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197 Herpes Simplex Virus Infections

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Herpes Simplex

Virus Infections ■ ■DEFINITION Herpes simplex viruses (HSV-1, HSV-2; Herpesvirus hominis) produce a variety of infections involving mucocutaneous surfaces, the periph eral nervous system (PNS), the central nervous system (CNS), and—on occasion—visceral organs. Prompt recognition and treatment reduce the morbidity and mortality rates associated with HSV infections. ■ ■ETIOLOGIC AGENT The genome of HSV is a 152-kb linear, double-stranded DNA molecule (molecular weight, ~100 × 106) that encodes >90 tran scription units with 84 identified proteins. The genomic structures of the two HSV subtypes are similar. The overall genomic sequence homology between HSV-1 and HSV-2 is ~50%, whereas the proteome homology is >80%. The homologous sequences are distributed over the entire genome map, and most of the 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, and a number of them appear to be important in host immunity. These type-specific regions have been used to develop serologic assays that distinguish between the two viral subtypes. The most commonly used protein is glycoprotein G (US-4), which differs markedly in size and antigenic sites between HSV-1 and HSV-2. Either restriction endo nuclease analysis or sequencing of viral DNA can be used to distinguish between the two subtypes and among strains of each subtype. Recombi nant viruses (HSV-1/HSV-

2) do circulate in nature. The variability of nucleotide sequences from clinical strains of HSV-1 and HSV-2 is such that HSV isolates obtained from two individuals can be differentiated by restriction enzyme patterns or genomic sequences. Epidemiologically related sources, such as sexual partners, mother–infant pairs, or persons involved in a common-source outbreak, can be inferred from such

patterns. Deep sequencing of sequential isolates suggests that more than one variant of HSV-1 or HSV-2 can be found in a single individual and minor mutational changes do occur within anatomic sites and over time.

The viral genome is packaged in a regular icosahedral protein shell (capsid) composed of 162 capsomeres (Chap. 195). The outer covering of the virus is a lipid-containing membrane (envelope) acquired as the DNA-containing capsid buds through the inner nuclear membrane of the host cell. Between the capsid and lipid bilayer of the envelope is the tegument. Viral replication has both nuclear and cytoplasmic phases. Only four of the 12 glycosylated envelope proteins appear to be essential for cell entry: glycoprotein D (gD), gH, gL, and gB. gD binds to cellular co-receptors that belong to the heparin sulfate or tumor necrosis factor receptor family of proteins, the immunoglobulin superfamily (nectin family), triggering a conformational change that alters activation of the gH-gL heterodimer complex that then activates gB and the fusogen glycoprotein gC. The ubiquity of these receptors contributes to the wide host range of herpesviruses. HSV replication is highly regulated. After fusion and entry, the nucleocapsid enters the cytoplasm and several viral proteins are released from the virion. Some of these viral proteins shut off host protein synthesis (by increasing cellular RNA degradation), whereas others “turn on” the transcrip tion of immediate early genes of HSV replication. These immediate early gene products, designated α genes, are required for synthesis of the subsequent polypeptide group: the β polypeptides, many of which are regulatory proteins and enzymes required for DNA replication. Most current antiviral drugs interfere with β proteins, such as viral thymidine kinase (TK) and DNA polymerase. The third (γ) class of HSV genes encodes viral structural and tegument proteins and mostly requires viral DNA replication for expression. New antiviral drugs directed at viral assembly and release are under development. CHAPTER 197 After viral genome replication and structural protein synthesis, nucleocapsids are assembled in the cell’s nucleus. Specific viral pro teases clip the end of the DNA into procapsid. In the nucleus, the nucleocapsid binds through the inner nuclear membrane to genetic vessels that fuse with the outer membrane and moves the capsid into the cytoplasm. In some cells, viral replication in the nucleus forms two types of inclusion bodies: 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 viral infection. The cytoplasmic capsids move along microtubules to the Golgi network where a second round of envelopment occurs. The capsids acquire their lipid envelope and most of the tegument. Cellular machinery transports the infectious virus out of the cell. Herpes Simplex Virus Infections Viral genomes are maintained by some neuronal cells in a repressed state called latency. Latency, which is associated with transcription of only a limited number of virus-encoded RNAs, accounts for the pres ence of viral DNA and RNA in neural tissue at times when infectious virus cannot be isolated. Maintenance and growth of neural cells from latently infected ganglia in tissue culture result in production of infec tious virions (explantation) and in subsequent permissive infection of susceptible cells (co-cultivation). Activation of the viral genome may then occur, resulting in reactivation—the normal pattern of regulated viral gene expression and replication and HSV release. The release of virions from the

neuron follows a complex process of anterograde transport down the length of neuronal axons. In experimental animals, ultraviolet light, systemic and local immunosuppression, and trauma to the skin or ganglia are associated with reactivation. A noncoding region of the viral genome initially felt to be three noncoding regions and now felt to be a more diverse set of noncod ing RNAs and micro-RNAs (miRNAs) collectively referred to as the latency-associated transcripts (LATs) are found in the nuclei of latently infected neurons, and deletion mutants of the LAT region exhibit reduced efficiency in their later reactivation. HSV DNA copy number is highly variable between neurons, with no direct correlation between HSV DNA copy numbers and LAT positivity. About 10% of ganglionic neurons contain viral DNA and only about 1% of these neurons express LATs. Substitution of HSV-1 LATs for HSV-2 LATs induces an HSV-1 reactivation pattern, suggesting this region of the genome apparently

maintains—rather than establishes—latency. Viral miRNA appears to silence expression of the key neurovirulence factor infected-cell protein 34.5 (ICP34.5) and to bind in an antisense configuration to the immediate-early protein ICP0 messenger RNA to prevent expression, which is vital to HSV reactivation. While 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 incompletely understood.

While latency is the predominant state of virus on a per-neuron basis, the high frequency of oral and genital tract reactivation for HSV-1 and HSV-2 suggests that the viruses are rarely quiescent within the entire biomass of ganglionic tissue. The virus appears to be in a dynamic state—“mostly suppressed”—but with continual individual cells showing various degrees of viral transcriptional activity, and only a few of these infected neurons giving rise to actual reactivation. There is increasing recognition that HSV infection of the autonomic ganglia plays an important role in both initial and reactivation infections. In fact, deaths of animals from HSV-2 infection appear to be related to autonomic dysfunction of the bowel. Both HSV-1 and HSV-2 are shed subclinically. Most persons infected with HSV-2 and HSV-1 have frequent subclinical bursts of reactivation lasting 2–6 h, and the host tissue-based immune system can contain viral reactivation in the tissue before the development of clinical reactivation. ■ ■PATHOGENESIS Exposure to HSV at mucosal surfaces or abraded skin sites permits entry of the virus into cells of the epidermis and dermis and initiation of viral replication therein. HSV infections are usually acquired sub clinically. Whether clinical or subclinical, HSV acquisition is associated with sufficient viral replication to permit infection of sensory and/or autonomic nerve endings. On entry into the neuronal cell, the virus— or, more likely, the nucleocapsid—is transported intra-axonally to the nerve cell bodies in ganglia. Viral particles tether onto cellular proteins that motor along microtubules from axon tips (neurite endings) to neuronal cell bodies. In humans, the transit interval of spread to the ganglia after virus inoculation into peripheral tissue is unknown. Dur ing the initial phase of infection, viral replication occurs in ganglia and contiguous neural tissue. Virus then spreads to other mucocutaneous surfaces through centrifugal migration of infectious virions via periph eral nerves. This mode of spread helps explain the large surface area involved, the high frequency of new lesions distant from the initial crop of vesicles that is characteristic in patients with primary genital or oral– labial HSV infection, and the ability to recover virus from neural tissue distant from neurons innervating the inoculation site. Contiguous spread of locally inoculated virus also may take place and allow further mucosal extension of disease. Recent studies have demonstrated HSV viremia—another mechanism for extension of infection throughout the body—in ~30–40% of persons with primary

