptoms and lead to involvement of deep structures of the eye.[289] Débridement, topical antiviral treatment, interferon therapy, or a combination of these methods hastens healing. Primary disease is often self-limited, but recurrences are common, and the deeper structures of the eye may sustain irreversible scarring due to immunopathologic injury. Both eyes are involved in approximately 5% of cases. Asymptomatic shedding appears to occur, although different studies report highly variable frequencies of viral detection.[290,291]

HSV-1 blepharitis and conjunctivitis are distinguishable from other self-limited viral conjunctivitis cases by the presence of vesicles on the eyelid margin. Chorioretinitis occurs in neonates or in patients with HIV infection who have disseminated infection.[292] HSV and VZV can also cause acute necrotizing retinitis, a devastating condition that leads to painless vision loss and affects both eyes about 25% of the time. This

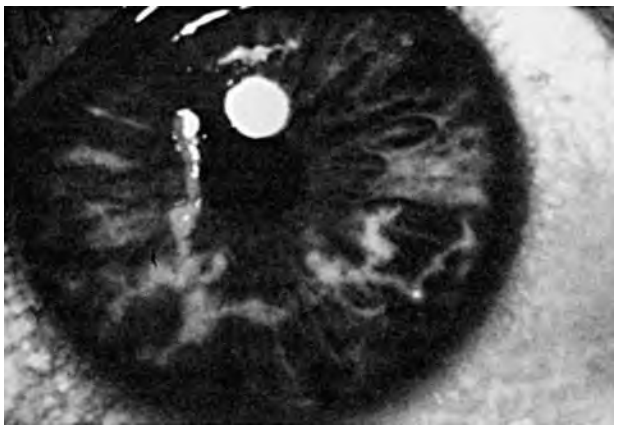


FIG. 135.10 Herpes simplex virus type 1 dendritic keratitis. *(From Pavan-Langston D, ed.* Ocular Viral Disease. Vol. 15. *Boston: Little, Brown; 1975:19–36.)*

entity can occur in immunocompetent individuals, pregnant women, and HIV-1–infected patients. Retinal necrosis is rapid, and prompt systemic antiviral chemotherapy, systemic corticosteroids to reduce inflammation, vitreal biopsy with PCR assay, and laser retinopexy are indicated. Residual blindness is common.[288,293,294]

HERPES SIMPLEX VIRUS ENCEPHALITIS

HSV is the most commonly identified cause of acute, sporadic viral encephalitis in the United States, accounting for 10% to 20% of all cases.[295] The estimated incidence is approximately 2.3 cases per 1 million persons per year. In contrast to enteroviral infections, cases are distributed throughout the year, and the age distribution appears to be biphasic, with peaks at 5 to 30 years of age and more than 50 years of age.[296] HSV-1 causes more than 95% of cases.[297,298]

The pathogenesis of HSV encephalitis varies. In children and young adults, primary HSV infection may result in encephalitis; presumably, exogenously acquired virus enters the CNS by neurotropic spread from the periphery through the olfactory bulb. Most adults with HSV encephalitis have clinical or serologic evidence of mucocutaneous HSV-1 infection before the onset of symptoms.[298] However, in about 25% of patients examined, the HSV-1 strains from the oropharynx and brain tissue of the same patient differ; thus some cases may result from reinfection with another strain of HSV-1 that reaches the CNS.[299] Reactivation of latent HSV-1 infection in trigeminal or autonomic nerve roots may be associated with extension of virus into the CNS through nerves innervating the middle cranial fossa. HSV DNA has been demonstrated by DNA hybridization in brain tissue obtained at autopsy from healthy adults.[298] Therefore reactivation of long-standing latent CNS infection is an additional potential mechanism for the development of HSV encephalitis.

The clinical hallmark of HSV encephalitis is acute onset of fever and focal neurologic (especially temporal lobe) symptoms. Differentiation of HSV encephalitis from other viral encephalitides, focal infections, and noninfectious processes is difficult.[300] The most sensitive noninvasive method for early diagnosis of HSV encephalitis is demonstration of HSV DNA in CSF by PCR, although uncommonly PCR testing may become positive only a few days after onset. Although titers of CSF and serum antibodies to HSV increase in most cases of HSV encephalitis, they rarely do so earlier than 10 days into the illness and as such are generally not helpful in establishing an early clinical diagnosis.[301–303]

Magnetic resonance imaging is the neuroimaging technique of choice for detection of abnormalities associated with HSV encephalitis, and gadolinium-enhanced lesions are often seen in the temporal lobe. Brain biopsy was performed extensively in the past to make the diagnosis of HSV encephalitis and has a low complication rate; demonstration of HSV antigen, HSV DNA, or HSV replication in brain tissue obtained by biopsy is highly sensitive. Brain biopsy is infrequently used now, but it provides the best opportunity to identify alternative, potentially treatable causes of encephalitis and may be considered when the clinical presentation is atypical or the diagnosis remains unclear.[300]

Most authorities recommend empirical use of intravenous acyclovir to patients with presumed HSV encephalitis until the diagnosis is confirmed or an alternative diagnosis is made. All suspected or confirmed cases should be treated with intravenous acyclovir at a dose of 30 mg/kg/day in three divided doses for 14 to 21 days.[304] Cases of clinical recurrence of encephalitis after therapy stopped have been reported that required more treatment. For this reason, some authorities prefer to treat initially for 21 days, and many continue therapy until HSV DNA has been eliminated from the CSF. Even with therapy, neurologic sequelae are frequent, especially in patients older than 35 years of age.

VISCERAL AND PULMONARY HERPES SIMPLEX VIRUS INFECTIONS

HSV infection of visceral organs usually results from viremia, and multiple-organ involvement is common. Occasionally, the clinical manifestations of HSV infection involve only the esophagus, lung, or liver. HSV esophagitis may result from direct extension of oropharyngeal HSV infection into the esophagus or by reactivation and spread of HSV to the esophageal mucosa through the vagus nerve.[305,306] It is a well-known complication in patients with AIDS and should be differentiated from *Candida* and CMV infections and aphthous ulcers by histologic examination. The predominant symptoms of HSV esophagitis are odynophagia, dysphagia, substernal pain, and weight loss. The distal esophagus is most commonly involved with multiple oval ulcerations on an erythematous base, with or without a patchy white pseudomembrane. With extensive disease, diffuse friability may involve the entire esophagus. Neither endoscopic nor barium examination differentiates HSV esophagitis from esophageal ulcerations related to *Candida,* thermal injury, radiation, or corrosives. Endoscopically obtained secretions for cytologic examination and culture provide the most useful diagnostic material. Systemic antiviral chemotherapy usually reduces symptoms and heals ulcerations.

HSV pneumonitis is uncommon except in severely immunosuppressed patients and may result from extension of herpetic tracheobronchitis into lung parenchyma.[307–309] Because oral shedding of HSV can lead to contamination, a positive HSV culture from a respiratory specimen should be interpreted with caution in an unlikely host or in the absence of radiologic evidence of disease. However, demonstration of virus from lower respiratory tract specimens should be evaluated promptly to determine whether there is evidence of tracheobronchitis or true parenchymal lung disease. HSV-1 pneumonia usually manifests as a focal necrotizing pneumonitis. Hematogenous dissemination of virus from sites of oral or genital mucocutaneous disease may also occur and produce bilateral interstitial pneumonitis. Bacterial, fungal, and parasitic copathogens are commonly present, and the mortality rate from untreated HSV pneumonia in immunosuppressed patients is high (>80%).[307,308] HSV has also been observed in association with acute respiratory disease syndrome.[310,311] Most authorities believe the presence of HSV in tracheal aspirates in such settings is due to reactivation of HSV in the tracheal region and localized tracheitis in patients with long-standing intubation. Such patients should be evaluated for the potential extension of HSV infection into lung parenchyma. Controlled trials evaluating the role antiviral agents for HSV play in the morbidity and mortality of acute respiratory disease syndrome have not been conducted.

HSV is an uncommon cause of hepatitis in immunocompetent patients. HSV infection of the liver is associated with fever, abrupt elevations of bilirubin and serum aminotransferase levels, and leukopenia (<4000 white blood cells/μL). Disseminated intravascular coagulation may also develop.[252]

GENITAL HERPES SIMPLEX VIRUS INFECTION IN HIV-INFECTED PATIENTS

Persistent HSV infection is a common clinical presentation of HIV infection.[212] HSV reactivation, especially perianal shedding in men and

subclinical vulvar shedding in women, is more frequent in HIV-positive patients than HIV-negative control subjects. As with the HIV-negative population, mucosal HSV-2 reactivation rates vary considerably among patients.[235,312] For example, HSV DNA was detected on 30% to 80% of days in two cohorts of HIV-positive patients.[312,313] Low $CD4^+$ counts and high HIV viral loads are associated with an increased frequency of HSV-2 shedding,[151,235,314,315] although not HSV-1 oral shedding.[316] Highly active antiretroviral therapy appears to reduce the frequency of genital lesions substantially but only modestly reduces the frequency of subclinical shedding.[151] HSV shedding and lesion rates appear to increase transiently after the initiation of antiretroviral therapy, perhaps relating to yet unidentified host or viral factors associated with immune reconstitution or immune reconstitution inflammatory syndrome.[317,318]

Increased Risk of HIV-1 Acquisition in Herpes Simplex Virus Type 2–Infected Patients

Perhaps the most impactful epidemiologic complication of HSV-2 infection is its role in increasing sexually acquired HIV-1 in women, heterosexual men, and MSM. Among MSM, antibodies to HSV-2 are detectable in most HIV-positive men[319] and in one-fourth of HIV-1–negative men.[95] Within discordant HIV-1 heterosexual partnerships both in the developed and the developing world, HSV-2 infection is common among potential transmitters (70% and 95%, respectively) and individuals at risk for HIV-1 infection.[320]

Case-control and cohort studies have shown that prior HSV-2 infection is associated with an increased risk for acquisition of HIV,[321–325] and mathematical models suggest that in many areas of the world it appears to be a substantial driver of micro-outbreaks of HIV-1.[326] Per-contact probability of HIV-1 acquisition is affected equally by HSV-2 serostatus and HIV-1 plasma viral load in the source partner (Table 135.1). Meta-analyses performed on all available prospectively conducted studies spanning four continents estimated consistently elevated risks for HIV-1 acquisition in persons with HSV-2 infection across sex and sexual preference.[320,327] One study indicated that approximately one-fourth of infections in a high-prevalence city in sub-Saharan Africa were directly attributable to HSV-2 and that HSV-2 facilitated spread of HIV into low-risk populations.[326] A separate review estimated a population attributable risk of 20% in populations with moderate HSV-2 prevalence such as the United States and 45% in populations with very high HSV-2 seroprevalence.[328] However, two well-designed clinical trials showed no effect of standard-dose acyclovir HSV-2 treatment on the acquisition of HIV-1 among HSV-2–positive persons,[329,330] despite reduced frequency of genital lesions and HSV-2 shedding. This lack of effect of antiviral therapy may relate to the minimal effect acyclovir has on subclinical shedding and subclinical inflammation in the genital tract.[152] More recent modeling suggests that equivalent route of transmission may drive some apparent HSV-2 attributable risk due to HIV-1.[331]

Besides its effect on acquisition among HIV-1–infected patients, HSV-2 also influences both mucosal and plasma HIV replication. HIV virions can be detected in genital herpes lesions, and higher HIV-1 titers are found in genital secretions during episodes of subclinical HSV-2 reactivation.[332,333] The regulatory proteins ICP0 and ICP4 can upregulate the rate of HIV replication in vitro,[334–336] and coinfection of epithelial cells by HSV-2 and HIV results in a higher copy number of HSV virions.[335] Additionally, transfection of HSV-2 genes into $CD4^+$ T cells enhances HIV-1 replication. HSV imprints a lasting focal inflammatory response of HIV-susceptible cells that is unaffected by antiviral therapy. Herpetic lesions are associated with an influx of activated $CD4^+$ lymphocytes,[152,186] which persist in the region after the lesion heals.[152] Detailed in situ studies indicate that an inflammatory focus of chemokine (C-C motif) receptor 5–expressing $CD4^+$ T cells as well as dendritic cell–specific intercellular adhesion molecule 3–grabbing nonintegrin–expressing dendritic cells remains after clinical healing.[152] These dendritic cell–$CD4^+$ T-cell interactions markedly facilitate both the passage and the replication capacity of $CD4^+$ T cells in vivo and have been shown to be an important focus of early HIV infection in nonhuman primates.[142] Antiviral therapy with acyclovir does not alter these findings,[152] which may explain why anti-HSV-2 therapy does not reduce HIV acquisition or transmission. HSV-2 shedding rate and genital inflammation appear to be higher in African relative to American heterosexual cohorts,[337,338] which may add to the enhanced risk of HIV-1 acquisition in this population.

TABLE 135.1 Per-Contact Probability of HIV-1 Acquisition Stratified by Plasma HIV-1 RNA in HIV-1 Seropositive Partner and HSV Serostatus in the Susceptible Partner

HIV-1 PLASMA RNA IN SOURCE PARTNER (copies/mL)	PER-CONTACT PROBABILITY IN HIV-1–SUSCEPTIBLE PARTNER	
	HSV-2 Positive	HSV-2 Negative
<1700	0.0001	0.00004
1700–12,499	0.0023	0.0005
12,500–38,499	0.0018	0.0002
>38,499	0.0036	0.0007

HIV, Human immunodeficiency virus; *HSV,* herpes simplex virus.
Modified from Quinn T, Wawer M, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med. *2000;342:921–929.*

Impact of Herpes Simplex Virus Type 2 Infection on HIV Transmission Probability From Coinfected Patients

Plasma HIV viral load is an important determinant of sexual transmission,[339] and both plasma and genital HIV-1 viral load are approximately 30% higher in HSV-2–infected patients during and for several weeks after HSV-2 recurrence (clinical and subclinical). These findings add plausibility to the observations that genital ulcer diseases increase the probability of HIV transmission[313,323,340,341] and that HSV-2 may enhance maternal-fetal HIV transmission.[342,343] Frequency of HSV-2 shedding correlates with HIV plasma viral load: twice-daily valacyclovir lowers HIV-1 plasma viral load by 0.2 to 0.5 $\log_{10}$ and decreases the frequency and mean quantity of HIV-1 shed in the genital tract.[341,344] Acyclovir also reduces HIV-1 viral load by 0.25 $\log_{10}$ and increases time to AIDS, which may be useful in select patients without access to HIV-targeting antiretroviral therapy. The relative decrease in HIV viral load correlates with the dose of acyclovir or valacyclovir used, independent of drug effect on genital HSV shedding, which suggests a direct antiviral effect on HIV.[345–348] Acyclovir did not lower HIV-1 transmission rate within serodiscordant couples, however, in a randomized clinical trial.[348]

The mechanism by which acyclovir reduces HIV-1 viral load is unresolved. It is possible that HSV-2 DNA polymerase inhibitors decrease HIV-1 viral load indirectly by decreasing the overall level of T-cell activation relating to HSV-2 recrudescence. However, acyclovir also acts directly on HIV-1 reverse transcriptase and may even predispose to development of clinically important HIV-1 reverse transcriptase mutations.[349] Acyclovir requires HSV thymidine kinase for its initial phosphorylation step; therefore in vivo, one would expect that its anti-HIV activity would require coinfection of a significant number of cells with both HIV-1 and HSV-2. A direct antiviral effect on HIV is suggested by the correlation of HIV viral load with valacyclovir dose, independent of drug effect on genital HSV shedding.[345] Yet the reductions in HIV plasma RNA appear only after 6 to 12 weeks and are not seen with episodic use of these agents. Although acyclovir can reduce viral load, its effects are not universal, and hence the impact of acyclovir on limiting the pace of HIV progression to AIDS does not warrant its routine clinical use in all patients coinfected with HIV and HSV-2.[346,347]

HERPES SIMPLEX VIRUS INFECTIONS IN IMMUNOCOMPROMISED HOSTS NOT INFECTED WITH HIV

Organ transplant recipients, patients undergoing cancer chemotherapy, and patients compromised by malnutrition or disorders of skin integrity such as burns or eczema are at risk for the development of severe HSV infections,[350–352] usually due to reactivation of endogenous virus. Primary

infection is relatively rare. HSV can rarely be transmitted via a solid-organ graft, which can be lethal, although this has not been observed in the antiviral era.[353]

