Infections with Herpesviruses I: Herpes Simplex Virus and Varicella-Zoster Virus

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Cover Illustration by Christine Schaar
INTRODUCTION

For Hippocrates and other ancient Greek scholars, the word “herpes” (meaning to creep or crawl) was used to describe lesions that spread.¹ Members of the Herpesviridae family are large, DNA-containing enveloped viruses. There are approximately 100 known herpesviruses infecting a broad spectrum of hosts in the animal kingdom; 8 human viruses are recognized (Table 1).

All herpesviruses establish latency in their natural hosts. Most have the ability to transform cells, but the full relevance of this ability is uncertain, because only lymphotropic viruses (eg, Epstein-Barr virus [EBV]) are known to be tumorigenic. Herpesviruses are ubiquitous, infecting most persons, and can induce disease in 3 distinct ways: (1) by destroying tissues directly, (2) by provoking immunopathologic responses (such as hemolytic anemia, erythema multiforme, and thrombocytopenia), and (3) by facilitating neoplastic transformation.

Because herpesviruses are fragile and do not survive long in the environment, transmission generally requires inoculation of fresh, virus-containing body fluid directly into susceptible tissues of an uninfected person. Except for varicella, most herpesvirus infections are transmitted asymptomatically. Between a third to half of genital herpes simplex virus (HSV) infections are acquired from asymptomatic sexual partners. An even greater proportion of EBV infections most likely are transmitted asymptomatically. Thus, episodes of asymptomatic shedding exceed those of symptomatic shedding. For example, asymptomatic shedding in cases of HSV infection occurs on 0.5% to 1% of days,² whereas asymptomatic shedding in cases of EBV infection occurs on 15% of days.³ The likelihood of virus transmission, however, depends on the quantity of virus shed; the titer of virus recoverable from symptomatic infections greatly exceeds that recoverable from asymptomatic infections.

This manual is the first installment of a 2-part series on infections with herpesviruses and will focus on HSV and varicella-zoster virus (VZV) infections, providing information on their pathology, epidemiology, clinical features, complications, diagnosis, and management. The second installment, which will be published as Volume 8, Part 1, of the Hospital Physician Infectious Diseases Board Review Manual, will address infections with cytomegalovirus, EBV, human herpesvirus 6 (HHV-6), HHV-7, and Kaposi’s sarcoma-associated herpesvirus (HHV-8).
CASE PRESENTATIONS

CASE PRESENTATION 1

A 34-year-old woman comes to the emergency department because of a 1-week history of progressive headache, neck stiffness, and a bloody, mucous-filled anal discharge. She reports having had unprotected anal and vaginal intercourse with a new partner approximately 2 weeks ago. On examination, her temperature is 37.9°C (100.2°F); a few ulcerations are noted in the intergluteal fold. Neurologic status is intact except for meningismus. Laboratory analysis of cerebrospinal fluid (CSF) shows lymphocytic pleocytosis, with a total leukocyte count of $532 \times 10^3$/$\text{mm}^3$; total protein level is 144 mg/dL, and glucose level is 47 mg/dL. No organisms are detected on a Gram’s stain of the CSF.

CASE PRESENTATION 2

A previously healthy 28-year-old Hispanic woman is admitted to the hospital for spontaneous vaginal delivery of a healthy full-term neonate. Within 24 hours of delivery, she develops pruritus associated with a vesicular rash and myalgias. She has lived in the United States for the past 3 years, having emigrated from Puerto Rico. On examination, her temperature is 38°C (100.4°F). There is mild tonsillar injection, but her lungs are clear to auscultation; abdominal findings are consistent with her postpartum status. Erythematous lesions are noted over her trunk, extremities, face, and scalp; a few are vesicular, and some crusting is present. Leukocyte count is $7.4 \times 10^3$/$\text{mm}^3$; results of liver function tests and chest radiography show no abnormalities.

HERPES SIMPLEX VIRUS, TYPES 1 AND 2

PATHOLOGY

HSV is a linear, double-stranded DNA virus consisting of an icosahedral capsid with a lipid-containing envelope. Exposure to the virus at mucosal surfaces or abraded skin permits entry of the virus into the body and initiation of replication in epidermal and dermal cells, resulting in the characteristic lesion of a thin-walled vesicle on an inflammatory base. Multinucleated cells (detectable on a Tzanck’s test) form, leading to ballooning degeneration, marked edema, and characteristic intranuclear inclusions (Cowdry type A inclusion bodies). The virus or nucleocapsid is transported by retrograde movement to nerve-cell bodies in sensory ganglia. After further replication, the virus spreads to other mucosal skin surfaces through centrifugal migration by way of peripheral sensory nerves. A larger affected surface area and a high frequency of new lesions distant from the initial crop of lesions is characteristic of primary HSV. The virus spreads from cell to cell as it replicates, resulting in cell destruction. However, scarring caused by HSV is uncommon.