HSV-2 infection; latent infection with both viral subtypes in both sensory and auto nomic ganglia has been demonstrated. For HSV-1 infection, trigeminal ganglia are most commonly infected, although extension to the inferior and superior cervical ganglia also occurs. With genital infection, sacral nerve root ganglia (S2–S5) are most commonly affected. Autonomic ganglia, pelvic nerves, and vaginal nerve roots are commonly infected. PART 5 Infectious Diseases After resolution of primary disease, infectious HSV can no longer be cultured from the ganglia; however, neuronal infection, as defined by the presence of viral DNA, persists in ganglionic cells in the anatomic regions of the initial infection. The mechanism of reactivation from latency is unknown, although increasingly evidence of limited viral genes or miRNAs is identified in latently infected neurons. Evidence exists for viral antigen and activated host T cells at the ganglia and periphery, and immune responses in ganglia as well as peripheral tissue appear to influence the frequency and severity of HSV reactiva tion. HSV-specific T cells have been recovered from peripheral nerve root ganglia. Many of these resident CD8+ T cells are juxtaposed with latently HSV-1-infected neurons in the trigeminal ganglia and can block reactivation with both interferon (IFN) γ release and gran zyme B–mediated degradation of the immediate-early protein ICP4. In addition, there appears to be a latent viral load in the ganglia that

correlates positively with the number of neurons infected and the rate of reactivation but inversely with the number of T cells present. It is not known whether reactivating stimuli transiently suppress these immune cells, independently upregulate transcription of lytic genes, or both. Moreover, host containment in the mucosa has been demonstrated. Once virus reaches the dermal–epidermal junction, there are three possible outcomes: (1) rapid host containment of infection near the site of reactivation; (2) spread of small amounts of virus into the epidermis, with a micro-ulceration associated with low-titer subclinical shedding; and (3) widespread replication and necrosis of epithelial cells and sub sequent clinical recurrence (the latter defined clinically by a skin blister and ulceration). Histologically, herpetic lesions involve a thin-walled vesicle or ulceration in the basal region, multinucleated cells that may include intranuclear inclusions, necrosis, and an acute inflammatory response. Re-epithelialization occurs once viral replication is restricted, almost always in the absence of a scar. Analysis of the DNA from sequential isolates of HSV or from iso lates from multiple infected ganglia in any one individual has revealed similar, if not identical, restriction endonuclease or DNA sequence patterns in most persons. As more sensitive genomic technologies are developed, evidence of multiple strains of the same subtype is increas ingly being reported. For example, infection of individual neurons with multiple strains of drug-susceptible and drug-resistant virus in severely immunosuppressed patients indicates that ganglia can be reseeded during chronic infection. Because exposure to mucosal shedding is relatively common during a person’s lifetime, current data suggest that exogenous infection with different strains of the same subtype does occur. The role strain variation plays in the varied reactivation pattern of disease is unknown. ■ ■IMMUNITY Host responses influence the acquisition of HSV disease, the severity of infection, resistance to the development of latency, the maintenance of latency, and the frequency of recurrences. Both antibody-mediated and cell-mediated reactions are clinically important. Immunocom promised patients with defects in cell-mediated immunity experience more severe and more extensive HSV infections than those with deficits in humoral immunity, such as agammaglobulinemia. Experi mental ablation of lymphocytes indicates that T cells play a major role in preventing lethal disseminated disease, although antibodies help reduce titers of virus in neural tissue. Some clinical manifestations of HSV appear to be related to the host immune response (e.g., stromal opacities associated with recurrent herpetic keratitis). The surface viral

glycoproteins have been shown to be targets of antibodies that mediate neutralization and immune-mediated cytolysis (antibody-dependent cell-mediated cytotoxicity [ADCC]). Monoclonal antibodies to HSV viral glycoproteins have, in experimental infections, conferred pro tection against subsequent neurologic disease or ganglionic latency, and reduced subsequent reactivation in animals model experiments. Human studies of monoclonal antibodies are underway. Multiple cell populations, including neutrophils, macrophages, and a variety of T lymphocytes, play a role in host defenses against HSV infections, as do lymphokines generated by T lymphocytes. In animals, passive transfer of primed lymphocytes confers protection from subsequent HSV challenge. Maximal protection usually requires the activation of multiple T-cell subpopulations, including cytotoxic T cells and T cells responsible for delayed hypersensitivity. The latter may confer protection by the antigen-stimulated release of lymphokines (e.g., IFNs), which in turn have a direct antiviral effect and both activate and enhance a variety of specific and nonspecific effector cells. Cellular and humoral immune responses to HSV have been detected both in human ganglia and in mucosal tissue at the site of reactivation. The HSV virion contains a variety of genes that are directed at the inhibi tion of host responses. These include gene ICP47, which can bind to the cellular transporter-activating protein TAP-1 and reduce the ability of this protein to bind HSV peptides to human leukocyte antigen class I, thereby reducing recognition of viral proteins by cytotoxic T cells of the host. This effect can be overcome by the addition of IFN-γ, but this reversal requires 24–48 h; thus, the virus has time to replicate and

invade other host cells. Entry of infectious HSV-1 and HSV-2 inhibits several signaling pathways of both CD4+ and CD8+ T cells, leading to their functional impairment in killing and influencing the spectrum of their cytokine secretion. HSV-specific CD8+ T-cell responses appear to be an important component in viral clearance from lesions. Immunosuppressed patients with frequent and prolonged HSV lesions have fewer functional CD8+ T cells directed at HSV. HSV-specific CD8+ T cells have been shown to persist in the genital skin at the dermal–epidermal junction contiguous to nerve endings for months after lesion resolution. Even during clini cal quiescence, these CD8+ T cells make both antiviral and cytotoxic proteins indicative of immune surveillance. These resident memory CD8+ T cells appear to be “first responders” capable of controlling viral reactivation at the site of viral release into the dermis. The com munication with surrounding keratinocytes using cytokine release of interferon gamma initiates antiviral resistance mechanisms to HSV epithelial cell infection. Innate immunity also influences HSV infec tion. Severe HSV-1 infections occur in individuals with natural killer (NK) cell defects. Severe familial HSV-1 infections are associated with TLR3 polymorphisms, and the TLR signaling protein UNC93B and TLR2 polymorphisms influence disease reactivation. This rapid “on and off” interplay between the virus and the host helps explain the variability in clinical disease severity between episodes in any single individual. Differences of 30–60 min in host responses can result in 100- to 1000-fold differences in viral levels and can determine whether an episode of disease is subclinical or clinical. There is a strong association between the magnitude of the CD8+ T-lymphocyte response and the clearance of virus from genital lesions. The location, effectiveness, and longevity of the CD8+ T lymphocytes (and other influencers of immune effector functions such as natural killer or CD4+ T-cell responses) may be important in the expression of disease and the likelihood of transmission over time. ■

■EPIDEMIOLOGY Seroepidemiologic studies have documented HSV infections world wide. The global prevalence of HSV-1 is estimated at 66% of the population (3.7 billion people), while 13.2% or 492 million people aged 15–49 were estimated to live with HSV-2. The past 15 years have shown that the prevalence of HSV-2 is even higher in the developing than in the developed world. In sub-