The probability and severity of HSV disease is in part determined by the intensity of immunologic suppression. For instance, in the era before the routine use of acyclovir during chemotherapy, the HSV disease rate was considerably higher following hematopoietic stem cell transplantation (HCT) (70%–80%) relative to solid-organ transplantation (SOT) (40%–50%).[354–362] Most HSV infections occurred within the first 30 days after SOT or HCT when T-cell immunosuppression is most profound.[182,363] Higher disease rates are also observed following T-cell depletion with OKT3 or antithymocyte globulin following SOT.[364] HSV-1–seropositive patients who received a bone marrow transplant from an HSV-seronegative donor are at higher risk for recurrence and are more likely to develop acyclovir-resistant strains of HSV than patients who received marrow from HSV-1–positive donors.[365] Haploidentical and cord transplants as well as prolonged corticosteroid use for graft-versus-host disease also portend a higher risk of HSV recurrence.[366–368]

Most kidney, liver, and bone marrow transplant recipients excrete HSV-1 in saliva during the first 2 to 3 weeks after grafting.[369] Although these reactivations are often initially asymptomatic, extensive mucocutaneous ulcerations may also occur (Fig. 135.11) and, if persistent, extend to the esophagus or lung. Genital HSV-2 in immunocompromised patients may manifest as typical self-limited lesions or persistent chronic ulcerations and may occasionally mimic hemorrhoids or human papillomavirus disease.[370] Besides having the potential to cause extensive and disfiguring mucocutaneous infections, in rare cases HSV may disseminate to visceral organs such as adrenal glands, liver, bone marrow, and gastrointestinal tract in such patients. Blood PCR is usually the diagnostic test of choice and is important to distinguish infection from bacterial sepsis, CMV hepatitis, or other causes of fulminant liver failure.[371–373]

Because of the high frequency of disease in untreated patients, the potential for severe and even fatal manifestations, and the difficulty in distinguishing HSV from chemotherapy-related mucositis, routine prophylaxis against HSV during the initial period after HCT, initiation of cytoreductive chemotherapy, or SOT is the standard of care to shorten the course or prevent mucocutaneous HSV infection. Prophylactic acyclovir dramatically reduced the 2-year incidence of HSV disease following HCT from 30% to 0.2%[374] and reduced bacteremia with oral pathogens in patients after chemotherapy in a single trial.[369]

FIG. 135.11 Severe mucocutaneous herpes simplex virus type 1 infection in a bone marrow transplant patient. *(From Corey L. Herpes simplex virus infections. In: Mandell GL, series ed; Rein MF, ed.* Atlas of Infectious Diseases. Vol. V. Sexually Transmitted Diseases. *Philadelphia: Churchill Livingstone; 1996.)*

Antiviral resistance is an important clinical issue in the immunocompromised host. Thymidine kinase mutations that confer drug resistance appear to develop sequentially in immunocompromised hosts who are not controlling infections mucosally.[375] Resistance develops more frequently in HCT patients receiving short-term prophylaxis or repeated treatment for recurrent disease than in patients on long-term high-dose prophylaxis.[374,376–380] Antivirals directed at other sites of viral replication and more recently immunotherapeutic compounds[381–383] are being developed as alternative treatments to acyclovir-resistant strains.

NEONATAL HERPES

Infants acquire infection through contact with HSV-infected secretions, usually at the time of delivery.[192,292,384] Of neonatal herpes, 90% is perinatally acquired, 5% to 8% is congenital, and the remaining minority is acquired postnatally.[292] HSV-2, which causes 70% of neonatal HSV infections, nearly always occurs during delivery. Although congenitally infected infants have been reported, these infants almost invariably are born to mothers who had primary HSV-1 or HSV-2 infection during pregnancy.[385,386] Features of congenital HSV-2 include microcephaly, hydrocephalus, and chorioretinitis. Neonatal HSV-1 infections may also be acquired through postnatal contact with health care workers or immediate family members who have symptomatic or asymptomatic orolabial HSV-1 infection.

Neonates (infants <6 weeks old) have the highest frequency of visceral or CNS infection or both of any HSV-infected population. If not treated, neonatal herpes undergoes dissemination or develops into CNS infection in more than 70% of cases. Without therapy, the overall rate of death from neonatal herpes is 65%; less than 20% of neonates with CNS infection develop normally.[292,387] CNS morbidity is less severe with HSV-1 than with HSV-2 infection.[388] Although skin lesions are the most commonly recognized features of disease, many infants do not acquire visible lesions until well into the course of disease.[389] Cutaneous involvement alone is not associated with mortality, albeit subclinical CNS infection may be present.

Intravenous acyclovir has markedly improved the outcome of infants with neonatal HSV infection. Early initiation of therapy is an important factor in influencing outcome, especially with CNS infection, and prolonged therapy with oral suppression is now recommended. High-dose (60 mg/kg/day) intravenous acyclovir divided in three daily doses for 21 days (14 days for cutaneous involvement only) reduces mortality and morbidity, but long-term disabilities are still common, especially in infants with HSV-2 infection involving the CNS.[390] Continuation of therapy with daily oral acyclovir for 6 months improves neurodevelopmental outcomes in infants who survive acute infection.[390]

Prevention Measures for Neonatal Herpes

Infants born by cesarean section to women before the rupture of membranes or by vaginal delivery to women with no evidence of recent HSV infection are at minimal risk for the development of HSV infection, and most hospitals do not recommend segregating the infant from the rest of the infants in the neonatal nursery. If a more cautious approach is desired, the infant can be put into an Isolette incubator to make hospital personnel aware of the necessity to use wound and skin precautions and proper hand-washing techniques.

Infants born to women with active lesions should be placed in isolation. Viral cultures, liver function studies, and CSF examinations should be obtained, and the infant should be closely observed for the first month of life. Any symptoms of neonatal disease (e.g., poor feeding, fever, hypothermia, skin lesions, lethargy, or seizures) should be investigated expeditiously for evidence of neonatal HSV infection, and empirical therapy should be administered before the availability of diagnostic test results.

Management of contact between infant and mother should be handled on an individual basis. In women who acquire primary genital herpes late in pregnancy, the high incidence of extragenital lesions suggests that separation of mother and infant is warranted until therapy has produced a clinical and virologic response. Because recurrent maternal genital herpes is rarely associated with dissemination of disease or the development of extragenital lesions in exposed extremities, protection

of the infant from exposure to infected genital secretions is adequate. When handling the infant in the hospital, the mother should wear a gown and observe proper hand-washing techniques. Orolabial herpes presents a greater risk of postnatal acquisition of HSV infection to the neonate than genital herpes.[14] Thus nursery personnel and other adults with external lesions caused by HSV should not engage in intimate contact with a neonate.

HERPES SIMPLEX VIRUS INFECTION IN PREGNANCY

Incidence data for neonatal HSV infection are similar to data for neonatal HIV infection before the advent of routine antiretroviral use in pregnancy and are higher than incidence data for congenital syphilis, toxoplasmosis, and congenital rubella during endemic years.[113] The prevalence of genital HSV infection during pregnancy as well as the incidence of neonatal HSV infection is influenced by socioeconomic status, age, and past sexual activity.[391] In the United States, 22% of all pregnant women and 55% of non-Hispanic black pregnant women are HSV-2 seropositive.[392] However, the highest risk for transmitting HSV in the perinatal period occurs during the acquisition of HSV near the time of labor.[113,393] Table 135.2 depicts the frequency of neonatal infection in relation to maternal serologic states. One of the major unanswered questions of HSV in pregnancy is the low frequency of reported neonatal HSV-2 infections among African infants born to HSV-2–seropositive women in sub-Saharan Africa, despite high HSV-2 seroincidence at child-rearing age and evidence of subclinical shedding near term.[394–396]

Clinical Course of Genital Herpes in Pregnancy

The clinical manifestations of recurrent genital herpes including frequency of subclinical versus clinical infection, duration of lesions, pain, and constitutional symptoms tend to be similar in pregnant and nonpregnant women. Recurrences increase in frequency over the course of pregnancy,[397,398] and women who enter pregnancy with HSV-2 seropositivity experience normal neonatal outcomes including birth weight and gestational age.[399] First-episode infections in pregnancy have more severe consequences for mother and infant.[385,393,400,401] Maternal visceral dissemination during the third trimester as well as prematurity or fetal growth restriction occasionally occur. The acquisition of primary HSV-1 or HSV-2 disease in pregnancy carries the risk for potential transplacental transmission of virus to the neonate and can result in spontaneous abortion, although this is relatively uncommon.[402] We recommend antiviral treatment of newly acquired genital HSV during pregnancy with 7 to 10 days of acyclovir, 400 mg three times a day, or valacyclovir, 500 to 1000 mg twice daily, to reduce the likelihood of disseminated infection in the mother. The effect of this intervention on reducing congenital or perinatal transmission to the infant is unknown.

TABLE 135.2 Transmission Rates of Neonatal HSV by Maternal HSV Serologic Status Among Women Who Delivered at the University of Washington and Madigan Army Hospitals

MATERNAL HSV SEROSTATUS	NO./TOTAL (%) OF INFANTS WITH NEONATAL HSV	RATE PER 100,000 LIVE BIRTHS[a]
HSV seronegative	6/11,115 (0.054)	54 (19.8–118)
HSV-1 seropositive only	6/23,480 (0.026)	26 (9.3–56)
All HSV-2 seropositive	3/13,795 (0.022)	22 (4.4–64)
HSV-2 only	2/5761 (0.035)	35 (4.2–126)
HSV-1 and HSV-2	1/8034 (0.012)	12 (0.3–7.0)

[a]95% confidence level.
HSV, Herpes simplex virus.
Modified from Brown ZA, Ashley RL, Selka S, et al. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA. *2003;289:203–209.*

Surveillance Strategies for Neonatal Transmission of Herpes Simplex Virus

Criteria for laboratory screening and surveillance as well as delivery procedures for women with recurrent genital HSV infections are questions frequently encountered by physicians caring for pregnant women.[403] The high HSV-2 prevalence rate in pregnancy and low incidence of neonatal disease (1 in 6000–20,000 live births) indicate that only a low proportion of infants are at risk for acquiring HSV (see Table 135.2).[74] Therefore cesarean section is not warranted for all women with recurrent genital disease.[404] Because intrapartum transmission of infection accounts for most cases, only women who shed HSV at delivery need to be considered for abdominal delivery.[192,404] Several studies showed no correlation between recurrence of viral shedding before delivery and the presence of viral shedding at term.[384,404,405] Hence weekly virologic monitoring and amniocentesis are not recommended.

The frequency of transmission from mother to infant is markedly higher in women who acquire HSV near term (30%–50%) compared with women who reactivate HSV-2 at delivery (<1%).[192] Although maternal HSV-2 antibody is protective, HSV-1 antibody offers little or no protection against neonatal HSV-2 infection.[406] Primary HSV-1 genital infection leads to a particularly high risk for transmission and accounts for an increasing proportion of neonatal HSV infections.[192,194] Moreover, during reactivation, HSV-1 appears more transmissible to the neonate than HSV-2.[406] Only 2% of women who are HSV-2 seropositive and undergo swabbing of cervical secretions at delivery have detectable virus, and only 1% of infants exposed in this manner develop infection, presumably because of the protective effects of maternally transferred antibodies and perhaps lower viral titers during reactivation.[192,393] Despite the low frequency of HSV transmission in this setting, 30% to 50% of infants with neonatal HSV infection are born to mothers with established genital herpes.[407]

HSV shedding at time of delivery (detected by isolation via cervicovaginal swab) is the greatest risk factor for intrapartum HSV transmission (relative risk, 346); however, culture-negative, PCR-positive cases of intrapartum transmission are well described. New acquisition of HSV (odds ratio [OR], 49), isolation of HSV-1 versus HSV-2 (OR, 35), cervical versus vulvar HSV detection (OR, 15), use of fetal scalp electrodes (OR, 3.5), and young maternal age confer further risk for transmission, whereas abdominal delivery is protective (OR, 0.14).[192] Physical examination poorly predicts the absence of shedding,[408] and PCR far exceeds culture in terms of sensitivity and speed. Therefore PCR detection at the onset of labor should be considered to aid clinical decision making for HSV-2–seropositive women. Because cesarean section appears to be an effective means of reducing maternal-fetal transmission, patients with recurrent genital herpes should be encouraged to come to the hospital early at the time of delivery for careful examination of the external genitalia and cervix plus swab for viral isolation. Women who have no evidence of lesions should have a vaginal delivery. The presence of active lesions on the cervix or external genitalia is an indication for abdominal delivery.[407]

This policy results in the exposure of some infants to episodes of asymptomatic cervical or vulvar shedding, or both.[408] The identification of HSV-exposed infants provides important information to the attending pediatrician. If first-episode exposure has occurred (e.g., if HSV serologic tests show that the mother is seronegative or if the mother is HSV-1 seropositive and the isolate at delivery is HSV-2), many authorities would initiate antiviral therapy for the infant with intravenous acyclovir.[409,410] At a minimum, viral cultures and PCR should be performed on samples obtained from the throat, nasopharynx, eyes, and rectum of these infants immediately and at 5- to 10-day intervals. Lethargy, skin lesions, or fever should be evaluated promptly. All infants from whom HSV is isolated 24 hours after delivery should be treated with intravenous acyclovir at recommended treatment doses.

The duration of ruptured membranes in women with clinically apparent lesions does not have a well-defined relationship to the transmission of HSV to the infant.[271] Delivery of infants by cesarean section, even in women with intact membranes, occasionally results in neonatal herpes. Prolonged contact with infected secretions may increase the risk for acquisition. Many authorities recommend that if

membranes are ruptured for more than 4 to 6 hours, cesarean section should no longer be considered protective against HSV transmission. However, transmission can occur from exposure to external genital lesions alone. Thus in women with recurrent genital herpes who have active external genital lesions during labor, we still recommend abdominal delivery.

Prevention of Herpes Simplex Virus Acquisition in Pregnancy by Use of Antiviral Agents

Controversy exists regarding the use of antiviral therapy during pregnancy. Antiviral therapy given after 36 weeks of gestation reduces, but does not totally eliminate, HSV-2 recurrence at delivery.[410,411] Systematic reviews suggest that the frequency of cesarean delivery can also be reduced.[412,413] Although mathematical models suggest such an approach may be cost-effective in reducing cesarean deliveries, there are no data supporting the ability of this approach to reduce neonatal infection. Because the risk for neonatal transmission is low among HSV-2–seropositive women, the routine use of antiviral chemotherapy among HSV-2–positive pregnant women would result in many women treated with few cases of neonatal HSV prevented even if the effects on reducing maternal-fetal transmission are high. As such, we do not believe that routine use of antiviral therapy at the end of gestation should be recommended until better information on efficacy and potential neonatal safety are assessed. As described earlier, a more logical approach that requires further study would be to screen low-risk seropositive mothers at delivery with rapid PCR and follow infants with HSV-2 exposure intensively after birth.

Targeting HSV-2–seronegative women could be an effective means to decrease mother-to-infant transmission, as 2% of women in one survey seroconverted during pregnancy, and one-third of these seroconversions occurred during the third trimester. Potential approaches range from counseling for routine abstinence in all women after 34 weeks of gestation to the use of routine serologic screening to identify HSV-susceptible women. Such women then would be counseled about the importance of engaging in only protected coitus during the latter parts of pregnancy. Of particular interest are the 20% of women who are in a serodiscordant relationship and are at high risk for primary infection (3.5% for HSV-1, 20% for HSV-2).[414] A third possible type of screening program could be to identify and treat the HSV-2–positive sex partners of seronegative pregnant women with antiviral therapy and observe them serially for seroconversion, although the expense would be substantial.[415] Clinical and demographic information do not differentiate women at high versus low risk for transmitting HSV to their infants.[416] Pregnancy may also enhance HSV acquisition, making standard prophylactic measures such as condoms potentially less effective.[417] Because nearly 30% of neonatal HSV is due to HSV-1, attention to reducing HSV-1 acquisition through orogenital sex is also important.

DIAGNOSIS OF ACTIVE HERPES SIMPLEX VIRUS INFECTIONS

Clinical criteria are critical for considering the diagnosis of HSV infections. Nevertheless, given the gravity of diagnosing a lifelong viral sexually transmitted infection, we believe that appropriate management of the patient should always include laboratory confirmation of the infection. A clinical diagnosis can often be inferred when characteristic multiple vesicular lesions appear on an erythematous base. In this situation, given the prolonged morbidity of first-episode genital HSV infection and the ability of antiviral agents to mitigate systemic symptoms and prevent development of new crops of ulcers, it is appropriate to initiate oral antiviral treatment while awaiting laboratory confirmation.