HSV has two unique biological properties that influence human disease: (1) the capacity to invade and replicate in the central nervous system (CNS) and (2) the capacity to establish latent infection. Latency has been demonstrated in trigeminal, sacral, and vagal ganglia. Reactivation of latent virus results in transport of viral genomes to the body surface. Development of clinically apparent lesions most likely depends on the amount of virus present, the nature of the virus, virus-cell interactions, and the rapidity of the host’s immune response in clearing the virus. Latency-associated nuclear transcripts have been identified.

EPIDEMIOLOGY

Descriptions of herpes labialis, a type of herpes simplex, date back to the time of Hippocrates. HSV is found worldwide, and humans are the only natural reservoir for its transmission to other humans. Investigations conducted in the 1940s and 1950s found that over 90% of all populations studied developed antibodies to HSV by the fourth decade of life. More recent studies, however, have found that age-specific prevalence rates of infection with HSV type 1 are decreasing in developed countries. The presence of antibodies to HSV type 2 correlates with past sexual activity. Several factors increase the risk for acquiring HSV type 2, namely female sex, divorced marital status, African American ethnicity, urban residence, male-with-male sexual activity, and commercial sex work.

Contact with active ulcerative lesions or with asymptotically excreting patients can result in transmission

Table 1. Human Herpesviruses

| HHV-1 (herpes simplex virus, type 1) |
| HHV-2 (herpes simplex virus, type 2) |
| HHV-3 (varicella-zoster virus) |
| HHV-4 (Epstein-Barr virus) |
| HHV-5 (cytomegalovirus) |
| HHV-6 |
| HHV-7 |
| HHV-8 (Kaposi’s sarcoma-associated herpesvirus) |

HHV = human herpesvirus.
of HSV. Asymptomatic salivary excretion of HSV type 1 has been reported in 2% to 9% of adults and 5% to 8% of children. HSV type 2 has been isolated from the genital tract of 0.3% to 5.4% of men and 1.6% to 8% of women attending clinics for sexually transmitted diseases. The titer of HSV in cultures from lesions is 100 to 1000 times higher than in cultures from asymptomatic excretion. Whether prior infection with HSV type 1 decreases risk of infection with HSV type 2 is unknown, but the finding that the increased frequency of genital herpes in western industrialized countries coincides with increasing numbers of seronegative persons entering their sexually active years suggests that antibodies to HSV type 1 might offer some protection against acquisition of HSV type 2.

**CLINICAL TYPES**

**Oral-Facial HSV Infection**

Oral-facial HSV infection is usually asymptomatic. Although 60% to 80% of the adult US population have antibodies to HSV type 1, recurrent infections of the lips (known as herpes labialis) or perioral area occur in 20% to 40% of the population. The incubation period is 2 to 12 days, and precipitating factors include sunlight, fever, local trauma, trigeminal (V) nerve manipulation, menstruation, and emotional stress. Although oral-facial HSV infection is usually asymptomatic, pharyngitis and gingivostomatitis can occur with primary infection, most often in children and young adults; HSV was isolated from 11% of college students admitted to an infirmary with pharyngitis. Fetid breath and fever are common, and toxicity can persist for many days. The duration of the illness is typically 2 to 3 weeks. Lesions can involve the hard and soft palates, gingiva, tongue, lip, and facial area. Commonly, exudative or ulcerative lesions of the posterior pharynx or tonsillar pillars are present.

Reactivation of HSV latent in the trigeminal ganglia results in either asymptomatic excretion of the virus in the saliva or development of ulcerations. Recurrence typically occurs at the vermilion border of the outer lower lip, rarely involving the mouth, nose, chin, or cheek. Reactivation typically is heralded by several (on average, 6) hours of prodromal symptoms consisting of burning, itching, tingling, or pain.