Saharan Africa, HSV-2 seroprevalence among pregnant women may approach 60%, and annual acquisition rates among teenage girls may verge on 20%. The global incidence has been estimated at ~23.9 million infections per year, with 491.5 million infected persons worldwide. As in the developed world, the rate of HSV-2 coital acquisition as well as the serologic prevalence are higher among women than among men. Most of this HSV-2 acquisition is preceded by acquisition of HSV-1; the frequency of genital HSV-1 in middle- and low-income countries is low at present. Infection with HSV-1 is acquired more frequently and earlier in life than infection with HSV-2. From 70 to 90% of adults have antibodies to HSV-1 by the fifth decade of life. In populations of low socioeconomic status, most persons acquire HSV-1 infection before the third decade of life. Antibodies to HSV-2 are not detected routinely until puberty. Antibody prevalence rates correlate with past sexual activity and vary greatly among different population groups. There is evidence that the prevalence of HSV-2 has decreased slightly over the past decade or so in the United States. Serosurveys indicate that 15–20% of the U.S. pop ulation has antibodies to HSV-2. In most routine obstetric and family planning clinics, 15–30% of women have HSV-2 antibodies, although only 10% of those who are seropositive for HSV-2 report a history of genital lesions. As many as 50% of heterosexual adults attending sexu ally transmitted disease clinics have antibodies to HSV-2. A wide variety of serologic surveys has catalogued the widespread epidemic of HSV-2 in Central America, South America, and Africa. In Africa, HSV-2 sero prevalence has ranged from 40 to 70% in obstetric and other sexually experienced populations. Antibody prevalence rates average ~5–10% higher among women than among men. Many studies continue to show that both incident and—more importantly—prevalent HSV-2 infection enhances the acquisition rate

of HIV-1. More specifically, HSV-2 infection is associated on a popula tion basis with a two- to fourfold increase in HIV-1 acquisition. This association has been amply demonstrated in heterosexual men and women in both the developed and developing worlds. Mathematical models suggest that ~33–50% of HIV-1 infections may be attributable to HSV-2 both in men who have sex with men (MSM) and in hetero sexual women in sub-Saharan Africa. Epidemiologically, regions of the world with high HSV-2 prevalence and selected populations within such regions have a higher population-based incidence of HIV-1.

HSV-2 facilitates the spread of HIV into low-risk populations; prev alent HSV-2 appears to increase the risk of HIV infection by seven- to ninefold on a per-coital basis. In addition, HSV-2 is more frequently reactivated in and transmitted by persons co-infected with HIV-1 than in persons not co-infected. Thus, most areas of the world with a high HIV-1 prevalence also have a high HSV-2 prevalence. The shedding of HIV-1 virions from herpetic lesions in the genital region facilitates the spread of HIV through sexual contact. HSV-2 reactivation is associated with a localized persistent inflammatory response consisting of high concentrations of CCR5-enriched CD4+ T cells as well as inflamma tory dendritic cells in the submucosa of the genital skin. These cells can support HIV infection and replication and thus are likely to account for the increased risk of HIV acquisition among persons with genital herpes. Unfortunately, antiviral therapy does not reduce this subclini cal postreactivation inflammation, probably because of the inability of current antiviral agents to prevent the release of small amounts of HSV antigen into the genital mucosa. Several studies suggest that many cases of “asymptomatic” genital HSV-2 infection are, in fact, simply unrecognized or confined to ana tomic regions of the genital tract that are not easily visualized. Asymp tomatic seropositive persons shed virus on mucosal surfaces almost as frequently as do those with symptomatic disease. This large reservoir of unidentified carriers of HSV-2 and the

frequent asymptomatic reac tivation of the virus from the genital tract have fostered the continued spread of genital herpes throughout the world. CHAPTER 197 Herpes Simplex Virus Infections HSV infections occur throughout the year. Transmission can result from contact with persons who have active ulcerative lesions or with persons who have no clinical manifestations of infection but who are shedding HSV from mucocutaneous surfaces. HSV reactivation on genital skin and mucosal surfaces is common. Most HSV-1 and HSV-2 episodes last 2–6 h; thus, replication of the virus and clearance by the host are rapid. Even with once-daily sampling, HSV DNA can be detected on 20% of days by polymerase chain reac tion (PCR). Corresponding figures for HSV-1 in oral secretions are similar. Rates of shedding are highest during the initial years after acquisition, with viral shedding occurring on as many as 30–50% of days during this period. Immunosuppressed patients shed HSV from mucosal sites at an even higher frequency (20–80% of days). These high rates of mucocutaneous reactivation suggest that exposure to HSV from sexual or other close contact (kissing, sharing of glasses or silverware) is common and help explain the continuing spread and high seroprevalence of HSV infections worldwide. Reactivation rates vary widely among individuals. Among people living with HIV, a low CD4+ T-cell count and a high HIV-1 load are associated with increased rates of HSV reactivation. Daily antiviral chemotherapy for HSV-2 infection can reduce shedding rates but does not eliminate shedding, as measured by PCR or culture. ■ ■CLINICAL SPECTRUM HSV has been isolated from nearly all visceral and mucocutaneous sites. The clinical manifestations and course of HSV infection depend on the anatomic site involved, the age and immune status of the host, and the antigenic type of the virus. Primary HSV infections (i.e., first infections with either HSV-1 or HSV-2 in which the host lacks HSV antibodies in acute-phase serum) are frequently accompanied by systemic signs and symptoms. Compared with recurrent episodes, pri mary infections, which involve both mucosal and extramucosal sites, are characterized by a longer duration of symptoms and virus isolation from lesions. The incubation period ranges from 1 to 26 days (median, 6–8 days). Both viral subtypes can cause genital and oral–facial

infections, and the infections caused by the two subtypes are clinically indistinguishable. However, the frequency of reactivation of infection is influenced by anatomic site and virus type. Genital HSV-2 infection is twice as likely to reactivate and recurs 8–10 times more frequently than genital HSV-1 infection. Conversely, oral–labial HSV-1 infection recurs more frequently than oral–labial HSV-2 infection. Asymptom atic shedding rates follow the same pattern.

Oral–Facial Infections Gingivostomatitis and pharyngitis are the most common clinical manifestations of first-episode HSV-1 infec tion, whereas recurrent herpes labialis is the most common clinical manifestation of reactivation HSV-1 infection. HSV pharyngitis and gingivostomatitis usually result from primary infection and are most common among children and young adults. Clinical symptoms and signs, which include fever, malaise, myalgias, inability to eat, irritabil ity, and cervical adenopathy, may last 3–14 days. Lesions may involve the hard and soft palate, gingiva, tongue, lip, and facial area. HSV-1 or HSV-2 infection of the pharynx usually results in exudative or ulcer ative lesions of the posterior pharynx and/or tonsillar pillars. Lesions of the tongue, buccal mucosa, or gingiva may occur later in the course in one-third of cases. Fever lasting 2–7 days and cervical adenopathy are common. It can be difficult to differentiate HSV pharyngitis clini cally from bacterial pharyngitis, Mycoplasma pneumoniae infections, and pharyngeal ulcerations of noninfectious etiologies (e.g., StevensJohnson syndrome). No substantial evidence suggests that reactivation of oral–labial HSV infection is associated with symptomatic recurrent pharyngitis. Reactivation of HSV from the trigeminal ganglia may be associ ated with asymptomatic

virus excretion in the saliva, development of intraoral mucosal ulcerations, or herpetic ulcerations on the vermilion border of the lip or external facial skin. About 50–70% of seropositive patients undergoing trigeminal nerve-root decompression and 10–15% of those undergoing dental extraction develop oral–labial HSV infec tion a median of 3 days after these procedures. Clinical differentiation of intraoral mucosal ulcerations due to HSV from aphthous, traumatic, or drug-induced ulcerations is difficult. PART 5 Infectious Diseases In immunosuppressed patients, HSV infection may extend into mucosal and deep cutaneous layers. Friability, necrosis, bleeding, severe pain, and inability to eat or drink may result. The lesions of HSV mucositis are clinically similar to mucosal lesions caused by cytotoxic drug therapy, trauma, or fungal or bacterial infections, and co-infections are common. Persistent ulcerative HSV infections are among the most common infections in patients with AIDS. HSV and Candida infections often occur concurrently. Systemic antiviral therapy speeds the rate of healing and relieves the pain of mucosal HSV infections in immunosuppressed patients. The frequency of HSV reactivation during the early phases of transplantation or induction chemotherapy is high (50–90%), and prophylactic systemic antiviral agents such as intravenous (IV) acyclovir and penciclovir or the oral congeners of these drugs are used to reduce reactivation rates. Patients with atopic eczema may also develop severe oral–facial HSV infections (eczema herpeticum), which may rapidly involve extensive areas of skin and occasionally disseminate to visceral organs. Extensive eczema her peticum has resolved promptly with the administration of IV acyclovir. Erythema multiforme may also be associated with HSV infections (see Figs. 59-9 and A1-24); some evidence suggests that HSV infec tion is the precipitating event in ~75% of cases of cutaneous erythema multiforme. HSV antigen has been demonstrated both in circulatory immune complexes and in skin lesion biopsy samples from these cases. Patients with severe HSV-associated erythema multiforme are candi dates for chronic suppressive oral antiviral therapy. HSV-1 and varicella-zoster virus (VZV) have been implicated in the etiology of Bell’s palsy (flaccid paralysis of the mandibular portion of the facial nerve). Some but not all trials have documented quicker reso lution of facial paralysis with the prompt initiation of antiviral therapy, with or without glucocorticoids. However, other trials have shown little benefit. There are advantages to the use of both antiviral drugs and glucocorticoids for moderate to severe Bell’s palsy. Some experts feel glucocorticoids alone are preferred for mild disease.