Herpetic lesions may also resemble skin ulcerations of other causes.[96,267] Mucosal HSV infection can appear as urethritis or pharyngitis without cutaneous lesions. When there is clinical uncertainty, laboratory diagnosis is essential to guide therapy.[83]

HSV infection is best confirmed by demonstration of HSV DNA in lesion scrapings or by isolation of virus in tissue culture.[267,269] The sensitivity of viral isolation is higher in vesicular lesions than ulcerative lesions, during first rather than recurrent episodes of disease, and in samples from immunosuppressed rather than immunocompetent patients. HSV DNA detection is the preferred diagnostic method, if available, because it is three to four times more sensitive than viral isolation, is less affected by variation in specimen transport, and is cost-effective as compared with culture.[269] Laboratory confirmation permits subtyping of the virus, which may help predict frequency of reactivation after first-episode oral or genital HSV infection, site of CNS infection, and likelihood of drug resistance.[418]

HSV causes a discernible cytopathic effect in a variety of cell culture systems, generally within 48 to 96 hours after inoculation. Spin-amplified culture with subsequent staining for HSV antigen shortens the time needed to identify HSV to less than 24 hours. Staining of scrapings from the base of the lesions with Wright, Giemsa (Tzanck preparation), or Papanicolaou stain demonstrates characteristic giant cells or intranuclear inclusions of HSV infection. These cytologic techniques are useful as quick office procedures to confirm the diagnosis, but they do not differentiate between HSV and VZV infections, they are relatively insensitive, and correct identification of giant cells requires experience.

DIAGNOSIS OF ESTABLISHED HERPES SIMPLEX VIRUS INFECTIONS

Development of type-specific serologic assays has markedly improved our understanding of HSV-1 and HSV-2 seroprevalence,[419–421] and these assays are useful clinical management tools. Most commercially available assays measure antibodies to purified HSV-1–specific or HSV-2–specific proteins such as glycoproteins gG1 and gG2, which are antigenically distinct between the two subtypes and thus allow for detection of HSV-2 in the presence of HSV-1 antibodies and vice versa. Seroconversion to gG1 and gG2 may take weeks to months to occur, and hence detection of these antibodies generally means long-standing infection.[419,422–424] The Western blot assay, which measures additional HSV-1–specific and HSV-2–specific antibodies, is the most accurate available serologic test and has a sensitivity and specificity of greater than 98% for distinguishing HSV-1–specific and HSV-2–specific antibodies.[425,426] Assays that use whole viral extracts or antigens are inaccurate and should not be used for any stage of clinical diagnosis or epidemiologic studies.[427,428] These assays are still sold commercially, however, and used in some laboratories.

Acute-phase and convalescent-phase serum can be useful in demonstrating seroconversion during primary HSV-1 or HSV-2 infection. Only 5% of patients with recurrent orogenital HSV infections have a fourfold or greater rise in HSV antibody titer in the interval between collection of two samples. Immunoglobulin M antibodies are not useful for defining recent or past acquisition.[429]

OVERVIEW OF THERAPIES FOR HERPES SIMPLEX VIRUS INFECTIONS

The advent of antiviral drugs for HSV-1 and HSV-2 infections has made management of these infections a part of standard clinical practice (see Chapter 46). For mucocutaneous and visceral HSV infections, acyclovir and its related compounds valacyclovir and famciclovir are the mainstays of therapy. Several antiviral agents are available for topical use in HSV eye infections, including idoxuridine, trifluorothymidine, topical vidarabine, and cidofovir. However, there is no role for topical therapy in mucocutaneous disease.[226] For HSV encephalitis and neonatal herpes, intravenous acyclovir should be used. Acyclovir-resistant virus can be encountered in immunocompromised hosts and is treated with foscarnet, cidofovir, or possible topical agents such as imiquimod. Although the possibility of acyclovir resistance is typically not of clinical importance in immunocompetent patients, a possible exception may be HSV keratitis, where prophylaxis may predict development of resistance.[430] Allergies to acyclovir are rare, and desensitization is theoretically possible, although uncommonly employed.

Acyclovir was the first antiviral agent clearly demonstrated to be effective against HSV infections. It is an acyclic nucleoside analogue that is a substrate for HSV-specific thymidine kinase and is selectively phosphorylated by HSV-infected cells to acyclovir monophosphate.[431,432] Cellular enzymes then phosphorylate acyclovir monophosphate to

acyclovir triphosphate, a competitive inhibitor of viral DNA polymerase. Acyclovir triphosphate is incorporated into the growing DNA chain of the virus and causes chain termination. Acyclovir has potent in vitro activity against HSV-1, HSV-2, and VZV,[433] with partial activity against CMV.

Numerous trials of acyclovir in mucocutaneous HSV infections of the immunocompetent and immunosuppressed host have been conducted.[434–439] Famciclovir, the oral formulation of penciclovir, is also clinically effective in the treatment of a variety of HSV-1 and HSV-2 infections.[440–443] Valacyclovir, a valyl ester of acyclovir, allows greater bioavailability of the active compound than acyclovir,[444–446] making valacyclovir useful for once-daily suppressive therapy and for short-course, 1- or 2-day treatment of orogenital HSV-1 infection.[447,448] Ganciclovir has activity against both HSV-1 and HSV-2, but because it is more toxic than acyclovir, valacyclovir, and famciclovir, it is generally not recommended for treatment of HSV infections.[449] Anecdotal clinical observations suggest it may also be less effective. Table 135.3 outlines treatment options for the use of these compounds. Despite the demonstrated effectiveness of the guanosine analogues, most infected people remain untreated.

TABLE 135.3 Antiviral Chemotherapy for HSV Infection

	Dosage/Regimen	Comment
Mucocutaneous HSV Infections		
Infections in Immunosuppressed Patients		
Acute symptomatic first or recurrent episodes	Oral acyclovir, 400 mg qid, famciclovir, 500 mg PO tid, or valacyclovir, 1 mg PO bid, for 7–10 days is effective. In severe cases, IV acyclovir, 5 mg/kg q8h, is given.	Treatment duration may be 7–14 days.
Suppression of reactivation disease	IV acyclovir, 5 mg/kg q8h, valacyclovir, 500 mg PO bid, or oral acyclovir, 400–800 mg 2–3 times per day, prevents recurrences during the immediate 30-day posttransplantation period.	Suppression of clinical HSV-2 is routine for patients undergoing stem cell and organ transplant. Valacyclovir, 2 g 4 times daily, is also effective in preventing CMV infection. Valacyclovir, 4 g 4 times daily, has been associated with TTP after extended use in HIV-positive patients. In HIV-infected patients, oral famciclovir, 500 mg bid, is effective in reducing clinical and subclinical reactivations of HSV-1 and HSV-2. If using acyclovir in HIV-infected patients, we generally start with the lower dose of 400 mg twice daily and increase to 800 mg twice daily if breakthrough recurrences occur. *Note:* Once-daily dosing of valacyclovir, 500 mg to 1 g, should be avoided in HIV-infected patients owing to concerns regarding lower efficacy.
Symptomatic recurrent genital herpes in HIV-1–infected patients	Oral acyclovir, 400 mg tid × 5–10 days Valacyclovir, 1000 mg bid × 5–10 days Famciclovir, 500 mg PO bid × 5–10 days	
Infections in Immunocompetent Patients		
Genital Herpes		
First episodes	Oral acyclovir, 400 mg tid (V) or 200 mg 5 times per day (I) × 7–10 days Oral valacyclovir, 1000 mg bid × 7–10 days (I) Famciclovir, 250 mg tid × 7–10 days (I) IV acyclovir, 5 mg/kg q8h for 5 days, is given for severe disease or neurologic complications such as aseptic meningitis.	Treatment can be extended if healing is incomplete after 10 days of therapy.
Symptomatic recurrent genital herpes	**Oral acyclovir,** 400 mg tid × 5 days (V), **800 mg PO tid × 2 days** or bid × 5 days (II) **Valacyclovir, 500 mg bid × 3 days** (I) or 1 g daily × 5 days (I) **Famciclovir,** 125 mg bid for 5 days (I), **1 g bid for 1 day** (I), or **500 mg once then 250 mg PO bid × 3 doses** (I)	All these therapies are effective in shortening lesion duration. Short-course options (1, 2, or 3 days of therapy) should be considered based on increased convenience, likelihood of adherence, and reduced cost and are **listed in bold.** Given the brief period of viral replication and rapid evolution of lesions, patients should be given drugs for self-administration when prodromal symptoms occur.
Suppression of recurrent genital herpes	Oral acyclovir, 400 mg bid (I) Valacyclovir, 500 mg daily (I) or 1000 mg daily (I) or 250–500 mg bid (I) prevents symptomatic reactivation. Patients with frequent reactivation (<9 episodes/yr) can take valacyclovir 500 mg daily; patients with >9 episodes/yr should take valacyclovir 1000 mg/daily or 500 mg bid. Famciclovir, 250 mg bid (I)	Consider in patients with frequent (>6 episodes) or severe recurrences, in immunocompromised patients, or as an adjunct to prevent transmission.
Orolabial HSV Infections		
First episode	Oral acyclovir, 15 mg/kg (up to 200 mg) 5 times per day (II) or 400 mg tid (V) × 7 days Famciclovir, 500 mg bid (V) Valacyclovir, 1000 mg bid (V) × 7 days	
Recurrent episodes	Oral acyclovir, 400 mg 5 times per day × 5 days (II) **Valacyclovir, 2000 mg bid × 1 day** (I) **Famciclovir, 1500 mg once** (I)	Self-initiated therapy with topical 1% penciclovir cream q2h during waking hours (I); topical acyclovir cream, 5% 5 times per day × 4 days (I). Short-course options should be considered based on increased convenience and likelihood of adherence and are **listed in bold.** Given the brief period of viral replication and rapid evolution of lesions, patients should be given drugs for self-administration when prodromal symptoms occur.
Suppression of reactivation of orolabial HSV	Oral acyclovir, 400 mg bid (II), or valacyclovir, 500 mg or 1000 mg daily (II), or famciclovir, 500 mg bid (V)	Consider in patients with frequent (>6 episodes) or severe recurrences, in immunocompromised patients, or as an adjunct to prevent transmission.

TABLE 135.3 Antiviral Chemotherapy for HSV Infection—cont'd

	Dosage/Regimen	Comment
Herpetic Whitlow		
	Oral acyclovir, 200 mg 5 times daily for 7–10 days	
HSV Proctitis		
	Oral acyclovir, 400 mg 5 times per day, is useful in shortening the course of infection.	In immunosuppressed patients or in patients with severe infection, IV acyclovir, 5 mg/kg q8h, may be useful.
Herpetic Eye Infections		
		In acute keratitis, topical trifluorothymidine, vidarabine, idoxuridine, acyclovir, penciclovir, and interferon all are beneficial. Débridement may be required; topical corticosteroids may worsen disease (see Chapter 113).
CNS HSV Infections		
HSV encephalitis	IV acyclovir, 10 mg/kg q8h (30 mg/kg/day) for 14–21 days	
HSV aseptic meningitis	IV acyclovir, 30 mg/kg/day for 7–10 days	No studies of systemic antiviral chemotherapy exist.
Autonomic radiculopathy		No studies are available.
Neonatal HSV Infections		
	Acyclovir, 60 mg/kg/day divided into 3 doses × 21 days	Monitoring for relapse should be undertaken; most authorities recommend continued suppression with oral acyclovir suspension for 3–4 mo.
Visceral HSV Infections		
HSV esophagitis	IV acyclovir, 15 mg/kg/day	In some patients with milder forms of immunosuppression, oral therapy with valacyclovir or famciclovir is effective.
HSV pneumonitis		No controlled studies exist. IV acyclovir, 10 mg/kg q8h, should be considered.
Disseminated HSV Infections		
		No controlled studies exist. IV acyclovir, 10 mg/kg q8h, nevertheless should be given. No definite evidence indicates that therapy decreases risk of death.
Erythema Multiforme–Associated HSV		
		Anecdotal observations suggest that oral acyclovir, 400 mg bid or tid, or valacyclovir, 500 mg bid, suppresses erythema multiforme.
Surgical Prophylaxis		
		Several surgical procedures such as laser skin resurfacing, trigeminal nerve root decompression, and lumbar disk surgery have been associated with HSV reactivation. IV acyclovir, 3 mg/kg, and oral acyclovir, 800 bid, valacyclovir, 500 bid, or famciclovir, 250 bid, is effective in reducing reactivation. Therapy should be initiated 48 h before surgery and continued for 3–7 days.
Infections With Acyclovir-Resistant HSV		
	IV foscarnet, 40 mg/kg q8h, should be given until lesions heal. IV cidofovir, 5 mg/kg once weekly, may also be effective.	Imiquimod is a topical alternative, as is topical cidofovir gel 1%, which is not commercially available and must be compounded at a pharmacy. These topical preparations should be applied to lesions once daily for 5 consecutive days.

[a]Note: I, II, III, IV, and V in parentheses represent level of evidence.
CMV, Cytomegalovirus; *CNS,* central nervous system; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *IV,* intravenous; *PO,* per os (orally); *TTP,* thrombotic thrombocytopenic purpura.
Modified from Cernik C, Gallina K, Brodell RT. The treatment of herpes simplex infections: an evidence-based review. Arch Intern Med. *2008;168:1137–1144; and Spruance S, Aoki FY, Tyring S, et al. Short-course therapy for recurrent genital herpes and herpes labialis: entering an era of greater convenience, better treatment adherence, and reduced cost.* J Fam Pract. *2007;56:30–36.*

Treatment of Primary Genital Herpes Simplex Virus Infection

Primary infection often manifests as prolonged severe genital ulcerations and sometimes nervous system involvement. Even patients with first-episode herpes who have mild clinical manifestations initially can develop severe or prolonged symptoms. Therefore all patients with first episodes of genital herpes should receive antiviral therapy for 7 to 10 days with one of several regimens (see Table 135.3), ideally within 72 hours of onset. Treatment extension beyond this time point is indicated if healing is slow. Adjunctive treatment with sitz baths is helpful for dysuria in female patients. If urinary retention develops, intermittent or indwelling bladder catheterization may be necessary until symptoms resolve.

Suppressive Therapy for Persistent Genital Herpes Simplex Virus Infection

Patients with recurrent genital HSV infection can be managed with no therapy if recurrences are mild and infrequent; episodic therapy can be used for recurrences; daily suppressive therapy is an option for patients with frequent or severe recurrences. The choice of episodic versus long-term suppressive therapy should also be individualized based on patient preference. Factors that may favor daily suppressive therapy are high frequency of recurrences (more than six per year), good patient adherence to antiviral therapy, lack of documented toxicity, affordability, patient wish to decrease risk for transmission to a partner, and patient anxiety over uncontrolled recurrences.

Suppressive therapy decreases recurrences and asymptomatic shedding by 70% to 80% and increases both median time to recurrence and quality of life. Many patients receiving such therapy report having experienced no symptomatic outbreaks. Patients on suppressive therapy report higher quality-of-life indices than patients on episodic treatment.[450] Safety and efficacy have been documented among patients receiving daily therapy with acyclovir for 6 years and with valacyclovir or famciclovir for 1 year.[451]

Although acyclovir and its derivatives are clinically effective, they do not completely suppress asymptomatic shedding, even when given at maximal doses three times per day.[451] Patients on daily therapy still experience short episodes of asymptomatic shedding. The viruses obtained from such episodes are drug sensitive. These breakthrough episodes appear to occur due to rapid kinetics of viral expansion during drug trough levels.[118,452]

Episodic Therapy for Persistent Genital Herpes Simplex Virus Infection

Shorter courses of therapy are increasingly being used for treatment of recurrent episodes of mucocutaneous HSV-1 or HSV-2 infection in immunocompetent patients. One-day courses of famciclovir and valacyclovir are clinically effective, more convenient, and generally less costly than longer courses of therapy.[439,441,453–456] Optimal outcomes are seen with early initiation of therapy (6–24 hours postinfection). This is easiest to achieve if the patient is prescribed medication between recurrences to allow initiation of self-treatment at home at the first sign of prodrome.

Therapy for Severe Herpes Simplex Virus Infection

Intravenous acyclovir (30 mg/kg/day, given as a 10-mg/kg infusion over 1 hour at 8-hour intervals) is effective in reducing the morbidity and mortality associated with HSV encephalitis.[304] Again, early initiation of therapy is a critical factor in outcome. The major side effect of intravenous acyclovir is transient renal insufficiency, usually caused by crystallization of the compound in the renal parenchyma. This adverse reaction can be avoided if the medication is given slowly over 1 hour and the patient is well hydrated. Because CSF levels of acyclovir average only 30% to 50% of plasma levels, the dosage of acyclovir used for treatment of CNS infection (30 mg/kg/day) is double that used for the treatment of mucocutaneous or visceral disease (15 mg/kg/day). For disseminated neonatal HSV, high-dose intravenous therapy is recommended (60 mg/kg/day in three divided doses) for 21 days.[457]

Prophylaxis of Herpes Simplex Virus in Immunocompromised Hosts and Development of Drug Resistance

Patients undergoing stem cell transplantation or solid-organ transplantation are at high risk of herpesvirus reactivation. In most patients, intravenous acyclovir or oral valacyclovir is highly effective in preventing HSV reactivations; high doses of valacyclovir also reduce CMV reactivations.[449] Although acyclovir-resistant strains of HSV are well described in these populations,[458–460] stem cell transplant recipients receiving daily suppressive antiviral therapy are less likely to develop acyclovir-resistant HSV compared with those who received episodic therapy with outbreaks.[374]

Patients with late-stage HIV infection are also at risk of developing severe, persistent mucosal infections. Acyclovir prophylaxis is indicated for patients with severe or frequent recurrences. Although resistant HSV-1 strains have been documented in local mucosal replicating sites in immunocompetent hosts receiving therapy and may be archived in the latent pool,[45] archived drug resistance does not typically have an effect on treatment outcome for HSV-1 and HSV-2 in immunocompetent hosts.[461]

Treatment of Drug-Resistant Herpes Simplex Virus

Most acyclovir-resistant strains of HSV have a deficiency in thymidine kinase, the enzyme that phosphorylates acyclovir.[462,463] Thus cross-resistance to famciclovir is usually found (see Chapter 46). Occasionally an isolate with altered thymidine kinase specificity arises and is sensitive to famciclovir but not to acyclovir. In some patients infected with thymidine kinase–deficient HSV, higher doses of acyclovir are associated with clearing of lesions.[464] In others, clinical disease progresses. Isolation of HSV from persisting lesions despite adequate dosages and blood levels of acyclovir should raise the suspicion of resistance.