Complications can occur in immunosuppressed patients in whom extension of infection into mucosal and deep cutaneous layers sometimes causes signs and symptoms clinically similar to those of chemotherapy-associated mucositis. Additionally, patients with atopic eczema also can acquire a severe oral-facial HSV infection, referred to as eczema herpeticum, which can rapidly involve extensive areas of skin and occasionally disseminate. Finally, the clinical cutaneous syndrome acquired by inoculation of HSV from oral-facial infection to the skin of the chest and back of wrestlers is known as herpes gladiatorum.

**Genital HSV Infection**

Primary genital HSV infection (usually, type 2) is characterized by fever, headache, malaise, myalgias, pain, itching, dysuria, vaginal and urethral discharge, and tender inguinal adenopathy. Bilaterally distributed lesions of the external genitalia, usually widely spaced, occur on the penile glans and shaft in men and on the vulva, perineum, buttocks, cervix, and vagina in women. The incubation period of this infection is 2 to 7 days. Although vesicular lesions can persist for several days in men, in women, lesions rapidly ulcerate and become covered with a grayish-white exudate. Healing takes approximately 3 weeks in cases of primary infections and 8 to 10 days in cases involving recurrences. Urinary retention syndrome occurs in 10% to 15% of women with primary genital HSV infection, and as many as 25% of all persons with primary genital HSV infection develop aseptic meningitis.

HSV has been isolated from the cervix of 1.6% to 8% of women attending sexually transmitted disease clinics and of 0.25% to 1.5% of women attending private gynecology clinics. Asymptomatic shedding is highest during the first year after genital HSV infection. Transmission of genital HSV infection between discordant (ie, 1 infected, 1 uninfected) monogamous sexual partners will occur at a rate of 10% to 15% annually, if no barrier precautions are used.

The frequency of clinical recurrence is as high as 60%. Recurrence depends on factors including sex (higher in men than in women), HSV type (higher in type 2 than type 1), and presence and titer of neutralizing antibodies; the severity of the primary infection also affects the likelihood of recurrence. Episodes of reactivation generally occur 2 to 9 times per year. Recurrences are more severe and involve a longer period of viral shedding in women than in men. Involvement of the cervix and urethra occurs in more than 80% of women with recurrent HSV infection. Less frequent systemic symptoms and faster healing times are seen in patients with recurrence who have had prior HSV type-1 infection. The clinical course of infection with primary genital HSV types 1 and 2 is similar, but recurrence rates differ. Over 80% of patients with a first episode of genital HSV type-2 infection have at least 1 recurrence within 12 months (median number of annual episodes, 4), compared with only 55% of those infected with HSV type 1.

A clear mucoid discharge and dysuria are characteristic of the urethritis associated with genital HSV infection.
Occasionally, upper genital tract disease with HSV endometritis and salpingitis occurs. HSV proctitis is typically seen in gay men and heterosexual women who engage in receptive anorectal intercourse. Anorectal pain, anorectal discharge, tenesmus, and constipation are the usual pre-receptive anorectal intercourse. Anorectal pain, anorectal seen in gay men and heterosexual women who engage in HSV. Acute necrotizing retinitis is an uncommon, with AIDS, usually as a manifestation of disseminated
metritis and salpingitis occurs. HSV proctitis is typically
complete loss of vision in the involved eye.

Central and Peripheral Nervous System Infections

HSV encephalitis. HSV encephalitis (HSE) is the most commonly reported viral infection of the CNS in the United States, accounting for 10% to 20% of cases. HSE occurs throughout the year. Although more than 95% of HSV infection occurs in adults, there is a biphasic age distribution of HSE, with the disease peaking between age 5 and 30 years and again after age 50 years.

In children and young adults, primary HSV can result in encephalitis; presumably, exogenously acquired virus enters the CNS by neurotropic spread via the olfactory bulb. Most adults with HSE have past clinical or serologic evidence of mucocutaneous HSV type-1 infection, and their present CNS infection might result from reactivation with another strain, from reactivation of latent trigeminal or autonomic nerve root infection, or from reactivation of latent CNS infection. HSE is characterized by acute onset of fever, focal neurologic (especially temporal lobe) symptoms, behavioral changes, speech difficulties, and olfactory hallucinations.

CSF findings can be minimal, especially early in HSE, but generally include moderate pleocytosis with mononuclear and polymorphonuclear cells, an increased erythrocyte count, an elevated protein level, and a normal glucose level. An increased HSV antibody level in serum and CSF occurs in most cases but is usually not present until 10 days after onset and so is not useful for acute diagnosis of HSE. Brain biopsy is considered definitive; CSF polymerase chain reaction (PCR) is both sensitive and specific and is now considered the diagnostic test of first choice. Magnetic resonance imaging or computed tomography can show edema, hemorrhage, necrosis, or a midline shift. Electroencephalography can demonstrate spike and slow wave activity localized to the temporal lobe; a burst suppression pattern is characteristic.