FIGURE 197-1 Genital herpes: primary vulvar infection, with multiple, extremely painful, punched-out, confluent, shallow ulcers on the edematous vulva and perineum. Micturition is often very painful. Associated inguinal lymphadenopathy is common. (Reprinted with permission from K Wolff et al: Fitzpatrick’s Color Atlas & Synopsis of Clinical Dermatology, 5th ed. New York, McGraw-Hill, 2005.) Genital Infections First-episode primary genital herpes is char acterized by fever, headache, malaise, and myalgias. Pain, itching, dysuria, vaginal and urethral discharge, and tender inguinal lymph adenopathy are the predominant local symptoms. Widely spaced bilateral lesions of the external genitalia are characteristic (Fig. 197-1). Lesions may be present in varying stages, including vesicles, pustules, or painful erythematous ulcers. The cervix and urethra are involved in

> “ 80% of women with first-episode infections. First episodes of genital herpes in patients who have had prior HSV-1 infection are occasionally associated with systemic symptoms: prior HSV-1 infection is associ ated with faster healing than true primary genital herpes. Detection of HSV DNA in serum has been found in

> ~30% of cases of true primary genital herpes. The clinical courses of acute first-episode genital herpes are similar for HSV-1 and HSV-2 infection. However, the recurrence rates of genital disease differ with the viral subtype: the 12-month recurrence rates among patients with first-episode HSV-2 and HSV-1 infections are ~90% and ~55%, respectively (median number of recur rences, 4 and <1, respectively). Recurrence rates for genital HSV-2 infections vary greatly among individuals and over time within the same individual. HSV has been isolated from the urethra and urine of men and women without external genital lesions. A clear mucoid dis charge and dysuria are characteristics of symptomatic HSV urethritis. HSV has been isolated from the urethra of 5% of women with the dysuria–frequency syndrome. Occasionally, HSV genital tract disease is manifested by endometritis and salpingitis in women and by pros tatitis in men. About 15% of cases of HSV-2 acquisition are associated with nonlesional clinical syndromes, such as aseptic meningitis, cer vicitis, or urethritis. A more complete discussion of the differential diagnosis of genital herpes is presented in Chap. 141. Both HSV-1 and HSV-2 can cause symptomatic or asymptomatic rectal and perianal infections. HSV proctitis is usually associated with rectal intercourse. However, subclinical perianal shedding of HSV is detected in women and men who report no rectal intercourse. This phenomenon is due to the establishment of latency in the sacral der matome or sacral autonomic ganglia from prior genital tract infection, with subsequent reactivation in epithelial cells in the perianal region. Such reactivations are often subclinical. Symptoms of HSV proctitis include anorectal pain, anorectal discharge, tenesmus, and constipa tion. Sigmoidoscopy reveals ulcerative lesions of the distal 10 cm of the rectal mucosa. Rectal biopsies show mucosal ulceration, necrosis,

polymorphonuclear and lymphocytic infiltration of the lamina propria, and (in occasional cases) multinucleated intranuclear inclusion-bearing cells. Perianal herpetic lesions are also found in immunosuppressed patients receiving cytotoxic therapy. Extensive perianal herpetic lesions and/or HSV proctitis is common among patients with HIV infection. The recent outbreak of Mpox infections globally has made the dif ferentiation of HSV anal rectal infection from Mpox infection of clini cal and therapeutic importance. PCR-based assays clearly distinguish between the two entities. Acyclovir should be used for HSV-2 infection and tecovirimat for monkeypox infection. 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; either viral type may be isolated from the lesion. Clinical signs and symptoms include abrupt-onset edema, erythema, and localized tenderness of the infected finger. Vesicular or pustular lesions of the fingertip that are indistinguishable from lesions of pyogenic bacterial infection are seen. Fever, lymphadenitis, and epi trochlear and axillary lymphadenopathy are common. The infection may recur. Prompt diagnosis (to avoid unnecessary and potentially exacerbating surgical therapy and/or transmission) is essential. Antivi ral therapy is usually recommended (see below). Herpes Gladiatorum HSV may infect almost any area of skin. Mucocutaneous HSV infections of the thorax, ears, face, and hands have been described among wrestlers. Transmission of these infections is

facilitated by trauma to the skin sustained during wrestling. Outbreaks of HSV among competitive wrestlers have illustrated the importance of prompt diagnosis and therapy to contain the spread of this infection. Eye Infections HSV infection of the eye is the most common cause of corneal blindness in the United States. HSV keratitis presents as an acute onset of pain, blurred vision, chemosis, conjunctivitis, and char acteristic dendritic lesions of the cornea. Use of topical glucocorticoids may exacerbate symptoms and lead to involvement of deep structures of the eye. Debridement, topical antiviral treatment, and/or IFN ther apy hasten healing. However, recurrences are common, and the deeper structures of the eye may sustain immunopathologic injury. Stromal keratitis due to HSV appears to be related to T-cell–dependent destruc tion of deep corneal tissue. An HSV-1 epitope that is autoreactive with T cell–targeting corneal antigens has been postulated to be a factor in this infection. Chorioretinitis, usually a manifestation of disseminated HSV infection, may occur in neonates or in patients with HIV infection. HSV and VZV can cause acute necrotizing retinitis as an uncommon but severe manifestation. While VZV infection is the most common cause of acute retinal necropsy, both HSV-1 and HSV-2 may also be associated with this syn drome. Emergent ophthalmology consulta tion is recommended as residual blindness may occur; both systemic and intravitical antiviral therapy is recommended. Central and Peripheral Nervous System Infections HSV accounts for 10–20% of all cases of sporadic viral encephalitis in the United States. The estimated incidence is ~2.3 cases per 1 million persons per year. Cases are distributed throughout the year, and the age distribution appears to be biphasic, with peaks at 5–30 and >50 years of age. HSV-1 causes

> “ 95% of cases. 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 neuro tropic spread from the periphery via the FIGURE 197-2 Computed tomography and diffusion-weighted magnetic resonance imaging scans of the brain of a patient with left-temporal-lobe herpes simplex virus encephalitis.