Therapy with foscarnet, which does not require phosphorylation by viral thymidine kinase, should be initiated for resistant HSV infections and is usually successful, although side effects from foscarnet including renal insufficiency, electrolyte wasting, nausea, paresthesias, and seizures are common.[465,466] Because of its toxicity and cost, intravenous foscarnet is reserved for patients with extensive mucocutaneous infections and laboratory-confirmed resistance. Of note, foscarnet can independently lead to genital ulceration.

Cidofovir is a nucleotide analogue and exists as a phosphonate or monophosphate form that also has anti-HSV activity. Most thymidine kinase–deficient strains of HSV are sensitive to cidofovir, which can be used topically or given intravenously on a weekly basis. Cidofovir ointment speeds healing of acyclovir-resistant lesions,[467,468] but the drug itself also can cause mucocutaneous ulcerations. The intravenous form very commonly causes renal failure, a Fanconi-like syndrome with proteinuria and bicarbonate wasting, neutropenia, and rash and gastrointestinal distress due to concurrent probenecid dosing.

Trifluridine ointment is useful for ophthalmic HSV infection and is anecdotally useful for resistant mucosal HSV infection in patients with AIDS.[469] Resiquimod, a topical TLR7 and TLR8 agonist, decreased shedding and recurrence rate of anogenital HSV-2, but further commercial development of this agent has ceased.[170] We and others have had success treating refractory ulcers due to drug-resistant HSV with imiquimod,[470] although this intervention has no effect on long-term recurrence rate.[471]

Novel Antiviral Agents for Herpes Simplex Virus Type 1 and Type 2 Infections

Amenamevir[472] and pritelivir[473] belong to a new class of antiviral compounds that inhibit the helicase/primase complex. Phase II studies have shown safety and a marked reduction in both HSV-2 shedding and days with genital lesions in immunocompetent patients.[31,474] These drugs were active against acyclovir-resistant viruses,[475–477] and thus inhibitors of these highly conserved complexes have potential as therapy for resistant HSV infections in immunosuppressed patients. Amenamevir and pritelivir are being studied for HSV patients with multiple orofacial and genital lesions.[478] Additional studies of these inhibitors for advancement to licensure are under consideration (see Chapter 46 for further discussion).[479]

COUNSELING AND PREVENTION

Many patients with first-episode genital HSV infection experience substantial morbidity and as a result miss work or school. Yet a significant proportion, particularly men, do not seek health care advice.[480] Many patients report feelings of depression and fear of rejection and discovery. These negative feelings tend to subside over time, although not completely.[481] Psychological distress can be both a cause and a consequence of genital lesions.[482] Therefore during acute illness, it is best to ensure symptomatic palliation by recommending antiviral therapy, antiinflammatory pain medicines, sitz baths, and local drying of the lesions. The patient should usually be taught about the chronicity of infection and natural history of recurrence and asymptomatic reactivation on later visits. Women's concerns regarding issues relating to pregnancy and childbirth should be addressed as well. The misconception that HSV causes cancer should be dispelled.

Some patients in primary care, pregnant women, or patients at sexually transmitted disease clinics who are asymptomatic will have their infection diagnosed from serologic study rather than symptoms. This is also likely to be a source of distress for patients, and the above-described counseling strategies should be used. Particular emphasis should be placed on recognition of subtle genital ulcers. Multiple

resources including websites (http://www.ashasexualhealth.org/) and printed materials are available to assist patients, their partners, and clinicians who become involved in counseling.

Finally, strategies for prevention of HSV-2 transmission should be emphasized to patients, particularly patients within serodiscordant relationships. Partially effective strategies include full disclosure to the susceptible partner, condom use, abstinence during symptomatic lesions or prodromes, and antiviral therapy.[101,102,483] Valacyclovir (500 mg daily) reduces transmission of genital herpes by 50% by suppression of episodes of subclinical shedding and is a primary, albeit imperfect, prevention strategy within serodiscordant partnerships.[101] The possibility of asymptomatic transmission should also be addressed.

Herpes Simplex Virus Vaccines

To date, no licensed vaccine is available for either HSV-1 or HSV-2. Based on the large public health burden of HSV and the continued spread of the HSV-2 epidemic worldwide, there is a need for such a vaccine.[484] Recommendations for increased research and development of a next generation of herpes simplex vaccines have been formulated by the US National Institute of Allergy and Infectious Diseases.[485] A review of the status of HSV vaccine research and development has been published on behalf of the World Health Organization Product Development for Vaccines Advisory Committee.[486] Most HSV vaccine studies have tested the monomeric surface glycoprotein gD2 and/or EB1. Consistent results have not been seen, and development of these vaccines has largely been discontinued.[487–489]

A deeper knowledge of factors possibly associated with protection against HSV is needed. It is hoped that the development of other successful herpesvirus vaccines such as those for CMV and VZV will spur further research on HSV-2. Advances in understanding T-cell immune responses to HSV have fostered the development of immunotherapeutic vaccines with the goal of limiting HSV-2 shedding, recurrences, and transmission among seropositive individuals.[490–496] Practically speaking, clinical trials of therapeutic vaccines are faster, require much smaller sample sizes, and potentially allow a rapid and less expensive pathway to licensure. In a recent phase II trial, a vaccine consisting of HSV-2 glycoprotein D2, a truncated ICP4, and Matrix-M2 adjuvant demonstrated a 50% reduction in shedding rate at 6 months.[497] A variety of additional approaches are entering human clinical trials.

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The complete reference list is available online at Expert Consult.

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136 Chickenpox and Herpes Zoster (Varicella-Zoster Virus)

Richard J. Whitley

SHORT VIEW SUMMARY

Definition
- Varicella-zoster virus (VZV) is an alphaherpesvirus that causes chickenpox and herpes zoster.

Epidemiology
- Chickenpox is the primary infection occurring in childhood.
- Chickenpox is usually a benign infection but can cause life-threatening disease in an immunocompromised host.
- Chickenpox is more likely to occur in late winter and early spring.
- Herpes zoster is the consequence of reactivation of latent virus, occurring mainly in elderly and immunocompromised individuals.
- Herpes zoster causes significant pain in many individuals, particularly elderly individuals.
- There is no seasonal predilection for occurrence of herpes zoster.

Microbiology
- VZV is a double-stranded DNA virus. Following primary infection, latency is established in sensory ganglia.

Diagnosis
- Diagnosis of chickenpox and herpes zoster is usually clinical.
- Chickenpox is characterized by a maculopapular, vesicular, and papular rash in all stages of evolution.
- Herpes zoster is usually a unilateral vesicular rash. Dissemination can occur in immunocompromised patients.
- A Tzanck smear of lesion scrapings may demonstrate intranuclear inclusions; however, its sensitivity as a diagnostic test is low.
- Polymerase chain reaction (PCR) can be applied to lesion scraping to detect VZV DNA and is the diagnostic procedure of choice.
- Viral culture can be used to make a diagnosis, but it is less sensitive than PCR.

Therapy
- Three drugs are licensed for treatment of VZV infections (see Table 136.1).
- Chickenpox in children 2 to 16 years of age can be treated with acyclovir at a dosage of 20 mg/kg four times per day for 5 days. For older patients, the dosage of acyclovir is 800 mg five times a day.
- The prodrugs valacyclovir and famciclovir are used by some experts to treat chickenpox.
- Herpes zoster can be treated with acyclovir at a dosage of 800 mg five times daily for 7 to 10 days, with valacyclovir at a dosage of 1 g three times daily for 7 to 10 days, or famciclovir at a dosage of 500 mg three times daily for 7 to 10 days.
- Herpes zoster is likely to require pain control with analgesics and medications such as pregabalin.

Prevention
- High-titer varicella-zoster immune globulin (VariZIG) can be administered to high-risk patients to attempt to prevent infection.
- A VZV vaccine is available to prevent chickenpox (Varivax). It is a two-dose series with the first administered at 12 to 15 months of age and the second administered between 4 and 6 years. This two-dose series has dramatically decreased the incidence of chickenpox and its associated complications.
- Two vaccines are approved to prevent herpes zoster in older individuals. A high-titer live VZV vaccine (Zostavax) and an inactive adjuvanted VZV vaccine (Shingrix) are available for adults older than 50 years of age. Each vaccine can reduce the incidence of herpes zoster. In 2018, the Advisory Committee on Immunization Practices recommendations stated that Shingrix is preferred to Zostavax and that Shingrix can be administered to adults who have previously received Zostavax.

Varicella-zoster virus (VZV) causes two distinct clinical diseases. Varicella, more commonly called chickenpox, is the primary infection and results from exposure of a person susceptible to the virus to someone who is actively infected. Chickenpox is ubiquitous and extremely contagious, but for the most part it is a benign illness characterized by a generalized exanthematous rash. It occurs seasonally and in epidemics. Recurrence of infection results in the localized entity known as *herpes zoster,* often referred to as *shingles,* a common infection among elderly and immunocompromised individuals. Live attenuated vaccines for the prevention of chickenpox (Varivax) and herpes zoster (Zostavax) are licensed in the United States. An inactivated adjuvanted vaccine (Shingrix) is licensed for prevention of herpes zoster in older adults in the United States. Vaccination is recommended for use in healthy children and in susceptible adults to prevent chickenpox (see Chapter 316). Both herpes zoster vaccines are recommended for adults older than 50 years of age to decrease the incidence of shingles, although Shingrix is preferred in the Advisory Committee on Immunization Practices (ACIP) recommendations (see later).

Historically, the incidence of chickenpox was that of the annual birth rate, but incidence has been tremendously reduced with widespread vaccination. Surveillance for varicella in three counties in California, Texas, and Pennsylvania from 1995 to 2000 showed reductions in cases of varicella by 71% to 84% in 1999 and 2000,[1] with only 500 cases occurring in 2004.[2] By 2010, varicella incidence declined by 98% in the two remaining sites (Antelope Valley, California, and West Philadelphia, Pennsylvania) (Fig. 136.1).[3,4] Since the implementation of a two-dose vaccine series, the incidence of chickenpox has decreased to approximately 5 cases in 100,000 in states with adequate reporting.[2] Approximately 1 million cases of herpes zoster, which result in more than 2 million physician visits annually, occur yearly in the United States. This approximation likely is an underestimation of disease occurrence. Many individuals with herpes zoster require long-term follow-up medical care for postherpetic neuralgia (PHN).

HISTORICAL OVERVIEW

Shingles has been recognized since ancient times as a unique clinical entity because of the dermatomal vesicular rash; however, chickenpox was often confused with smallpox.[5] In 1875 Steiner successfully transmitted VZV by inoculation of the vesicular fluid from a person with chickenpox to human "volunteers."[6] The infectious nature of VZV was further defined by von Bokay,[7,8] who observed chickenpox in people who had close contact with other people with herpes zoster. He correctly described the mean incubation period of approximately 2 weeks for the development of chickenpox in susceptible patients and the average range in days. In 1925, Kundratitz[9] showed that the inoculation of vesicular fluid from patients with herpes zoster into

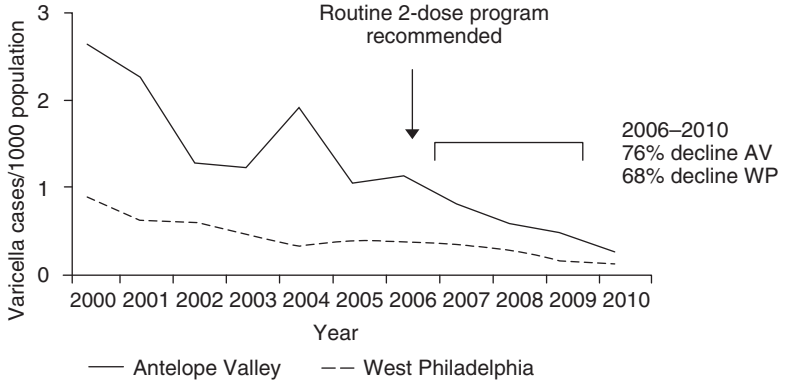

FIG. 136.1 Impact of a two-dose varicella vaccination program in three sentinel counties. *(From Bialek SR, Perella D, Zhang J, et al. Impact of a routine two-dose varicella vaccination program on varicella epidemiology.* Pediatrics. *2013;132:e1134-1140.)*

susceptible individuals resulted in chickenpox. Similar observations were reported by Brunsgaard[10] and others,[11] and in 1943 Garland[12] suggested that herpes zoster was the consequence of the reactivation of latent VZV.

Since early in the 20th century, similarities in the histopathologic features of skin lesions and in epidemiologic and immunologic studies indicated that varicella and herpes zoster were caused by the same agent.[13,14] Tyzzer[15] described the histopathologic features of skin lesions resulting from VZV infections and noted the appearance of intranuclear inclusions and multinucleated giant cells. These descriptions came from histologic studies performed on serial skin biopsy specimens that were obtained during the first week of illness. The histopathologic descriptions were amplified by Lipschitz in 1921[16] for herpes zoster.

Isolation of VZV in 1958 permitted a definition of the biology of this virus.[14] Viral isolates from patients with either chickenpox or herpes zoster demonstrated similar changes in tissue culture, specifically the appearance of eosinophilic intranuclear inclusions and multinucleated giant cells. These findings are virtually identical to findings present on clinically available biopsy material. Taken together, these data provided a universal acceptance that both diseases were caused by VZV. By 1958, Weller and colleagues[14,17-19] established that there were neither biologic nor immunologic differences between the viral agents isolated from patients with these two clinical entities. Later studies identified VZV by rigorous biochemical methods.[20] Viral DNA from a patient with chickenpox who subsequently developed herpes zoster was examined by restriction endonuclease analysis, and the molecular identity of these two viruses was verified.[21]

PATHOGEN AND ITS REPLICATION

VZV is a member of the Herpesviridae family and shares structural characteristics with other members of the family. The virus has icosapentahedral symmetry and contains centrally located double-stranded DNA with a surrounding envelope. The size of the virus is approximately 150 to 200 nm, and it has a lipid-containing envelope with glycoprotein spikes.[22,23] The naked capsid has a diameter of approximately 90 to 95 nm.[24-26] The DNA contains 125,000 base pairs, or approximately 80 megadaltons, and encodes about 75 proteins. The organization of the viral genome is similar to that of other herpesviruses. There are unique long (105-kb) and unique short (5.2-kb) regions of the viral genome. Each unique sequence contains terminal repeat sequences. With replication, the unique short region can invert on itself and result in two isomeric forms.[22,27,28] Notably, a large portion of the VZV genome is colinear with herpes simplex type 1 (HSV-1). For example, within the unique long region of VZV, 56 of the 62 genes have HSV-1 homologues. Similarly, in the unique short region all four genes have homologues.

Eight VZV glycoproteins have been identified: gB, gC, gE, gH, gI, gK, gL, and gM/N. These glycoproteins have been the subject of intense investigative interest because they represent the primary markers for both humoral and cell-mediated immune responses.[22]

Only enveloped virions are infectious, likely accounting for the lability of VZV. Furthermore, the envelope is sensitive to detergent, ether, and air-drying. VZV is highly cell associated and spreads from cell to cell by direct contact. Virus can be isolated in a variety of continuous and discontinuous cell culture systems of human and simian origin. Approximately 8 to 10 hours after infection, virus-specific immunofluorescence can be detected in the cells immediately adjacent to the initial focus of infection. This parallels the microscopic observation of the radial spread of the cytopathologic process.[29,30] Electron microscopic studies demonstrate the appearance of immature viral particles within 12 hours of the onset of infection. As with HSV, the naked capsids acquire their envelope at the nuclear membrane, being released into the perinuclear space where large vacuoles are formed.[24,31] Infectious virus is then spread to adjacent cells after fusion of plasma membranes.

EPIDEMIOLOGY OF VARICELLA-ZOSTER VIRUS INFECTIONS

Chickenpox

Humans are the only known reservoir for VZV. Chickenpox follows exposure of the susceptible or seronegative person to VZV and represents the primary form of infection. Although it is assumed that the virus is spread by the respiratory route and replicates in the nasopharynx or upper respiratory tract, retrieval of virus from individuals incubating VZV has been uncommon. However, the application of polymerase chain reaction (PCR) techniques to nasopharyngeal secretions of exposed and susceptible individuals has detected VZV DNA and supports this hypothesis.[32] Chickenpox was a common infection of childhood and affects both sexes equally and people of all races. To a certain extent, the virus is endemic in the population at large; however, it becomes epidemic among susceptible individuals during seasonal periods of late winter and early spring.[33] Intimate contact appears to be the key determinant for transmission.

With the implementation of childhood vaccination programs in some countries, the epidemiology of chickenpox is changing dramatically with a decreasing incidence. However, many countries still do not employ universal immunization; as a consequence, the epidemiology of infection remains as known historically.

Overall, chickenpox is a disease of childhood because 90% of cases occur in children younger than 13 years. Typically the virus is introduced into the susceptible school-aged or preschool child. In a study by Wells and Holla,[34] 61 of 67 susceptible children in kindergarten through the fourth grade contracted chickenpox. Approximately 10% of individuals older than 15 years are considered susceptible to VZV infection. The incubation period of chickenpox (i.e., the time interval between exposure of a susceptible person and the time the vesicular rash develops in an index case) is generally regarded to be 14 to 15 days, but disease can appear within a range of 10 to 20 days.[35,36] Secondary attack rates among susceptible siblings within a household are between 70% and 90%.[37] Patients are infectious for approximately 48 hours before the period of

vesicle formation and generally for 4 to 5 days thereafter until all vesicles are crusted.

Although chickenpox exists worldwide among children, it occurs more frequently in adults who reside in tropical regions than in adults who reside in other geographic areas. Stokes[38] noted a higher incidence of chickenpox among soldiers serving abroad during World War II, in whom the incidence was 1.41 to 2.27 per 1000 persons annually. These rates contrast with rates in the United States, which were approximately half those reported among the soldiers.

Herpes Zoster

The epidemiology of herpes zoster is different. VZV characteristically becomes latent after primary infection within the dorsal root ganglia. Reactivation leads to herpes zoster, a sporadic disease. Histopathologic examination of the nerve root after infection with VZV demonstrates characteristics indicative of VZV infection. In people who die after recent herpes zoster infection, an examination of the dorsal root ganglia reveals satellitosis, lymphocytic infiltration in the nerve root, and degeneration of the ganglia cells.[39,40] Intranuclear inclusions can be found within the ganglia cells. Although it is possible to demonstrate the presence of VZV by electron microscopy, it has not been possible to isolate virus in cultures as has been done after HSV infection, usually from explants of dorsal root ganglia. Nevertheless, the application of PCR to extracted ganglionic DNA demonstrates latent viral DNA in neurons of sensory ganglia, including dorsal root, cranial, and enteric ganglia.[41] The biologic mechanism by which VZV establishes latency remains unknown.

Herpes zoster is a disease that occurs at all ages. It affects approximately 1 million annually or 20% or more of the population throughout the life span, although mainly elderly adults.[42,43] Herpes zoster occurs in individuals who are seropositive for VZV or, more specifically, in individuals who have had chickenpox. Reactivation appears to depend on a balance between virus and host factors. Most patients who develop herpes zoster have no history of exposure to other people with VZV infection at the time of the appearance of lesions. The highest incidence of disease varies between 5 and 10 cases per 1000 for people older than 60 years.[17] Approximately 4% of patients experience a second episode of herpes zoster; however, recurrences of dermatomal lesions are usually caused by HSV. This finding was verified in the Shingles Prevention Study on vaccination.[44] In a 7-year study by McGregor,[45] the annualized rate of herpes zoster was 4.8 cases per 1000 patients, and three-fourths of the patients were older than 45 years. Immunocompromised individuals have a higher incidence of both chickenpox and shingles.[46-49] Herpes zoster occurs within the first 2 years of life in children born to women who have had chickenpox during pregnancy. These cases probably reflect in utero chickenpox with reactivation early in life.

PATHOGENESIS

Chickenpox occurs in susceptible individuals who are exposed to virus after close personal contact. Histopathologic findings of human VZV infections, whether chickenpox or herpes zoster, are virtually identical. The vesicles involve the corium, or dermis. As viral replication progresses, the epithelial cells undergo degenerative changes characterized by ballooning, with the subsequent appearance of multinucleated giant cells and prominent eosinophilic intranuclear inclusions. Under unusual circumstances, necrosis and hemorrhage may appear in the upper portion of the dermis. As the vesicle evolves, the fluid becomes cloudy as a consequence of the appearance of polymorphonuclear leukocytes, degenerated cells, and fibrin. Ultimately, either the vesicles rupture and release infectious fluid or the fluid gradually becomes reabsorbed.

As noted earlier, transmission is likely by the respiratory route, followed by localized replication at an undefined site, with lymphatic spread and seeding of the reticuloendothelial system and, ultimately, viremia. The occurrence of viremia in patients with chickenpox is supported by the detection of virus in peripheral blood mononuclear cells and by the diffuse and scattered nature of the skin lesions, and it can be verified in selected cases by the recovery of virus from the blood.[50] The mechanism of VZV reactivation that results in herpes zoster is unknown.

CLINICAL MANIFESTATIONS

Chickenpox

Chickenpox is generally a benign, self-limited disease in immunocompetent children, the incidence of which has markedly decreased with more widespread use of the varicella vaccine. There are fewer than 14 deaths per year in the United States in immunocompetent children.[51] For a healthy unimmunized child, chickenpox-associated mortality is fewer than 2 per 100,000 cases, although this is higher in infants.[22] This risk increases by more than 15-fold for adults. The presenting manifestations of chickenpox are a rash, low-grade fever, and malaise. In a few patients, a prodrome of the reported symptoms may occur 1 to 2 days before the onset of the exanthem. For the most part, chickenpox in an immunocompetent child is associated with lassitude and a temperature of 100°F to 103°F of 3 to 5 days' duration. Subsequent constitutional symptoms include malaise, pruritus, anorexia, and listlessness; these symptoms gradually resolve as the illness abates. The skin manifestations, which are the hallmark of infection, consist of maculopapules, vesicles, and scabs in varying stages of evolution. The lesions initially contain clear vesicular fluid, but over a short period of time they pustulate and scab. Most lesions are small, having an erythematous base with a diameter of 5 mm to as large as 12 to 13 mm. The lesions can be round or oval; central umbilication occurs as healing progresses. The lesions have often been referred to as "dew drop–like" during the early stages of formation. If they do not rupture within a few hours, the contents rapidly become purulent in appearance. Lesions appear on the trunk and face and rapidly spread centrifugally to involve other areas of the body. Successive crops of lesions generally appear over a period of 2 to 4 days. Thus early in the disease, the hallmark of the infection is the appearance of lesions at all stages, as noted previously. The lesions can also be found on the mucosa of the oropharynx and the vagina; however, these sites are less commonly involved. The crusts completely fall off within 1 to 2 weeks after the onset of infection and leave a slightly depressed area of skin.

Immunocompromised children, particularly children with leukemia, have more numerous lesions, often with a hemorrhagic base. Healing takes nearly three times longer in this population.[46] These children are at greater risk for visceral complications, which occur in 30% to 50% of cases and can be fatal in 15% of cases in the absence of therapy. A notable complication of chickenpox is secondary bacterial infection of the lesions, often in association with gram-positive organisms. Streptococcal toxic shock is a rare but potentially lethal complication of varicella. Infection in the neutropenic host can be systemic, beyond cutaneous involvement.

The most frequent noncutaneous site of involvement after chickenpox is the central nervous system (CNS); the neurologic abnormalities are manifested as acute cerebellar ataxia or encephalitis.[35,52-54] Cerebellar ataxia has been estimated to occur in 1 in 4000 cases among children younger than 15 years. Cerebellar ataxia can appear as late as 21 days after the onset of rash. It is more common, however, for acute cerebellar ataxia to manifest within 1 week of the onset of the exanthem. An extensive review by Underwood[54] of 120 cases demonstrated that ataxia, vomiting, altered speech, fever, vertigo, and tremor all were common on physical examination. Cerebrospinal fluid (CSF) from these patients often demonstrates lymphocytosis and elevated levels of protein. This is usually a benign complication in children and resolves within 2 to 4 weeks. PCR techniques can detect VZV DNA in the CSF.[55]

A more serious CNS complication is encephalitis, which can be life threatening in adults. Encephalitis is reported to occur in 0.1% to 0.2% of individuals with chickenpox.[53] Underwood's review[54] reported this illness to be characterized by depression in the level of consciousness with progressive headaches, vomiting, altered thought patterns, fever, and frequent seizures. The duration of disease in these patients is at least 2 weeks. Some patients experience progressive neurologic deterioration that leads to death. Mortality in patients who develop encephalitis has been estimated to range from 5% to 20%, and neurologic sequelae can occur in 15% of survivors.

A serious and life-threatening complication is the appearance of varicella pneumonitis, a complication that occurs more commonly in adults and in immunocompromised individuals.[33,52] Among adults, it is estimated to occur in 1 in 400 cases of infection; not infrequently, in

the absence of clinical symptoms, it appears 3 to 5 days into the course of illness and is associated with tachypnea, cough, dyspnea, and fever. Pregnant women during the second and third trimesters of gestation are particularly vulnerable to pneumonitis with primary infection. Chest radiographs usually reveal nodular or interstitial pneumonitis. Varicella pneumonitis can be life threatening when it occurs in pregnant women during the second or third trimester.

In a prospective study of male military personnel, radiographic abnormalities were detected in nearly 16% of enlisted men who developed varicella, although only one-fourth of these men had evidence of cough.[56] Only 10% of the men with radiographic abnormalities developed evidence of tachypnea, indicating that asymptomatic pneumonitis may exist more commonly than was initially predicted. Other manifestations of noncutaneous and nonneurologic involvement include the appearance of myocarditis, nephritis, bleeding diatheses, and hepatitis. Furthermore, isolated abdominal presentations of chickenpox have been reported.[32,41]

Perinatal varicella is associated with a high death rate when maternal disease develops 5 days before delivery or up to 48 hours postpartum.[57,58] In large part, this is the consequence of the newborn failing to receive protective transplacental antibodies as well as the immaturity of the neonatal immune system. Under such circumstances, mortality has been reported to be 30%. Affected children have progressive disease involving visceral organs, especially the lung. The outcome in these children was summarized by Brunell.[59] Congenital varicella, although uncommon, is characterized by skin scarring, hypoplastic extremities, eye abnormalities, and evidence of CNS impairment.[60]

Varicella has been associated epidemiologically with the development of Reye syndrome and coadministration of aspirin. Therefore the administration of aspirin is contraindicated in individuals with varicella. Cutaneous complications include the development of secondary skin infections, especially infections caused by *Staphylococcus aureus.*

Chickenpox in the Immunocompromised Patient

Chickenpox in an immunocompromised child or adult is a cause of significant morbidity and mortality. As noted previously, the duration of healing of cutaneous lesions can be extended by a minimum of threefold. However, a more important problem is the progressive involvement of visceral organs. Data from a variety of immunocompromised patient populations ranging from patients with lymphoproliferative malignancies and solid tumors to bone marrow transplant recipients indicate a broad spectrum of disease. In the absence of therapy, approximately one-third of children develop progressive disease with involvement of multiple organs, including the lungs, liver, and CNS.[46] Most of these children develop pneumonitis within the first week after the onset of infection, as do 20% of all children who acquire chickenpox. Mortality in this patient population is approximately 15% to 18%.[46,61,62] Patients with lymphoproliferative malignancies who require continuous chemotherapy appear to be at greatest risk for visceral involvement.

In individuals undergoing hematopoietic stem cell transplantation, the incidence of VZV infections over the first year has been estimated to be 30% by 1 year after transplantation. Of these infections, 80% occurred within the first 9 months after transplantation, and 45% of patients had cutaneous or visceral dissemination (see Chapter 307). Overall, 23 deaths occurred in one prospective series.[48] Risk factors identified for the acquisition of VZV infection included age between 10 and 29 years, diagnosis other than chronic myelogenous leukemia, posttransplant use of antithymocyte globulin, allogeneic transplant, and acute or chronic graft-versus-host disease. Graft-versus-host disease increases the probability of visceral dissemination significantly. Patients receiving HSV prophylaxis with acyclovir 800 mg orally twice daily or valacyclovir 500 mg orally twice daily or receiving treatment for cytomegalovirus reactivation with ganciclovir derive a degree of protection against reactivation of VZV.

Herpes Zoster

Herpes zoster, or shingles, is characterized by a unilateral vesicular eruption with a dermatomal distribution. Thoracic and lumbar dermatomes are most commonly involved (Fig. 136.2). Herpes zoster may involve the eyelids when the first or second branch of the fifth cranial nerve is affected, but herpes zoster ophthalmicus is a sight-threatening condition. Although lesions on the tip of the nose are said to presage corneal lesions, absence of such skin lesions does not guarantee corneal sparing. Keratitis may be followed by severe iridocyclitis, secondary glaucoma, or neuroparalytic keratitis. Ophthalmologic consultation should be requested for any patient with suspected herpes zoster ophthalmicus. Generally the onset of disease is heralded by pain within the dermatome that precedes the lesions by 48 to 72 hours. Early in the disease course, erythematous, maculopapular lesions appear and rapidly evolve into a vesicular rash. Vesicles may coalesce to form bullous lesions. In the normal host, these lesions continue to form over 3 to 5 days, with the total duration of disease being 10 to 15 days. However, it may take 1 month before the skin returns to normal. Rarely, individuals will develop an entity known as *zoster sine herpete,* which refers to dermatomal pain in the absence of lesions and is confirmed by serologic boosting of antibody responses.[22]

FIG. 136.2 **Herpes zoster involving the lumbar dermatome.**

Unusual cutaneous manifestations of herpes zoster in addition to herpes zoster ophthalmicus include involvement of the maxillary or mandibular branch of the trigeminal nerve, which results in intraoral involvement with lesions on the palate, tonsillar fossa, floor of the mouth, and tongue. When the geniculate ganglion is involved, Ramsay Hunt syndrome may occur, with pain and vesicles in the external auditory meatus, loss of taste on the anterior two-thirds of the tongue, and ipsilateral facial palsy.

No known factors are responsible for the precipitation of episodes of herpes zoster. If herpes zoster occurs in children, the course is generally benign and not associated with progressive pain or discomfort. In adults, systemic manifestations are mainly associated with pain, as noted in the following paragraphs.

The most significant clinical manifestations of herpes zoster are the associated acute neuritis and, later on, PHN. Modeling of pain attributed to herpes zoster defines three phases of disease: acute, subacute, and chronic.[63] Historically the latter two make up PHN. As identified later, the impact of therapy on each phase can be defined. PHN, although uncommon in young people, may occur in 25% to 50% of patients older than 50 years.[64-66] Up to 50% of adults older than 50 years have debilitating pain that persists for more than 1 month. PHN may cause constant pain in the involved dermatome or consist of intermittent stabbing pain. Pain may be worse at night or on exposure to temperature changes; at its worst, neuralgia can be incapacitating.[67]

Extracutaneous sites of involvement include the CNS, as manifested by meningoencephalitis or encephalitis. The clinical manifestations are similar to manifestations of other viral infections of the brain. However, a rare manifestation of CNS involvement by herpes zoster is granulomatous cerebral angiitis, which usually follows zoster ophthalmicus. Involvement of the CNS with cutaneous herpes zoster is probably more common than recognized clinically. Frequently, patients who undergo CSF examination for other reasons during episodes of shingles are found to have evidence of pleocytosis without significantly elevated protein levels. These patients are without signs of meningeal irritation and infrequently complain of headaches. A notable neurologic complication is the late appearance of cerebral angiitis after herpes zoster ophthalmicus.

Angiitis typically manifests as an ischemic stroke and can occur several months after herpes zoster of the trigeminal ganglia. This problem has been noted in several patients and defined as being progressive with a high mortality rate. Other nervous system manifestations of chickenpox include meningitis, transverse myelitis, and Reye syndrome.