olfactory bulb. However, most adults with HSV encephalitis have clini cal or serologic evidence of mucocutaneous HSV-1 infection before the onset of CNS symptoms. In ~25% of the cases 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. Two theories have been proposed to explain the development of actively replicating HSV in localized areas of the CNS in persons whose ganglionic and CNS isolates are similar. Reactivation of latent HSV-1 infection in trigeminal or autonomic nerve roots may be associated with extension of virus into the CNS via nerves innervating the middle cranial fossa. HSV DNA has been dem onstrated by DNA hybridization in brain tissue obtained at autopsy— even from healthy adults. Thus, reactivation of long-standing latent CNS infection may be another mechanism for the development of HSV encephalitis. Recent studies have identified genetic polymorphisms among families with a high frequency of HSV encephalitis. Peripheralblood mononuclear cells, fibroblasts, and neurons from these patients (predominantly children) appear to secrete reduced levels of IFN in response to HSV. Genetic mutations in TLR3 documented in patients with HSV encephalitis suggest that some cases of sporadic HSV encephalitis may be related to host genetic determinants. The clinical hallmark of HSV encephalitis has been the acute onset of fever and focal neurologic symptoms and

signs, especially in the temporal lobe (Fig. 197-2); gadolinium enhancing lesions are seen in the temporal lobe by magnetic resonance imaging (MRI). Clinical differentiation of HSV encephalitis from other viral encephalitides, focal infections, or noninfectious processes is difficult. Elevated cere brospinal fluid (CSF) protein levels, leukocytosis (predominantly lym phocytes), and red blood cell counts due to hemorrhagic necrosis are common in HSV encephalitis. While brain biopsy has been the gold standard for defining HSV encephalitis, a highly sensitive and specific PCR for detection of HSV DNA in CSF has largely replaced biopsy for defining HSV CNS infection. Although titers of antibody to HSV in CSF and serum increase in most cases of HSV encephalitis, they rarely do so earlier than 10 days into the illness and, therefore, although useful in retrospect, generally are not helpful in establishing an early clinical diagnosis. In rare cases, demonstration of HSV antigen, HSV DNA, or HSV replication in brain tissue obtained by biopsy is highly sensitive; examination of such tissue also provides the opportunity to identify alternative, potentially treatable causes of encephalitis. Antiviral therapy with acyclovir reduces the rate of death from HSV encephalitis. Most authorities recommend the administration of IV CHAPTER 197 Herpes Simplex Virus Infections

acyclovir to patients with presumed HSV encephalitis until the diag nosis is confirmed or an alternative diagnosis is made. All confirmed cases should be treated with IV acyclovir (30 mg/kg per day in three divided doses for 14–21 days). After the completion of therapy, the clinical recurrence of encephalitis requiring more treatment has been reported. 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 common, especially among persons >50 years of age.

HSV DNA has been detected in CSF from 3 to 15% of persons pre senting to the hospital with aseptic meningitis. HSV meningitis, which is usually seen in association with primary genital HSV infection, is an acute, self-limited disease manifested by headache, fever, and mild photophobia and lasting 2–7 days. Lymphocytic pleocytosis in the CSF is characteristic. Neurologic sequelae of HSV meningitis are rare. HSV is the most commonly identified cause of recurrent lymphocytic meningitis (Mollaret’s meningitis). Demonstration of HSV antibodies in CSF or persistence of HSV DNA in CSF can establish the diagno sis. For persons with frequent recurrences of HSV meningitis, daily antiviral therapy has reduced the frequency of recurrent episodes of symptomatic meningitis. Autonomic nervous system dysfunction, especially of the sacral region, has been reported in association with both HSV and VZV infections. Numbness, tingling of the buttocks or perineal areas, urinary retention, constipation, CSF pleocytosis, and (in males) impotence may occur. Symptoms appear to resolve slowly over days or weeks. Occasionally, hypoesthesia and/or weakness of the lower extremities persists for many months. Transitory hypoesthesia of the area of skin innervated by the trigeminal nerve and vestibular system dysfunction (as measured by electronystagmography) are the predominant signs of disease. Rarely, transverse myelitis, manifested by a rapidly progressive symmetric paralysis of the lower extremities or Guillain-Barré syndrome, follows HSV infection. Similarly, PNS involvement (Bell’s palsy) or cranial polyneuritis may be related to reactivation of HSV-1 infection. PART 5 Infectious Diseases There is increasing experimental evidence suggesting an association between herpesvirus pathogens, specifically HSV-1, and the develop ment of sporadic Alzheimer’s disease (AD). HSV-1 DNA is detected in brain tissue of patients with AD, and epidemiologically, HSV-1 anti bodies are a significant risk factor for later AD onset. A wide variety of models of AD indicate that HSV-1 infection can induce neuronal

death, tau phosphorylation, and intracellular expression of isoforms of amyloid precursor protein cleavage products that produce multicellu lar-like plaque structures associated with AD. There are no cogent data to indicate antiviral therapy would be of benefit to anyone with AD. An adequately powered prospective study of prolonged antiviral therapy has not been conducted. HSV Lymphadenitis HSV-1 or HSV-2 lymphadenitis has been reported, with increasing frequency especially among patients with chronic lymphocytic leukemia. This condition represents a diagnos tic dilemma often confused with lymphomatous transformation and occurs absent of oral or genital lesions. One histologic hint between HSV and lymphoblastic transformation is the presence of necrosis in biopsy tissue in HSV lymphadenitis. Isolation of HSV or demonstra tion of HSV DNA in tissue confers the diagnosis. Concomitant HSV viremia may also be present. Intravenous acyclovir has been associated with resolution of infection and clinical improvement. Visceral Infections HSV infection of visceral organs usually results from viremia, and multiple-organ involvement is common. Occasionally, however, the clinical manifestations of HSV infection involve only the esophagus, lung, or liver. HSV esophagitis may result from direct extension of oral–pharyngeal HSV infection into the esophagus or may occur de novo by reactivation and spread of HSV to the esophageal mucosa via the vagus nerve. The predominant symp toms of HSV esophagitis are odynophagia, dysphagia, substernal pain, and weight loss. Multiple oval ulcerations appear on an erythematous base with or without a patchy white pseudomembrane. The distal esophagus is most commonly involved. With extensive disease, diffuse

friability may spread to the entire esophagus. Neither endoscopic nor barium examination can reliably differentiate HSV esophagitis from Candida esophagitis or from esophageal ulcerations due to thermal injury, radiation, or corrosives. Endoscopically obtained secretions— for cytologic examination and culture or DNA detection by PCR—provide the most useful material for diagnosis. Systemic antiviral therapy usu ally reduces the severity and duration of symptoms and heals esopha geal ulcerations. HSV pneumonitis is uncommon except in severely immunosup pressed patients and may result from extension of herpetic tracheo bronchitis into lung parenchyma. Focal necrotizing pneumonitis usually ensues. Hematogenous dissemination of virus from sites of oral or genital mucocutaneous disease may also occur, producing bilateral interstitial pneumonitis. Bacterial, fungal, and parasitic pathogens are commonly present in HSV pneumonitis. The mortality rate from untreated HSV pneumonia in immunosuppressed patients is high (>80%). HSV has also been isolated from the lower respiratory tract of persons with acute respiratory distress syndrome and prolonged intu bation. Most authorities believe that the presence of HSV in tracheal aspirates in such settings is due to reactivation of HSV in the tracheal region and localized tracheitis in persons with long-term intubation. Such patients should be evaluated for extension of HSV infection into the lung parenchyma. While retrospective reviews of HSV tracheitis in intensive care unit patients suggest benefit from antiviral therapy, well-powered controlled trials assessing the role of antiviral agents used against HSV in ventilation-associated morbidity and mortality have not been conducted. The role of lower respiratory tract HSV infection in overall rates of morbidity and mortality associated with these condi tions is unclear. HSV is an uncommon cause of hepatitis in immuno competent 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. Other reported complications of HSV infection include monar ticular arthritis, adrenal necrosis, idiopathic thrombocytopenia, and glomerulonephritis. Disseminated HSV infection in immunocompe tent patients is rare. In immunocompromised patients, burn patients, or malnourished individuals, HSV occasionally