Classically, VZV infection involves sensory ganglia; however, motor paralysis can occur as a consequence of the involvement of the anterior horn cells, in a manner similar to that encountered with polio. Patients with involvement of the anterior horn cells are particularly likely to have excruciating pain. Other neuromuscular disorders associated with herpes zoster include Guillain-Barré syndrome, transverse myelitis,[68] and myositis.[69] Herpes zoster in an immunocompromised patient is more severe than in a healthy person. Lesion formation continues for up to 2 weeks, and scabbing may not occur until 3 to 4 weeks into the disease course.[70] Patients with lymphoproliferative malignancies are at risk for cutaneous dissemination and visceral involvement, including varicella pneumonitis, hepatitis, and meningoencephalitis. Although some immunocompromised patients with dermatomal zoster who remain febrile and develop progressive lesions outside the dermatome may become severely ill, disseminated herpes zoster is rarely fatal even in immunocompromised patients.

Herpes zoster has been recognized as a frequent infection in individuals with human immunodeficiency virus (HIV) infection, occurring in 8% to 11% of patients. Although the occurrence of cutaneous dissemination is infrequent, complications such as VZV retinitis, acute retinal necrosis, and chronic progressive encephalitis have been reported.[71] The use of anti–tumor necrosis factor-α monoclonal antibodies has been associated with an increased incidence of herpes zoster.[72]

Chronic herpes zoster may also occur in immunocompromised patients, particularly patients with HIV infection. Patients have experienced new lesion formation with an absence of healing of the existing lesions. These syndromes can be particularly debilitating and have been associated with the isolation of VZV isolates resistant to acyclovir.

DIAGNOSIS

The diagnosis of both chickenpox and shingles is usually made by history and physical examination. In the first part of the 21st century, the differential diagnosis of varicella and herpes zoster is less confusing than it was 20 to 30 years ago. Smallpox or disseminated vaccinia was confused with varicella because of the similar appearance of the cutaneous lesions, and it could again pose a problem in the era of bioterrorism. With the worldwide eradication of smallpox, these disease entities only serve to confound the diagnosis if used by a bioterrorist or as a complication of vaccination. The characteristic skin rash of chickenpox with lesions in all stages of development provides the basis for the clinical diagnosis of infection. The presence of pruritus, pain, and low-grade fever also helps establish the diagnosis of chickenpox. The localization and distribution of a vesicular rash make the diagnosis of herpes zoster highly likely; however, other viral exanthemas can occasionally be confused with this disease.

Impetigo and varicella can also be confused clinically. Impetigo is usually caused by group A β-hemolytic streptococci, often follows an abrasion of the skin or inoculation of bacteria at the site of the skin break, and can be associated with the formation of small vesicles in the surrounding area. Systemic signs of disease may be present if progressive cellulitis or secondary bacteremia develops. Unroofing lesions and performing a Gram stain of the scraping of the base of the lesion should reveal gram-positive cocci in chains, suggestive of streptococci, or gram-positive cocci in clusters, suggestive of staphylococci, another cause of vesicular skin lesions, or both organisms. Treatment for these latter infections is distinctly different from treatment for chickenpox and requires administration of an appropriate antibiotic.

In a smaller number of cases, disseminated vesicular lesions can be caused by HSV. In these cases, disseminated HSV infection is usually a consequence of an underlying skin disease such as atopic dermatitis or eczema. An unequivocal diagnosis can be made only by isolation of the virus in tissue culture.

Disseminated enteroviral infections, particularly those caused by group A coxsackieviruses, have been reported to cause widespread distal vesicular lesions. These rashes are more commonly morbilliform in nature, with a hemorrhagic component rather than a vesicular or vesiculopustular appearance. Generally, these infections occur during the enterovirus season in late summer and early fall and are associated with lesions of the oropharynx, palms, and soles. This latter finding is helpful in distinguishing enteroviral disease from chickenpox.

Unilateral vesicular lesions in the dermatomal pattern should immediately lead the clinician to suspect a diagnosis of shingles. HSV and coxsackievirus infections can also cause dermatomal vesicular lesions. In such situations, diagnostic viral cultures remain the best method of establishing the cause of infection. Confirmation of the diagnosis is possible through the isolation of VZV in susceptible tissue culture cell lines or by the demonstration of either seroconversion or serologic rises using standard antibody assays of acute and convalescent serum specimens. A Tzanck smear, performed by scraping the base of the lesion, can demonstrate multinucleated giant cells; however, the sensitivity of this test is no better than 60% and does not distinguish HSV from VZV. Commercially available reagents are useful for direct fluorescent antibody staining of smears obtained from scraping vesicular lesions. With atypical skin lesions, such smears have adequate sensitivity and specificity to guide early management decisions. In some laboratories, PCR has become the diagnostic technique of choice because of sensitivity, specificity, and specimen stability. However, its expense and lack of uniform performance standards have limited routine diagnostic use. Useful antibody assays include immune adherence hemagglutination assay, fluorescence antibody to membrane antigen assay, and enzyme-linked immunosorbent assay.[73] The application of PCR to the CSF can be used to detect VZV DNA and therefore infections of the CNS. A positive PCR in the CSF may be seen in dermatomal zoster, and it is most useful when typical skin lesions of herpes zoster may not be present. PCR may detect evidence of VZV DNA is a nasal swab in individuals with herpes zoster, even before the appearance of rash.

THERAPY

The medical management of chickenpox and shingles in the normal host is directed toward reduction of complications. For chickenpox, hygiene is important, including bathing, astringent soaks, and closely cropped fingernails to avoid a source for secondary bacterial infection associated with scratching of the pruritic skin lesions. Pruritus can be decreased with topical dressing or the administration of antipruritic drugs. Soaks with aluminum acetate, or Burow solution, in the management of herpes zoster can be both soothing and cleansing.[74] Acetaminophen should be used to reduce fever in patients with chickenpox because of the association between aspirin and Reye syndrome.

Acyclovir is approved in the United States for the treatment of both chickenpox and herpes zoster in the normal host (Table 136.1). Oral acyclovir therapy in healthy children, adolescents, and adults shortens the duration of lesion formation by about 1 day, reduces the total number of new lesions by approximately 25%, and diminishes constitutional symptoms in one-third of patients.[22,23,74-77] The American Academy of Pediatrics recommends therapy for adolescents and adults as well as high-risk groups of patients (e.g., premature infants, children with bronchopulmonary dysplasia) within 24 hours of onset of disease. In children 2 to 18 years old, the oral dosage is 20 mg/kg four times daily for 5 days (maximum 800 mg daily). Adolescents and adults can receive up to 800 mg five times a day. Oral therapy of herpes zoster in the normal host accelerates cutaneous healing and reduces acute neuritis.

Acyclovir has been evaluated in controlled studies for all herpesvirus infections. Acyclovir is a guanine derivative that has a high degree of selectivity for the inhibition of VZV replication because of its selected phosphorylation and activation by the virus-coded thymidine kinase and its subsequent selective inhibition of the viral DNA polymerase. It is estimated that the concentration of acyclovir required to inhibit VZV replication in vitro is 2.1 to 6.3 μM, which is easily achieved after intravenous administration of acyclovir.[78] However, such concentrations are not easily achieved even after administration of high-dose oral acyclovir as summarized.[79] The recommended dosage for acyclovir is 10 mg/kg administered intravenously every 8 hours or, as suggested by some, 500 mg/m^2 intravenously every 8 hours, especially in children

TABLE 136.1 Antiviral Therapy of Varicella-Zoster Infection

INFECTION	DRUG	ROUTE	DOSAGE
Chickenpox (immunocompetent host)	Acyclovir	Oral	20 mg/kg (maximum 800 mg) 4–5 times daily × 5 days
Chickenpox (immunocompromised host)	Acyclovir	IV	10 mg/kg q8h × 7 days
Herpes zoster (immunocompetent host)	Valacyclovir Famciclovir Acyclovir	Oral Oral Oral	1 g tid × 7 days 500 mg q8h × 7 days 800 mg 5 times daily × 7–10 days
Herpes zoster (immunocompromised host)	Acyclovir Valacyclovir Famciclovir	IV Oral Oral Oral	10 mg/kg q8h × 7 days 800 mg 5 times daily × 7 days 1 g tid × 7 days[a] 500 md tid × 10 days[a]

[a]Not approved for this indication by the US Food and Drug Administration.
IV, Intravenous.
Modified from Baden L, Dolin R. Antiviral chemotherapy. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. *19th ed. New York: McGraw-Hill Education; 2015:1174.*

and in patients at risk for complications; otherwise oral treatment is the preferred management strategy.

The prodrugs of acyclovir and penciclovir—valacyclovir and famciclovir, respectively—have been licensed for therapy of herpes zoster.[80,81] The use of valacyclovir results in enhanced oral bioavailability, approximately 60%, compared with poor oral absorption of acyclovir. Oral bioavailability of famciclovir is approximately 80%. Both drugs appear superior to acyclovir for acceleration of cutaneous healing and are at least equally, if not more, efficacious for resolution of pain. Valacyclovir is administered to adults at a dosage of 1 g three times daily for 7 to 10 days.[80] The dosage of famciclovir is 500 mg three times daily for 7 to 10 days[80] Both medications are well tolerated. These medications primarily affect the acute and subacute phases of disease, as noted earlier. All three licensed therapeutics in North America are generic.

Resistance to acyclovir has been encountered in immunosuppressed patients including patients with hematologic-oncologic conditions and HIV-infected patients.[82-86] Foscarnet has been used to treat herpes zoster with resistant VZV. Dosage recommendations are 60 mg/kg every 8 hours adjusted for renal function for at least 10 days or until lesions are healed. Cidofovir has been used to treat acyclovir-resistant VZV, although experience in its use is limited.[82]

The concomitant administration of corticosteroids and an antiviral remains controversial. In one study, such regimens failed to affect PHN, although resolution of acute neuritis was accelerated.[87] This study was not placebo controlled. A placebo-controlled trial, using a 2×2 factorial design, demonstrated significant improvement in quality of life.[88] Patients older than 50 years who received acyclovir (800 mg five times daily for 3 weeks) and tapering doses of prednisone (60 mg daily for 7 days, 30 mg daily for 7 days, and 15 mg daily for 7 days) experienced resolution of acute neuritis, were able to sleep uninterrupted, and returned to their usual activity levels more promptly than did control subjects and had lower analgesic requirements. Complications were not encountered; however, patients at risk for complications of high-dose steroid therapy were excluded.

Management of varicella pneumonitis and other complications requires excellent supportive nursing care in addition to evaluation on an individual basis of the potential need for antiviral therapy. The management of acute neuritis and PHN can be particularly problematic. The judicious use of analgesics ranging from nonnarcotic to narcotic derivatives is required, and drugs such as amitriptyline hydrochloride, fluphenazine hydrochloride, lidocaine patches, gabapentin, and pregabalin may be used.[89-91] Furthermore, intrathecal administration of narcotics has been reported to be of value.[92]

PREVENTION

In the normal host, prophylaxis of chickenpox is achieved via vaccination. The potential for transmission of VZV in the hospital to immunosuppressed patients, particularly children, is a serious problem. Patients who require hospitalization because of varicella are a source of nosocomial infection. Because approximately 10% of adults are seronegative, the risks in the hospital environment can be high. Individuals most likely to become infected are nurses and other medical personnel providing care to infected patients. Airflow can be a means of transmission of infection from one area to another in the hospital environment.

In immunocompromised individuals who have not been previously exposed to chickenpox, the administration of varicella-zoster immune globulin (VariZIG[93]) (see Chapter 316) has been shown to be useful for both prevention and amelioration of symptomatic chickenpox.[94-97] VariZIG should be administered to an immunodeficient patient younger than 15 years who has a negative or unknown history of chickenpox, who has not been vaccinated against VZV, and who has had contact in the household with a playmate or in a shared hospital room for more than 1 hour. Administration of VariZIG may prolong the incubation period of illness.

Recent guidelines also recommend administration of VariZIG to a pregnant woman who is known to be seronegative and who has had a significant exposure. VariZIG should also be administered to a newborn infant whose mother had onset of chickenpox fewer than 5 days before delivery or up to 48 hours postpartum. For preterm hospitalized infants, guidelines for use have been recommended by the American Academy of Pediatrics Red Book Committee.[98] The use of VariZIG for susceptible immunocompetent individuals older than 15 years must be evaluated on an individual basis.

A vaccine was licensed for the prevention of chickenpox in immunocompetent individuals in 1995.[99-105] Studies performed indicated protection after vaccination, but disease occasionally occurred, especially in small outbreaks, and led to an ACIP recommendation of two doses of vaccine for children as implemented in 2006 (see Chapter 316). The Oka strain of VZV was developed by Takahashi and colleagues in Japan and studied as a vaccine extensively in both healthy and leukemic children. In immunocompromised children, serologic evidence of host response after vaccination has been achieved in 89% to 100% of vaccinated individuals. However, vaccine-induced rash is not uncommon and occurs in variable percentages of patients from approximately 6% to 47%. The factor most predictive of the appearance of rash is the degree of immunosuppression. Specifically, for children with acute lymphoblastic leukemia, the likelihood of rash can be 40% to 50%. The subsequent occurrence of natural varicella after community exposure was decreased in larger control studies and averaged 8% to 16%. Vaccination did not appear to increase the likelihood of subsequent herpes zoster during the period of follow-up.

The ACIP recommends routine childhood vaccination with two doses of vaccine.[106] In clinical trials, the development of antibody responses was higher than in the immunocompetent host and was between 94% and 100%. Vaccine-induced rash was far less common in these individuals and occurred at a frequency of 0.5% to approximately 19% overall, with the rate for subsequent appearance of varicella after community exposure averaging between 1% and 5%. The impact of this vaccine is now being appreciated.

The Oka vaccine was also evaluated in adults to prevent shingles, but a significantly higher titer of live attenuated virus was required to elicit significant and durable increases in cell-mediated immune (CMI) responses. Thus Zostavax was developed specifically for protection against herpes zoster. The zoster vaccine contains, on average, 19,400 plaque-forming units (PFU) per dose,[107] whereas the chickenpox vaccines contain either approximately 9800 PFU per dose (quadrivalent measles, mumps, rubella, and varicella vaccine)[108] or 1350 PFU per dose (monovalent varicella vaccine).[93] A zoster vaccine, to be effective, should boost an older person's CMI responses and therefore mimic immunologic benefit of exposure of VZV-immune adults to chickenpox.[109]

Several dose-ranging studies of vaccine defined a boost in waning CMI responses in older individuals.[110-112] The Shingles Prevention Study evaluated the high-titer, live attenuated zoster vaccine[44] in nearly 40,000 subjects older than 60 years of age with a mean follow-up of 3 years. Benefit was defined in three specific areas. First, the incidence of herpes zoster was 50% lower in the vaccine group than in placebo recipients (5.4 cases per 1000 person-years vs. 11.1 cases per 1000 person-years, $P < .001$). For patients who developed herpes zoster during the study, vaccine virus was not detected by PCR. Second, the incidence of PHN was 67% lower among vaccine recipients (0.5 cases per 1000 person-years vs. 1.4 cases per 1000 person-years, $P < .001$). In addition, the median duration of pain among subjects in whom herpes zoster developed was shorter in the vaccine group, albeit of marginal clinical value (21 days vs. 24 days, $P = .003$). Third, vaccination significantly decreased the burden of illness overall for patients who developed zoster (as assessed by an area under the curve evaluation, $P = .008$). When patients were analyzed according to two age groups, younger elderly (60–69 years old) and older elderly (≥70 years old), differences in vaccine efficacy were noted. Vaccination was more effective in preventing herpes zoster among the younger elderly group versus the older elderly group. However, it prevented PHN and burden of illness to a similar extent in both groups. The risk of subsequent development of herpes zoster does not appear to be increased in vaccine recipients.[113]

In 2006, the US Food and Drug Administration approved the zoster vaccine for prevention of herpes zoster in adults 60 years of age or older[44,107] and subsequently for adults older than 50 years in 2011.[114] However, the Centers for Disease Control and Prevention and ACIP recommend the zoster vaccine only for individuals 60 years of age or older because of concerns for possible waning of protection during the later years, when the risks of herpes zoster are greatest.[115] A recent study described the waning of efficacy of the zoster vaccine; efficacy in regard to the incidence of zoster persisted for 8 years, whereas efficacy in regard to the burden of illness related to zoster lasted for 10 years.[115] Use of a second, "booster" dose of vaccine to address the problem of waning immunity is under consideration.[115] This vaccine is not indicated for the treatment of PHN or herpes zoster.

In January 2018 the ACIP approved an adjuvanted inactivated subunit vaccine (Shingrix) to prevent herpes zoster.[116] The approval was based on the results of two randomized, placebo-controlled clinical trials in which two doses of Shingrix were administered to more than 30,000 participants 50 years of age or older[117] and 70 years of age or older.[118] Efficacy was 96.6% to 97.4% in participants 50 to 69 years of age and 91.3% in participants ≥70 years of age. Prevention of postherpetic neuralgia was 88.5% to 91.2%. The two-dose regimen of Shingrix resulted in frequent mild-to-moderate local and systemic reactions, although serious adverse reactions were no more frequent than in patients receiving placebo, and administration of Shingrix to previous recipients of Zostavax was shown to be well tolerated and immunogenic.[119] The ACIP recommended that Shingrix be approved for prevention of herpes zoster in individuals ≥ 50 years of age and that it was preferable to Zostavax.[116] It also recommended that Shingrix can be given to previous recipients of Zostavax. Additional follow-up studies of Shingrix are planned, including administration to immunocompromised individuals.[117]

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The complete reference list is available online at Expert Consult.

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137 Cytomegalovirus

William J. Britt

SHORT VIEW SUMMARY

Definition

- Human cytomegalovirus (HCMV) is a widespread cause of infection in normal and immunocompromised hosts.
- HCMV is a major cause of multiorgan dysfunction in immunocompromised patients, including allograft recipients and individuals with untreated or poorly controlled HIV/AIDS.
- HCMV is the most common intrauterine viral infection and can result in neurodevelopmental sequelae in infants infected in utero.
- HCMV has also been associated with a number of other diseases in normal hosts, including immune senescence.
- HCMV rarely causes symptoms in normal individuals, and almost all acute infections are clinically silent.

Epidemiology

- HCMV infection is ubiquitous, with over 50% of the US population infected by adulthood and over 100% infected in many regions of world. HCMV infection results in lifelong persistence with intermittent shedding and thus circulates continuously.
- Community spread of HCMV occurs through contact with oral and genital secretions. Infants commonly acquire HCMV through breastfeeding. HCMV is a sexually transmitted infection.
- In allograft recipients, HCMV infections can be acquired from transplanted allografts or from reactivation of virus in previously infected allograft recipients. Increasing risk of disease in this population is associated with increasing suppression of T-lymphocyte responses.
- Reinfection is common in immunocompromised persons and has also been demonstrated in immunocompetent individuals following exposure to new strains of HCMV.

Microbiology

- HCMV is a member of the Betaherpesvirinae subfamily of the Herpesviridae family of herpesviruses. It is a large, enveloped, double-stranded DNA virus (235,000 base pairs) encoding over 150 proteins.
- Serologic assignment of strains of HCMV is not available, but serologically distinct strains have been identified. Next-generation sequencing has demonstrated multiple viral genotypes (quasispecies) in infected individuals.

Diagnosis

- In immunocompromised hosts, HCMV can cause protean manifestations; thus accurate diagnosis requires laboratory testing.
- Although HCMV can be recovered by tissue culture, serology and nucleic acid amplification testing are mainstays of diagnostics for HCMV.

Therapy

- Several antiviral agents are available for prophylaxis and treatment of HCMV infections in immunocompromised hosts, but they have significant toxicities, and prolonged use can result in the development of resistance and treatment failure (see also Chapter 46).
- In some transplantation centers, HCMV hyperimmune globulins are employed together with antiviral chemotherapy for high-risk patients.

Prevention

- Attention to infection control measures, such as hand hygiene and contact precautions, has been shown to reduce the spread of HCMV.
- Humanized and human monoclonal antibodies with potent in vitro virus neutralizing activity are in clinical trials for treatment and prevention of severe HCMV infections.
- Development of vaccines for prevention of HCMV infection and the modulation of HCMV disease represents a high priority of both government agencies and pharmaceutical companies.

Human cytomegalovirus (HCMV) was isolated independently in the laboratories of Drs. Thomas Weller, Margaret Smith, and Wallace Rowe in the 1950s and was designated as cytomegalovirus (CMV) by Weller.[1–3] Interestingly, Weller isolated HCMV from an infant with findings that were consistent with congenital CMV infection and later demonstrated that sera from infants with clinical findings of cytomegalic inclusion disease were reactive with the virus.[4,5] This observation was of considerable interest because cytomegalic inclusion disease of the newborn, a syndrome that included hepatosplenomegaly, petechial rashes, intracranial calcifications, microcephaly, and histopathologic findings of large, inclusion-bearing cells in tissues from affected infants, had long been suspected to be caused by an infectious agent.[6–8] In contrast to the association of HCMV and cytomegalic inclusion disease of the newborn, the clinical importance of infections with HCMV in adults was limited to its association with heterophil-negative mononucleosis, until it was linked to a number of disease syndromes in solid-organ transplant (SOT) recipients and shown to be an important cause of pneumonitis and death in hematopoietic transplant recipients.[9–14] Subsequently, HCMV was shown to be one of the most important opportunistic infections in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), contributing to both morbidity and mortality in these patients.[15–20] Although highly active antiretroviral therapy has dramatically changed the natural history of HIV infection, HCMV still represents a clinically important pathogen in a subset of these patients.[21,22] Over the last 2 decades, the spectrum of disease associated with HCMV in transplant recipients has broadened considerably, particularly in its role in chronic rejection and loss of the transplanted graft. In addition, HCMV infections in nonimmunocompromised individuals have been linked to a number of diseases associated with chronic inflammation, including coronary artery disease, exacerbations of symptoms in patients with inflammatory bowel disease, immune senescence in the aged population, multiple sclerosis, and human cancers.[23–39] In several instances, the contribution of HCMV infection to specific disease remains only an association; however, it is important to consider that the impact of HCMV infections on the health of a population could be significant because over 60% of adults in the United States are infected with HCMV, and in many regions of the world over 95% of the population is infected.[40,41] Thus as our understanding of the biology of this large DNA virus increases, it is highly likely that its role in the expression of a number of human diseases will be further defined and, perhaps, provide new avenues for improved therapeutics for management of these diseases.

MICROBIOLOGY

Virus Structure

HCMV, or human herpesvirus (HHV)-5, is the prototypic member of the Betaherpesvirinae subfamily of the family of Herpesviridae. Other members of the Betaherpesvirinae subfamily that infect humans include HHV-6 and HHV-7 and the large number of species-specific CMVs that infect other mammals. HCMV is the largest and most complex herpesvirus, with a 235,000 double-stranded DNA genome that encodes approximately 165 open reading frames.[42,43] The HCMV virion is approximately 220 nm in diameter, and virion proteins are distributed in three regions: the capsid, tegument, and envelope.[44,45] Tegumented subviral particles are enveloped in the cytoplasm of infected cells by budding into viral glycoprotein-enriched membranous vesicles prior to egress from the cell (Fig. 137.1). The icosahedral capsid is approximately 130 nm in diameter and although only about 20% larger than the capsid of herpes simplex virus (HSV), the HCMV capsid must package a genome that is over 50% larger than that of HSV.[44,46] Thus HCMV is likely near its capacity to package viral genomes, and acquisition of new genetic material during virion genome replication is likely selected against secondary to constraints imposed by the size of the HCMV genome. Conversely, deletion or truncation of viral genes that are not essential for virus replication could potentially increase the efficiency of genome packaging and virus replication, resulting in the persistence of viral mutants lacking genes not essential for virus replication, a phenomenon observed during in vitro passage of HCMV. The mature HCMV virion contains over 100 virus-encoded proteins as well as host proteins acquired during the complex nuclear and cytoplasmic assembly pathway of the particle.[47,48] The capsid contains four well-studied proteins that range in size from 150 to 8.5 kDa and are homologous in terms of size and function with capsid components of other herpesviruses.[45] In addition to virion tegument proteins and envelope glycoproteins that share homologous structural and functional features with their counterparts in other herpesviruses, HCMV also encodes a significant number of nonstructural proteins that can be detected within the infected cell but not in the virion. Nonstructural viral proteins provide a large number of functions required for efficient replication of the viral genome and assembly of progeny virions. In addition, virus encoded nonstructural proteins provide essential functions required for the regulation of cellular responses to HCMV infection, including significant alterations in cellular intermediary and lipid metabolism, inhibition of apoptosis and necroptosis, immune evasion of innate and adaptive immune responses, and maintenance of genome persistence during latency.[45]

Replication

HCMV replication follows a temporally regulated pattern of viral gene expression that is characteristic of the replication of herpesviruses. This includes immediate-early genes, expressed shortly after infection, that have been shown to regulate intrinsic host cell responses to infection as well initiating the transcription of viral genes essential for genome replication and virus assembly. Early viral genes represent the second class of viral genes expressed during productive infection. Protein products of these viral genes function primarily in viral DNA replication and packaging but also regulate host cell functions to optimize virus replication. Importantly, HCMV DNA replication results in an exponential increase in the number of viral genomes and ultimately, progeny virions. Thus functions critical for genome replication, such as those provided by viral genes encoding the DNA polymerase, terminase complex, and phosphotransferase, represent targets of currently licensed antiviral agents. Lastly, late viral genes are those encoding proteins such as components of the outer tegument layer and envelope, which are required for assembly of the infectious virion.

Both replication of HCMV DNA and the morphogenesis of the virion capsid take place in the nucleus. Following structural maturation of the capsid, newly synthesized concatemeric viral DNA is cleaved by a virus-encoded terminase that results in packaging of unit-length, linear genomic DNA.[49–51] Subsequently, viral DNA-containing capsids acquire an inner layer of tegument proteins during their egress from the nucleus, including essential interactions between proteins and capsid protein, that stabilize the interaction between the capsid and the inner tegument layer of the virion.[52] As the immature particle is transported along the cellular cytoskeleton, additional tegument proteins are applied to the maturing particle until the tegumented particle is enveloped in a modified intracellular membranous compartment distal to the *trans*-Golgi network that has been designated as the viral assembly compartment.[53,54] Formation of this intracellular compartment requires extensive reorganization of the cellular secretory and endocytic systems, and its formation is essential for efficient virion envelopment and infectious virion production.[53–56] The envelope of HCMV is structurally complex and is formed by lipid-containing host cell membranes that contain well over 20 different virus-encoded proteins. Several virion envelope proteins have been shown to be targets of virus-neutralizing antibodies and in experimental animal models have been shown to induce protective antiviral responses (see Fig. 137.1). These findings, together with correlations between antibody responses in humans and control of HCMV infections, have led to the selection of these components of the virion as potential targets for vaccine induced immunity. There is no evidence that host cell proteins are excluded from or selectively incorporated into the virion envelope during HCMV envelopment; thus host cell proteins can also be found in the virion envelope. Although specific functions for virion-associated host cell proteins in the infectious cycle of HCMV have been suggested based on in vitro findings, definitive evidence of an essential role of virion host cell proteins in HCMV replication is limited.[57,58]

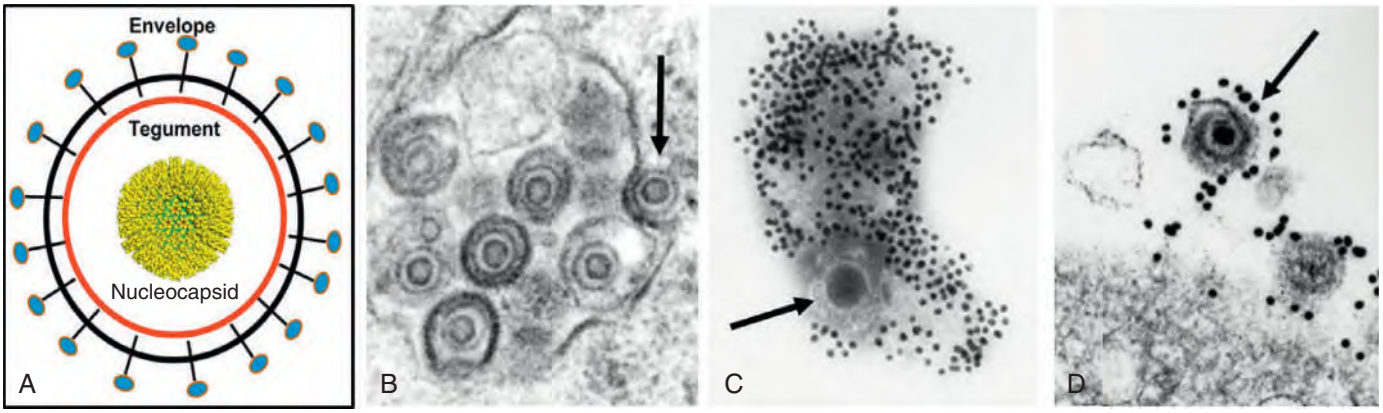

FIG. 137.1 Morphology of HCMV particles. (A) Cartoon of HCMV virion with nucleocapsid shown in yellow, the surrounding tegument layer of proteins indicated by the red oval, and outermost region, the envelope, studded with virion glycoproteins. (B) Electron micrograph showing intracytoplasmic vacuole with tegumented particle budding into vacuole *(arrow)* that also contains enveloped particles. (C) Single virion treated with detergent to remove envelope and tegument proteins detected with antitegument antibodies and electron-dense round nanogold particles (magnification ×70,000). The nucleocapsid is apparent in the lower left *(arrow)*. (D) Arrow indicates envelope of extracellular virions decorated with antienvelope antibodies and nanogold particles (magnification ×70,000).

Following envelopment, the virus is released from the cell either through a cellular exocytic pathway or after lysis of the cell. Alternatively, virus may spread cell-to-cell by less well-defined mechanisms. Regardless of the mode of spread, infectivity of progeny virions is absolutely dependent on assembly of a complete virion envelope, specifically the incorporation of virion envelope proteins, including glycoproteins B, H, L, O, M, and N, that have been shown to be required for early steps of virus entry into permissive cells. Mature, infectious progeny can be detected approximately 48 hours after infection, making the eclipse period (interval from infection to progeny virus production) of HCMV over twice as long as that of HSV and nearly eight times as long as influenza virus.

Persistence in the Host

In addition to shared strategies for replication and regulation of host cell responses, once infected, herpesviruses persist for the lifetime of the host. Although mechanisms of HCMV persistence are less well understood than those of alphaherpesviruses or gammaherpesviruses, HCMV persistence at the level of the infected host and not within an individual cell likely includes both a low-level chronic productive infection together with a state of true latency, in which only a limited number of viral genes are expressed and genome replication does not occur. This latter paradigm of restricted expression of HCMV genes during latency has recently been challenged utilizing more contemporary methodologies to define viral gene transcription during latency. These studies have suggested that a large number of viral genes are transcribed during latency in $CD34^+$ cells.[59,60] HCMV persistence has been demonstrated in epithelial cells from a number of organs, including the salivary gland, breasts, intestines, and prostate; however, it is unclear if HCMV DNA detected in these tissues represents a source of infectious virus that could be reactivated from latency, although studies in small animal models have demonstrated reactivation from latently infected salivary glands.[61] In contrast, HCMV latency has been extensively studied in $CD34^+$ myeloid mononuclear cells, a cell type that can be mobilized from the bone marrow and trafficked as $CD14^+$ cells to different tissues. Reactivation of HCMV from latency in $CD34^+$ myeloid mononuclear cells has been shown following differentiation of latently infected myeloid cells into tissue macrophages, thus providing a mechanism for infectious virus dissemination from a reservoir of latently infected cells.[62,63]

Viral functions interacting with the host cell that allow establishment and regulation of latency are incompletely defined and include modifications of cellular chromatin that restrict transcription from a number of viral promoters.[64] In addition, major changes in host cell metabolism and expression of immunomodulatory cytokines have been described.[65,66] Although a number of in vitro and in vivo models have provided new insight into the establishment and maintenance of HCMV latency, this aspect of the biology of HCMV remains incompletely defined and is an active area of study. Finally, whether a chronic low-level productive infection can be differentiated from latency with asynchronous but frequent reactivations in an infected host is likely of limited importance to the clinical significance of persistent HCMV infection in the normal host. Yet some level of productive infection appears to be maintained in the infected host, because studies have shown stability over decades of antiviral antibody responses against both nonstructural and structural virion proteins, and HCMV-specific $CD8^+$ T-lymphocyte responses from persistently infected individuals are directed at a wide variety of both nonstructural and structural virion proteins, including proteins expressed late in the replicative cycle.[67] These data argue that during HCMV persistence, the adaptive immune response of an infected host is presented with a large number of virus-encoded proteins similar to the immune system of individuals undergoing acute HCMV infection.