disseminates to other visceral organs, such as the adrenal glands, pancreas, small and large intestines, and bone marrow. Dissemination, even recurrent dis semination, is being increasingly recognized in persons with chronic lymphocytic leukemia. Rarely, primary HSV infection in pregnancy disseminates and may be associated with the death of both mother and fetus. This uncommon event is usually related to the acquisition of primary infection in the third trimester. Disseminated HSV infection is best detected by the presence of HSV DNA in plasma or blood. Neonatal HSV Infections Of all HSV-infected populations, neo nates (infants <6 weeks) have the highest frequency of visceral and/or CNS infection. Without therapy, the overall rate of death from neonatal herpes is 65%; <10% of neonates with CNS infection develop normally. Although skin lesions are the most commonly recognized features of disease, many infants do not develop lesions at all or do so only well into the course of disease. Neonatal infection is usually acquired perinatally from contact with infected genital secretions at delivery. Congenitally infected infants have been reported. Of neonatal HSV infections, 30–50% are due to HSV-1 and 50–70% to HSV-2. A recent review of U.S. Medicaid databases indicates a frequency of ~1000 cases of neonatal HSV yearly, a rate of between 1 per 2000 and 1 per 3000 live births. The risk of developing neonatal HSV infection is 10 times higher for an infant born to a mother who has recently acquired HSV than for other infants. Neonatal HSV-1 infections may also be acquired through postnatal contact with immediate family members who have symptomatic or asymptomatic oral–labial HSV-1 infection or through nosocomial transmission within the hospital. All neonates with presumed herpes should be treated with IV acyclovir and then placed on maintenance oral antiviral therapy for the first 6–12 months of life. Antiviral chemotherapy with high-dose IV acyclovir (60 mg/kg per day) has reduced the mortality rate from neonatal herpes to ~15%.

However, rates of morbidity, especially among infants with HSV-2 infection involving the CNS, are still very high. HSV in Pregnancy In the United States, 21% of all pregnant women and 51% of non-Hispanic black pregnant women are seroposi tive for HSV-2. However, the risk of mother-to-child transmission of HSV in the perinatal period is highest when the infection is acquired near the time of labor—that is, in previously HSV-seronegative women. The clinical manifestations of recurrent genital herpes—including the frequency of subclinical versus clinical infection, the duration of lesions, pain, and constitutional symptoms—are similar in pregnant and nonpregnant women. Recurrences increase in frequency over the course of pregnancy. However, when women are seropositive for HSV-2 at the outset of pregnancy, no effect on neonatal outcomes (including birth weight and gestational age) is seen. First-episode infections in pregnancy have more severe consequences for mother and infant. Maternal visceral dissemination during the third trimester occasionally occurs, as does premature birth or intrauterine growth retardation. The acquisition of primary disease in pregnancy, whether related to HSV-1 or HSV-2, carries the risk of transplacental transmis sion of virus to the neonate and can result in spontaneous abortion, although this outcome is relatively uncommon. For newly acquired genital HSV infection during pregnancy, most authorities recommend treatment with acyclovir (400 mg three times daily) or valacyclovir (500–1000 mg twice daily) for 7–10 days. However, the impact of this intervention on transmission is unknown. The high HSV-2 prevalence rate in pregnancy and the low incidence of neonatal disease in these women (1 case per 6000–20,000 live births) indicate that only a few infants are at risk of acquiring HSV. Therefore, cesarean section is not warranted for all women with recurrent genital disease. Because intrapartum transmission of infection accounts for the majority of cases, abdominal delivery need be considered only for women who are shedding HSV at delivery. Several studies have shown no correlation between recurrence of viral shedding before delivery and viral

shed ding at term. Hence, weekly virologic monitoring and amniocentesis are not recommended. The frequency of transmission from mother to infant is markedly higher among women who acquire HSV near term (30–50%) than among those in whom HSV-2 infection is reactivated at delivery (<1%). Although maternal antibody to HSV-2 is protective, antibody to HSV-1 offers little or no protection against neonatal HSV-2 infection. Primary genital infection with HSV-1 leads to a particularly high risk of trans mission during pregnancy and accounts for an increasing proportion of neonatal HSV cases. Moreover, during reactivation, HSV-1 appears more transmissible to the neonate than HSV-2. Only 2% of women who are seropositive for HSV-2 have HSV-2 isolated from cervical secretions at delivery, and only 1% of infants exposed in this man ner develop infection, presumably because of the protective effects of maternally transferred antibodies and perhaps lower viral titers during reactivation. Despite the low frequency of transmission of HSV in this setting, 30–50% of infants with neonatal HSV are born to mothers with established genital herpes. Isolation of HSV by cervicovaginal swab at the time of delivery is the greatest risk factor for intrapartum HSV transmission (relative risk = 346); however, culture-negative, PCR-positive cases of intrapartum trans mission 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 of transmission, whereas cesar ean delivery is protective (OR = 0.14). Physical examination poorly predicts the absence of shedding, and PCR far exceeds culture in terms of sensitivity and speed. Therefore, PCR detection at the onset of labor should be used to aid clinical decision-making for women with HSV-2 antibody. 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 as well as collection of a swab sample for viral isolation. Women who have no evidence of lesions can have a vaginal delivery. The presence

of active lesions on the cervix or external genitalia is an indication for cesarean delivery.

If first-episode exposure has occurred (e.g., if HSV serologies show that the mother is seronegative or if the mother is HSV-1-seropositive and the isolate at delivery is found to be HSV-2), many authorities would initiate antiviral therapy for the infant with IV acyclovir. At a minimum, samples for viral cultures and PCR should be 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 h after delivery should be treated with IV acyclovir at recommended doses. ■ ■DIAGNOSIS Both clinical and laboratory criteria are useful for diagnosing HSV infections. A clinical diagnosis can be made accurately when charac teristic multiple vesicular lesions on an erythematous base are present. However, herpetic ulcerations may resemble skin ulcerations of other etiologies and considerable overlap including coinfection between HSV and Mpox infections exist. Mucosal HSV infections may also present as urethritis or pharyngitis without cutaneous lesions. Thus, laboratory studies to confirm the diagnosis and to guide therapy are recommended. While staining of scrapings from the base of the lesions with Wright’s, Giemsa’s (Tzanck preparation), or Papanicolaou’s stain to detect giant cells or intranuclear inclusions of Herpesvirus infection is a well-described procedure, few clinicians are skilled in this tech nique, the sensitivity of staining is low (<30% for mucosal swabs), and these cytologic methods do not differentiate between HSV and VZV infections. CHAPTER 197 HSV infection is best confirmed in the laboratory by detection of virus, viral antigen, or viral DNA in

scrapings from lesions. HSV DNA detection by PCR is the most sensitive laboratory technique for detect ing mucosal or visceral HSV infections and is the recommended test for laboratory confirmation of a diagnosis. HSV causes a discernible cytopathic effect in a variety of cell culture systems, and this effect can be identified within 48–96 h after inoculation. Spin-amplified culture with subsequent staining for HSV antigen has shortened the time needed to identify HSV to <24 h. Culture is indicated when antiviral sensitivity testing is required. The sensitivity of all detection methods depends on the stage of the lesions (with higher sensitivity for vesicu lar than for ulcerative lesions), on whether the patient has a first or a recurrent episode of the disease (with higher sensitivity in first than in recurrent episodes), and on whether the sample is from an immu nosuppressed or an immunocompetent patient (with more antigen or DNA in immunosuppressed patients). Laboratory confirmation permits subtyping of the virus; information on subtype may be useful epidemiologically and may help to predict the frequency of reactivation after first-episode oral–labial or genital HSV infection. Herpes Simplex Virus Infections Both type-specific and type-common antibodies to HSV develop during the first several weeks after infection and persist indefinitely. Serologic assays with whole-virus antigen preparations, such as com plement fixation, neutralization, indirect immunofluorescence, passive hemagglutination, radioimmunoassay, and enzyme-linked immuno sorbent assay, can differentiate uninfected (seronegative) persons from those with past HSV-1 or HSV-2 infection, but they do not reliably distinguish between the two viral subtypes or help establish an active clinical diagnosis of HSV-2. Serologic assays that identify antibodies to the type-specific glycoprotein G of the two viral subtypes (G1 and G2) are available commercially and can be used to distinguish between the human antibody responses to HSV-1 and HSV-2. Point-of-care assays that provide results from capillary blood or serum during a clinic visit are available. False-positive and false-negative assays do occur, and there is a need for commercially available assays to distinguish prevalent HSV-2 infection, especially on the backgroiund of earlier acquired HSV-1. A western blot assay that can detect several HSV type-specific proteins can also be used and is, at present, the best con firmatory assay. The presence of type-specific HSV-2 antibody implies past HSV-2 infection—i.e., latent infection, likely subclinical reactiva tion, increased risk of HSV-1 acquisition, and potential transmission to others.