Host Interaction and Responses

The highly restricted species specificity of CMVs has been associated with large numbers of orthologous viral genes that regulate host cell responses to infection. These genes are often very similar in their functions and in some cases exist in blocks of genes that are colinear in the genomes of different CMVs. It is believed that these viral genes have coevolved with the host to enable CMVs to successfully persist but with the cost of strict species specificity, thus preventing maintenance of CMVs in intermediate hosts. CMVs utilize multiple strategies to ensure persistence in human populations. CMVs are efficiently transmitted from infected mothers to their infants in the perinatal period and as a sexually transmitted infection. In both cases, the ensuing infection is routinely associated with asymptomatic infection with prolonged virus shedding, thus providing an efficient mechanism for maintenance of this virus in a population. In addition, immunity to CMV is incompletely protective and reinfection with genetically diverse strains of HCMV has been well described in normal individuals.[68–72]

A large number of viral functions are thought to optimize HCMV infection and persistence in the host cell. These include the inhibition of cell death pathways (apoptosis, necroptosis, and pyroptosis) that are activated by virus infection, control of the cell cycle to optimize viral DNA replication, inhibition of cellular stress responses such as the unfolded protein response in the endoplasmic reticulum, modification of host cell metabolism, inhibition of cell death during HCMV replication, and perhaps most widely studied, evasion of host innate and adaptive immune responses[73–88] (Table 137.1). A discussion of the mechanisms by which HCMV can modify these host responses is beyond the scope of this chapter; however, the extraordinarily complex relationship between HCMV and the host immune response warrants a brief description because the most robust disease phenotypes associated with HCMV infection are seen in the immunocompromised host.

Following HCMV infection, expression of both immediate and early genes modifies innate responses. These range from blocking cellular intrinsic resistance mechanisms, such as silencing initial viral gene transcription by the host death domain–associated protein (Daxx) of the promyelocytic leukemia nuclear body; to inhibition of both the nuclear interferon-inducible protein 16 and cytosolic (cyclic GMP-AMP synthase), DNA sensor pathways limiting type I interferon gene expression; and finally limiting nuclear factor-κB–driven inflammatory responses.[89–96] A number of viral effector functions are responsible for inhibition of these early host cell responses, including virus-encoded microRNAs and proteins within the tegument of incoming virions, and viral proteins expressed as products of immediate-early genes.[89,94,97–100] A more well-described group of viral gene products target the antiviral activities of cellular innate responses such as natural killer (NK) cells and activated macrophages. Reported immune evasion mechanisms that inhibit NK cell activity include limiting cell surface expression of NK cell–activating ligands, expression of viral proteins that mimic major histocompatibility complex (MHC) molecules, and expression of inhibitory NK ligands such as human leukocyte antigen (HLA)-E.[101–110] Direct evidence supporting an important role of HCMV immune evasion functions that target NK cell activity in HCMV infections comes from studies in animal models, including recent studies in rhesus macaques that have clearly demonstrated that in the absence of virus-encoded NK cell immune evasion functions, CMV infection was dramatically attenuated.[111] Finally, $CD4^+$ and $CD8^+$ T-lymphocyte recognition of HCMV-infected cells has been shown to be significantly inhibited by

TABLE 137.1 HCMV Modifications of Host Cell Responses to Facilitate Replication and Persistence

HOST CELL FUNCTION	HCMV MODIFICATION	REFERENCES
Cell cycle regulation	Inhibition of cell cycle progression	73–77
Glucose and lipid metabolism	Increased utilization of glucose and altered lipid metabolism	78, 80–84
Stress response	Inhibition of cellular stress response	79, 82, 85
Cell death pathways	Inhibition of apoptosis and necroptosis	86–88
Host immune responses to viral infection	Inhibition of intrinsic, innate, and adaptive immune responses	90–96, 103, 105, 107, 110, 111, 114

mechanisms that include degradation of both class I and II MHC molecules and interference with peptide loading of class II MHC molecules.[105,112–114] The in vivo importance of viral-encoded immune evasion functions that limit recognition of HCMV-infected cells by effectors of the adaptive immune response has been modeled in rhesus macaques. In these experiments, mutant rhesus CMVs that failed to degrade class I MHC molecules secondary to deletion of orthologues of HCMV immune evasion genes were shown to be highly attenuated in macaques.[115]

Pathogenesis of HCMV Infection

Although the findings of end-organ disease in multiple organ systems following HCMV dissemination in immunocompromised individuals has suggested that HCMV disease can readily be explained by lytic virus replication and cytopathology, the magnitude of clinical disease observed in some HCMV-infected individuals often is inconsistent with the level of virus replication. Such observations have suggested that mechanisms other than viral cytopathology could contribute to some clinical manifestations of HCMV infection, and that the severity of disease cannot be directly attributed to the level of virus replication in an individual patient. Thus components of the host innate and adaptive immune responses likely contribute to the clinical expression of HCMV infection in some patients. However, it is important to note that an accurate quantification of the contribution of virus replication and that of host responses to disease following CMV infection has only been accomplished in animal models of HCMV infections.[116–118] Thus the distinction between the effects of virus replication and host responses to the clinical expression of HCMV infection should perhaps only be a starting point for the discussion of mechanisms of HCMV disease in different patient populations. A categorization to simplify the discussion of the plethora of clinical manifestations associated with HCMV infection disease would be (1) clinical manifestations associated with high levels of virus replication in severely immunocompromised patients in which tissue damage can be attributed to viral infection, and (2) a more diverse set of disease phenotypes in patients with residual immunity in which host responses to HCMV could represent a significant component of clinically apparent disease. Admittedly, these distinctions are an arbitrary attempt to describe different mechanisms of disease, and the spectrum of clinical disease that is observed in most patients with HCMV infection likely reflects variable combinations of both host responses and direct effects of virus replication, including virus persistence driving ongoing host innate and adaptive immune responses.

Pathogenesis of HCMV in the Setting of Immunosuppression and Virus Dissemination

The clinical spectrum of disease in immunocompromised patients with uncontrolled HCMV replication was well appreciated by clinicians caring for allograft recipients prior to the advent of effective antiviral therapy.[10–14] End-organ disease (including hepatitis), bone marrow dysfunction, colitis, pneumonitis, and, less commonly, central nervous system (CNS) disease (including encephalitis) were reported in both solid-organ and hematopoietic allograft recipients. Concomitant with the recognition of HCMV as a cause of disease in allograft recipients, clinicians linked the severity of disease to the degree of immunosuppression. Disseminated HCMV infection with a similar spectrum of end-organ disease was also common in HIV/AIDS patients in the era prior to highly active antiretroviral therapies.[17,19,20] In contrast to the infrequent occurrence in allograft recipients, retinitis was one of the most recognizable clinical expressions of disseminated HCMV infection in patients with HIV/AIDS.[119–122] In patients with widely disseminated infection, replicating HCMV could be recovered from peripheral blood, often from buffy coat leukocytes, and histopathologic findings consistent with HCMV infection, including large cells with characteristic nuclear inclusions, so-called owl's eye inclusions secondary to the clear halo surrounding the inclusion (Fig. 137.2). Interestingly, in more recent studies in which the level of HCMV viremia could be more accurately quantified with polymerase chain reaction (PCR), higher viral loads were associated with the presence of owl's eye inclusions in tissue sections from HCMV-infected patients, suggesting a direct correlation between detection of histopathologic findings of HCMV infection and the level of virus replication.[123]

Early findings in both solid-organ allograft and hematopoietic transplant recipients demonstrated that control of virus replication and dissemination was dependent on the timely development of HCMV-specific T-lymphocyte responses and were subsequently confirmed in a number of studies in transplant recipients.[124–133] Correlations were demonstrated between T-lymphocyte responses and the risk for invasive HCMV disease and, importantly, direct evidence of the importance of HCMV-specific T-lymphocyte responses was initially provided by the transfer of ex vivo expanded HCMV-specific $CD8^+$ T lymphocytes into patients at risk for HCMV infection and disease.[134] Similarly, the risk for invasive HCMV infections in HIV/AIDS patients before the widespread use of highly active antiretroviral agents was directly related to the loss of HCMV-specific T-lymphocyte responses.[135–137] In these patients, the risk of HCMV disease fell dramatically with the introduction of effective HIV antiretroviral therapy, and the decrease in invasive HCMV disease was directly correlated with the reconstitution of adaptive immune responses.[135]

From observations in both transplant recipients and patients with HIV/AIDS, the control of HCMV replication requires the presence of effective HCMV-specific T-lymphocyte responses, whether HCMV infection is classified as a primary infection, such as that which could occur after transplantation with a graft from an infected donor (Donor+/Recipient−), or following recrudescence of infection in an individual who was previously immunocompetent.[128,129,138,139] When effective antiretroviral agents became available, HCMV replication could be inhibited, dissemination limited, and virus replication significantly inhibited in end organs. Thus significant benefit from antiviral therapy was observed in

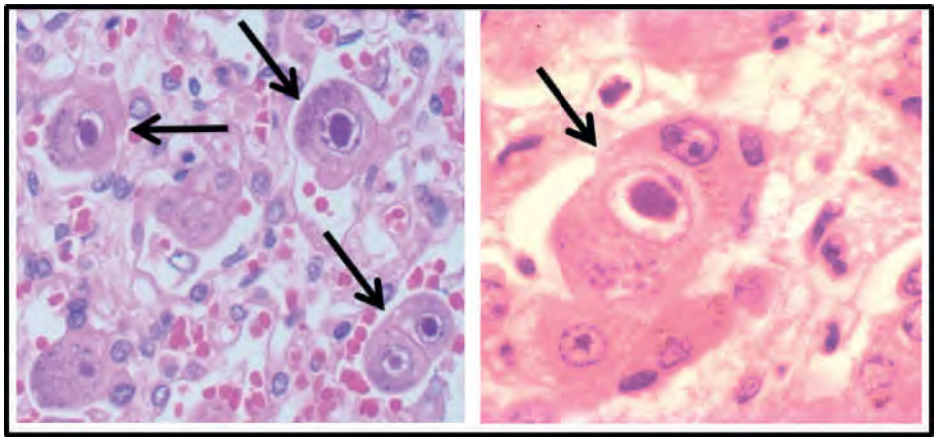

FIG. 137.2 Characteristic cytomegalic cells with owl's eye inclusions *(arrows).* Note size of HCMV-infected cells and nuclei as compared to surrounding uninfected cells. (Hematoxylin and eosin staining; magnification ×20 *[left]*, ×40 oil immersion *[right]*.)

these patients, particularly early in the posttransplantation period when suppression of adaptive immune responses is often most intense.[140] However, as has been demonstrated both in clinical studies of antiviral treatment, prophylaxis, or both, and by transfer of HCMV-specific $CD8^+$ T cells to suppress HCMV replication in transplant recipients, failure to adequately reconstitute HCMV-specific adaptive immunity can result in HCMV disease late in the posttransplantation period.

Pathogenesis of Diseases That Lack a Direct Relationship to Levels of Virus Replication

In early studies, solid-organ allograft recipients with HCMV infections and high levels of virus replication often succumbed to multiorgan disease, whereas a leading cause of death in hematopoietic transplant recipients was HCMV pneumonia/pneumonitis.[141] In contrast to findings in other organ systems in these patients, patients with fatal HCMV pneumonia often exhibited only focal areas of HCMV infection and once clinical disease became evident, treatment with antivirals often provided limited benefit. Similarly, in immunocompromised patients with HCMV colitis, severe symptomatology can be observed that is discordant with widely separated and focal areas of colonic involvement, findings that suggest that disease in these patients likely includes components of the host response. Findings from studies in solid-organ allograft recipients have also suggested that lytic virus replication leading to tissue damage was an unlikely explanation for the spectrum of disease in these patients.[142–145] Furthermore, the majority of HIV/AIDS patients with clinically apparent HCMV encephalitis were found to have focal encephalitis with areas of microglial nodules and not a necrotizing encephalitis that is more characteristic of uncontrolled virus replication.[142] These clinical observations suggest that diseases associated with low levels of HCMV replication are not the result of direct viral damage but are indirect and presumably secondary to host responses to HCMV infection. Furthermore, HCMV infection has been proposed to contribute to chronic rejection of renal and heart allografts in numerous clinical studies and in experimental animal models of allograft rejection.[146–148,149–152,153–158] Although precise mechanisms that could account for the contribution of HCMV infection to allograft rejection remain to be completely defined, findings from patient specimens and from experimental animal models strongly argue that the contribution of ongoing HCMV-induced inflammation in the graft together with incompletely controlled lytic HCMV infection could be responsible for disease in these patients.

HCMV infection in nonimmunocompromised hosts has long been associated with a number of chronic diseases, including atherosclerotic heart disease and more recently aging and immune senescence.[23,24,27,30–32,159–172] A discussion of specific mechanisms associated with HCMV infection that contribute to chronic disease is beyond the scope of this chapter, but common to many of the proposed mechanisms is the capacity of HCMV to induce chronic inflammation in the persistently infected host. This latter biologic feature of HCMV infection in normal individuals is perhaps best illustrated by finding that up to 10% to 15% of the total peripheral blood $CD8^+$ T-lymphocyte responses of normal individuals infected with HCMV, and even a greater percentage in aged individuals, can be directed at HCMV.[67,170] As described previously, the suite of immune evasion functions encoded by HCMV presumably contribute to its capacity to efficiently express a limited set of viral genes and in some cases, replicate in sites of inflammation during persistence. Interestingly, host inflammatory responses appear to contribute to HCMV gene expression.[173–182] Thus lifelong persistence of HCMV in normal individuals leads to a symbiosis between HCMV and the host that results in some level of chronic activation of innate and adaptive immunity.

Routes of Transmission and Sources of HCMV Infection

Infection with HCMV is common in most populations in the world and in most areas of the world, and is acquired during early childhood. In the United States, over 50% of the population is infected with HCMV, with the prevalence of infection dependent on both race and socioeconomic status.[40] The rates of HCMV infection in the United States increase steadily throughout adult life, with increased rates of infection noted during adolescence.[41,183–185] In southern Asia, Africa, and many countries in South America, the HCMV seroprevalence is nearly 100% in adults and similarly high in young children and adolescents.[40,186–195] In adults, community acquisition of HCMV follows exposure to saliva, urine, and genital secretions, including semen, from an infected individual. Intimate contact, including sexual activity, is an important route of HCMV transmission, because higher rates of HCMV infection have been described in populations with high rates of sexually transmitted infections.[15,196–201] HCMV is considered a sexually transmitted infection in adults.

A second important risk factor for HCMV infection is exposure to young children. Infants and children can acquire HCMV through intrauterine infection, during parturition, through exposure to breast milk containing HCMV, and through exposure to other children infected with HCMV. Intrauterine infection resulting in congenital HCMV infection occurs in approximately 1 in 200 births in the United States and perhaps as often as 1 in 100 live births in some regions of the world.[195,202–205] Furthermore, HCMV is readily transmitted by breast milk, and between 50% and 70% of breastfed infants of HCMV seropositive women will become infected, depending on the duration of breastfeeding.[206–210] Thus breast milk transmission likely contributes to the high HCMV seroprevalence in children reported in Asia, South America, and Africa. Regardless, if infected with HCMV early in life as the result of an intrauterine infection, during delivery, or following ingestion of HCMV-infected breast milk, infants routinely shed significant amounts of infectious virus in saliva and urine for prolonged periods of time.[208] Thus infected infants can serve as reservoirs for spread of this virus under conditions that favor close contact with an infected child, such as those provided by parents or other caregivers, family, individuals living in crowded conditions with an infected infant, or other young children and caregivers in group care facilities.[211–216] Furthermore, the spread of HCMV among young children within families and within group care settings is more frequent when children are under 2 years of age.[217,218]

HCMV can be acquired in hospitalized patients through exposure to blood products and following transplantation of an organ from a HCMV-infected donor. Nosocomial transmission was infrequent even prior to the introduction of universal precautions in health care facilities.[219] Transmission of HCMV by blood products containing HCMV has been recognized for decades, and an extensive literature describes various attempts to limit HCMV transmission by this route. Perhaps the most universally accepted approach is to utilize only blood products from HCMV seronegative donors. However, the seroprevalence of HCMV is over 50% in most donor populations, and thus such an approach would greatly compromise the supply and availability of blood products. In high-risk recipient populations such as extremely premature infants and individuals undergoing allogeneic hematopoietic stem cell transplantation (HSCT), utilization of leukocyte-reduced blood from HCMV-seronegative donors has been advocated,[220,221] whereas other investigators have argued that the use of unselected leukocyte-reduced blood products is sufficient.[222,223–227] A recent survey of transfusion practices indicated that the standard of practice in over 90% of transfusion services included the use of leukocyte-reduced blood products, but the use of leukocyte-depleted products from HCMV seronegative donors for high-risk populations was not as consistent.[228] This variability in the donor selection based on HCMV seroreactivity was reflected in the conclusions in a publication from the American Association of Blood Banks and by a recent review of this topic.[229,230] In contrast to the contentious debate about the transmissibility of HCMV in blood products, HCMV transmission by an allograft from an infected donor is established. Transmission has occurred following transplantation of solid organs, as well as from hematopoietic cells.

CLINICAL MANIFESTATIONS

Infection in the Immunocompetent Host (Infectious Mononucleosis)

HCMV is commonly acquired throughout life, and infection is subclinical in almost all infected individuals. HCMV was first well described as a cause of an infectious mononucleosis syndrome, and in early studies, HCMV was estimated to account for between approximately 10% and 20% of cases of heterophil-negative mononucleosis in adults.[9,231–235] The