PART 5 Infectious Diseases Acute- and convalescent-phase serum samples can be useful in demonstrating seroconversion during primary HSV-1 or HSV-2 infec tion. However, few available tests report titers, and increases in index values do not reflect first episodes in all patients. Serologic assays based on type-specific proteins should be used to identify asymptomatic car riers of HSV-1 or HSV-2. No reliable IgM method for defining acute HSV infection is available. Several studies have shown that persons with previously unrecog nized HSV-2 infection can be taught to identify symptomatic reactiva tions. Individuals seropositive for HSV-2 should be told about the high frequency of subclinical reactivation on mucosal surfaces that are not visible to the eye (e.g., cervix, urethra, perianal skin) or in microscopic ulcerations that may not be clinically symptomatic. Transmission of infection during such episodes is well established. HSV-2-seropositive persons should be educated about the high likelihood of subclinical shedding and the role that condoms (male or female) may play in reducing transmission. Antiviral therapy with valacyclovir (500 mg once daily) has been shown to reduce but not eliminate the transmis sion of HSV-2 between sexual partners. TREATMENT Herpes Simplex Virus Infections Many aspects of mucocutaneous and visceral HSV infections are amenable to antiviral chemotherapy. For mucocutaneous infec tions, acyclovir and its congeners famciclovir and valacyclovir have been the mainstays of therapy. Several antiviral agents are available for topical use in HSV eye infections: idoxuridine,

trifluorothymi dine, topical vidarabine, and cidofovir and, more recently, topical pritelivir. For HSV encephalitis and neonatal herpes, IV acyclovir is the treatment of choice. Most licensed antiviral agents for use against HSV inhibit the viral DNA polymerase. One class of drugs, typified by the drug acyclovir, is made up of substrates for the HSV enzyme TK. Acyclovir, ganciclovir, famciclovir, and valacyclovir are all selectively phos phorylated to the monophosphate form in virus-infected cells. Cellular enzymes convert the monophosphate form of the drug to the triphosphate, which is then incorporated into the viral DNA chain. Acyclovir is the agent most frequently used for the treat ment of HSV infections and is available in IV, oral, and topical formulations. Valacyclovir, the valyl ester of acyclovir, offers greater bioavailability than acyclovir and thus can be administered less frequently. Famciclovir, the oral formulation of penciclovir, is clini cally effective in the treatment of a variety of HSV-1 and HSV-2 infections. Ganciclovir is active against both HSV-1 and HSV-2; however, it is more toxic than acyclovir, valacyclovir, and famci clovir and generally is not recommended for the treatment of HSV infections. Anecdotal case reports suggest that ganciclovir may also be less effective than acyclovir for the treatment of HSV infections. All three recommended compounds—acyclovir, valacyclovir, and famciclovir—have proved effective in shortening the duration of symptoms and lesions of mucocutaneous HSV infections in both immunocompromised and immunocompetent patients (Table 197-1). IV and oral formulations prevent reactivation of HSV in sero positive immunocompromised patients during induction chemo therapy or in the period immediately after bone marrow or solid organ transplantation. Chronic daily suppressive therapy reduces the frequency of reactivation disease among patients with frequent genital or oral–labial herpes. Only valacyclovir has been subjected to clinical trials that demonstrated reduced transmission of HSV-2 infection between sexual partners. IV acyclovir (30 mg/kg per day, given as a 10-mg/kg infusion over 1 h at 8-h intervals) is effective in reducing rates of death and morbidity from HSV encephalitis. Early initiation of therapy is a critical factor in outcome. The major side effect associated with IV acyclovir is transient renal insufficiency, usually due to crystallization of the compound in the renal paren chyma. This adverse reaction can be avoided if the medication is given slowly over 1 h and the patient is well hydrated. Because CSF levels of acyclovir average only 30–50% of plasma levels, the dos age of acyclovir used for treatment of CNS infection (30 mg/kg per day) is double that used for treatment of mucocutaneous or visceral disease (15 mg/kg per day). Even higher doses of IV acyclovir are used for neonatal HSV infection (60 mg/kg per day in three divided doses). Antiviral drugs neither eradicate latent infection nor affect the risk, frequency, or severity of subclinical or clinical recurrence after the drug is discontinued. Increasingly, shorter courses of therapy are being used for recur rent mucocutaneous infection with HSV-1 or HSV-2 in immuno competent patients. One-day courses of famciclovir and valacyclovir are clinically effective, more convenient, and generally less costly than longer courses of therapy (Table 197-1). These short-course regimens should be reserved for immunocompetent hosts. SUPPRESSION OF MUCOCUTANEOUS HERPES Recognition of the high frequency of subclinical reactivation pro vides a well-accepted rationale for the use of daily antiviral therapy to suppress reactivations of HSV, especially in persons with frequent clinical reactivations (e.g., those with recently acquired genital HSV infection). Immunosuppressed persons, including those with HIV infection, may also benefit from daily antiviral therapy. Daily acy clovir and valacyclovir reduce the frequency of HSV reactivations among HIV-positive persons. Regimens used include acyclovir (400–800 mg twice daily), famciclovir (500 mg twice daily), and valacyclovir (500 mg twice daily); valacyclovir at a dose of 4 g/d was associated with thrombotic thrombocytopenic purpura in one study of HIV-infected persons. Daily acyclovir therapy is associated with a modest reduction in the titer of HIV RNA in plasma (0.5-log10 reduction) and in

the genital mucosa (0.33-log10 reduction). Epi sodes of subclinical reactivation still occur with chronic acyclovir or valaciclovir therapy. REDUCED HSV TRANSMISSION TO SEXUAL PARTNERS Once-daily valacyclovir (500 mg) has been shown to reduce trans mission of HSV-2 between sexual partners. Transmission rates are higher from males to females and among persons with frequent HSV-2 reactivation. Serologic screening can be used to identify at-risk couples. Daily valacyclovir appears to be more effective at reducing subclinical shedding than daily famciclovir. ACYCLOVIR RESISTANCE Clinically relevant acyclovir-resistant strains of HSV do occur. Most of these strains have an altered substrate specificity for phos phorylating acyclovir. Thus, cross-resistance to famciclovir and valacyclovir is usually found. Occasionally, an isolate with altered TK specificity arises and is sensitive to famciclovir but not to acy clovir. In some patients infected with TK-deficient virus, higher doses of acyclovir are associated with clearing of lesions. In others, clinical disease progresses despite high-dose therapy. The major ity of clinically significant acyclovir resistance has been seen in immunocompromised patients. HSV-2 isolates appear to be more resistant than HSV-1 strains. The frequency of acyclovir resistance is not systematically monitored; the lack of appreciable change in the frequency of acyclovir resistance in the general population past 45 years probably reflects the reduced transmission of TK-deficient mutants. Isolation of HSV from lesions persisting despite adequate dosages and blood levels of acyclovir should raise the suspicion of acyclovir resistance. Clinical management of acyclovir resistance can be challenging. Therapy with the antiviral drug foscarnet (40–80 mg/kg IV every 8 h until clinical resolution) is the only cur rently well demonstrated approach (Chap. 196). Because of its toxic ity and cost, this drug is usually reserved for patients with extensive mucocutaneous infections. Cidofovir is a nucleotide analogue and exists as a phosphonate or monophosphate form. Most TK-deficient strains of HSV are sensitive to cidofovir. Cidofovir ointment speeds healing of acyclovir-resistant lesions, but the topical drug itself can cause mucocutaneous ulcerations. No well-controlled trials of systemic cidofovir have been reported. Occasional cases may respond to topical imiquimod. Anecdotal case reports of successful

TABLE 197-1 Antiviral Chemotherapy for Herpes Simplex Virus (HSV) Infection I. Mucocutaneous HSV infections A. Infections in immunosuppressed patients

1. Acute symptomatic first or recurrent episodes: IV acyclovir (5 mg/kg q8h) or oral acyclovir (400 mg qid), famciclovir (500 mg bid or tid), or valacyclovir

(500 mg bid) is effective. Treatment duration may vary from 7 to 21 days. IV therapy may be given for 2–10 days until clinical improvement and followed by oral therapy. 2. Suppression of reactivation disease (genital or oral–labial): IV acyclovir (5 mg/kg q8h) or oral valacyclovir (500 mg bid) or acyclovir (400–800 mg 3–5 times per day) prevents recurrences during the 30-day period immediately after transplantation. Longer-term HSV suppression is often used for persons with continued immunosuppression. In bone marrow and renal transplant recipients, oral valacyclovir (2 g/d) is also effective in reducing cytomegalovirus infection. Oral valacyclovir at a dose of 4 g/d has been associated with thrombotic thrombocytopenic purpura after extended use in HIV-positive persons. In HIV-infected persons, oral acyclovir (400–800 mg bid), valacyclovir (500 mg bid), or famciclovir (500 mg bid) is effective in reducing clinical and subclinical reactivations of HSV-1 and HSV-2. B. Infections in immunocompetent patients

1. Genital herpes a. First episodes: Oral acyclovir (200 mg 5 times per day or 400 mg tid), valacyclovir (1 g bid), or famciclovir (250 mg tid) for 7–14 days is effective. IV acyclovir (5 mg/kg q8h for 5 days) is given for severe disease or neurologic complications such as aseptic meningitis. b. Symptomatic recurrent genital herpes: Short-course (1- to 3-day) regimens are preferred because of low cost, likelihood of adherence, and convenience. Oral acyclovir (800 mg tid for 2 days), valacyclovir (500 mg bid for 3 days), valacyclovir (1 g orally once a day for 3 days), or famciclovir (750 or 1000 mg bid for 1 day, a 1500-mg single dose, or 500 mg stat followed by 250 mg q12h for 2 days) effectively shortens lesion duration. Other options include oral acyclovir (200 mg 5 times per day), valacyclovir (500 mg bid), and famciclovir (125 mg bid for 5 days). c. Suppression of recurrent genital herpes: Oral acyclovir (400–800 mg bid) or valacyclovir (500 mg daily) is given. Patients with >9 episodes per year should take oral valacyclovir (1 g daily or 500 mg bid) or famciclovir (250 mg bid or 500 mg bid).
2. Oral–labial HSV infections a. First episode: Oral acyclovir is given (200 mg 5 times per day or 400 mg tid); an oral acyclovir suspension can be used (600 mg/m2 qid). Oral famciclovir

(250 mg bid) or valacyclovir (1 g bid) has been used clinically. The duration of therapy is 5–10 days. b. Recurrent episodes: If initiated at the onset of the prodrome, single-dose or 1-day therapy effectively reduces pain and speeds healing. Regimens include oral famciclovir (a 1500-mg single dose or 750 mg bid for 1 day) or valacyclovir (a 2-g single dose or 2 g bid for 1 day). Self-initiated therapy with 6-timesdaily topical penciclovir cream effectively speeds healing of oral–labial HSV infection. Topical acyclovir cream has also been shown to speed healing or single dose oral amenamevir 1200 mg. c. Suppression of reactivation of oral–labial HSV: If started before exposure and continued for the duration of exposure (usually 5–10 days), oral acyclovir (400 mg bid) prevents reactivation of recurrent oral–labial HSV infection associated with severe sun exposure. 3. Surgical prophylaxis of oral or genital HSV infection: Several surgical procedures, such as laser skin resurfacing, trigeminal nerve-root decompression, and lumbar disk surgery, have been associated with HSV reactivation. IV acyclovir (3–5 mg/kg q8h) or oral acyclovir (800 mg bid), valacyclovir (500 mg bid), or famciclovir (250 mg bid) effectively reduces reactivation. Therapy should be initiated 48 h before surgery and continued for 3–7 days. 4. Herpetic whitlow: Oral acyclovir (200 mg) is given 5 times daily (alternative: 400 mg tid) for 7–10 days. 5. 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. 6. Herpetic eye infections: In acute keratitis, topical trifluorothymidine, vidarabine, idoxuridine, acyclovir, penciclovir, and interferon are all beneficial. Debridement may be required. Topical steroids may worsen disease. II. Central nervous system HSV infections A. HSV encephalitis: IV acyclovir (10 mg/kg q8h; 30 mg/kg per day) is given for 10 days or until HSV DNA is no longer detected in cerebrospinal fluid. B. HSV aseptic meningitis: No studies of systemic antiviral chemotherapy exist. If therapy is to be given, IV acyclovir (15–30 mg/kg per day) should be used. C. Autonomic radiculopathy: No studies are available. Most authorities recommend initial therapy with IV acyclovir (5–10 mg/kg q8h) followed by oral therapy for 21 days. III. Neonatal HSV infections: IV acyclovir (60 mg/kg per day, divided into 3 doses) is given. The recommended duration of IV treatment is 21 days. Monitoring for relapse should be undertaken. Continued suppression with oral acyclovir suspension should be given for 3–4 months. IV. Visceral HSV infections A. HSV esophagitis: IV acyclovir (15 mg/kg per day) is given. In some patients with milder forms of immunosuppression, oral therapy with

valacyclovir or famciclovir is effective. B. HSV pneumonitis and lymphadenitis: No controlled studies exist. IV acyclovir (15 mg/kg per day) should be considered. V. Disseminated HSV infections: No controlled studies exist. IV acyclovir (5 mg/kg q8h) should be tried. Adjustments for renal insufficiency may be needed. No definite evidence indicates that therapy will decrease the risk of death. VI. Erythema multiforme associated with HSV: Anecdotal observations suggest that oral acyclovir (400 mg bid or tid) or valacyclovir (500 mg bid) will suppress erythema multiforme. VII. Infections due to acyclovir-resistant HSV: IV foscarnet (40 mg/kg IV q8h) should be given until lesions heal. The optimal duration of therapy and the usefulness of its continuation to suppress lesions are unclear. The helicase-primase inhibitor pritelivir, 400 mg oral loading dose on day 1 followed by 100 mg once daily for 21–28 days, has reported effectiveness. Some patients may benefit from cutaneous application of trifluorothymidine or 1% cidofovir gel, both of which must be compounded at a pharmacy. These preparations should be applied once daily for 5–7 days. Topical imiquimod can be considered. IV cidofovir (5 mg/kg weekly) may be considered. VIII. Acyclovir and pregnancy: No adverse effects to the fetus or newborn have been attributable to acyclovir. Acyclovir can be used in all stages of pregnancy and among women who are breastfeeding (the drug can be found in breast milk). Suppressive acyclovir treatment in late pregnancy (acyclovir 400 mg orally tid or valacyclovir 500 mg orally bid from ~34 weeks until delivery) reduces the frequency of cesarean delivery among women with recurrent genital herpes. Such treatment may not protect against transmission to neonates. treatment of acyclovir resistant HSV with oral pritelivir have been reported in immunocompetent persons. Drugs from a new class that inhibit HSV-specific helicase/primase activity, amenamevir and pritelivir, are under clinical investigation and appear to offer a better toxicity profile for the treatment of acyclovir-resistant strains of HSV. Amenamevir is licensed for varicella-zoster infections in

CHAPTER 197 Herpes Simplex Virus Infections Japan, and a recent study has shown promise in recurrent oral– labial HSV. ACYCLOVIR EFFICACY IN THE DEVELOPING WORLD Initial studies of acyclovir-like drugs were performed solely in the developed world. While acyclovir, valacyclovir, and famciclovir are

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