Untreated, HSE has a rapidly deteriorating course over several days, progressing to coma and death in 60% to 80% of cases. Intravenous administration of acyclovir (ACV) can reduce mortality and morbidity if started early, but a high index of suspicion of the disease is required for early treatment.

HSV meningitis. HSV meningitis is an acute, self-limited disease usually seen in association with primary genital HSV. Lymphocytic pleocytosis is detected in cerebrospinal fluid. Sequelae are rare. Currently, it is not known whether antiviral chemotherapy shortens the course of the disease.

Herpetic sacral radiculomyelitis. Autonomic nervous system dysfunction, especially of the sacral region, has
been reported in association with HSV (and VZV) infection. Herpetic sacral radiculomyelitis is characterized by numbness, tingling of the buttock or perineal areas, urinary retention, constipation, pleocytosis of the CSF, and impotence (in men). Symptoms resolve slowly over days to weeks; occasionally, hypesthesia or weakness of the lower extremities can persist for months.

**Other neurologic manifestations of HSV infection.** Transverse myelitis, manifested by rapidly progressive symmetrical paralysis of the lower extremities, and Guillain-Barré syndrome are rare neurologic manifestations of HSV infection.¹

**Visceral Disease**

Deep organ involvement in cases of HSV infection usually results from viremia, and multiple organ involvement is common. Esophagitis can result from direct extension of HSV from lesions in the oropharynx into the esophagus or by reactivation of HSV and spread of virus to the esophageal mucosa by the vagus (X) nerve. Endoscopic biopsy is required for definitive diagnosis of HSV-related esophagitis. HSV also is an uncommon cause of hepatitis presenting with fever, abrupt elevations of serum bilirubin and transaminase levels, and leukopenia.

**Infections in Immunocompromised Hosts**

Dissemination occasionally can occur in immunocompromised or malnourished patients or in patients with burns. There are reports of primary HSV infection acquired in the third trimester of pregnancy that disseminates to involve multiple visceral sites, leading to necrotizing hepatitis (with or without thrombocytopenia), disseminated intravascular coagulopathy, and encephalitis (with a mortality exceeding 50%).¹ Renal, cardiac, and bone-marrow transplant recipients frequently excrete HSV type 1 in throat washings during the first few weeks after grafting. Often asymptomatic, the infection can evolve into tracheobronchitis, pneumonia, esophagitis, or hepatitis. Patients with hematologic and lymphoreticular neoplasms and children with congenital thymic disorders can develop severe, chronic, or progressive mucocutaneous HSV. HSV-infected persons who have skin disorders such as burn wounds, eczema, pemphigus, Darier’s disease, or Sézary syndrome might be unable to effectively localize their infections, resulting in widespread cutaneous involvement. Finally, severe HSV infections are a major feature of AIDS, and genital HSV infection is a risk factor for acquisition of HIV infection.

**Neonatal Herpes Simplex Virus Infection**

Perinatal HSV infection is the most common form of neonatal infection, accounting for 80% of cases.¹ Most cases involve HSV type 2 and result from intrapartum contact of the fetus with infected genital secretions during delivery. The risk is 10 times greater when the mother has primary as opposed to recurrent disease (30%–50%:< 3%); increased risk is associated with use of fetal scalp electrodes and with prolonged rupture of membranes.¹ Neonates have the highest frequency of visceral and CNS HSV infection, ranging from mild localized infection to fatal dissemination with sepsis. Neurologic signs often predominate; skin lesions can appear late in the course of the disease. Disseminated disease and brain involvement have a high mortality if not treated with ACV therapy. CNS disease causes significant morbidity even with ACV therapy. Skin, eye, and mouth disease without CNS involvement has a somewhat better prognosis.

Congenital (ie, in utero) infection is rare, usually occurring in neonates born to mothers who have primary HSV, and is confirmed by culture within first 48 hours of life. Affected infants can have jaundice, hepatosplenomegaly, bleeding diathesis, microcephaly, microphtalmia, seizures, temperature instability, chorioretinitis, and skin vesicles. Congenital disease, which is frequently fatal, is characterized by the triad of skin vesicles (or scarring), eye disease, and microcephaly or hydranencephaly.¹

Postnatal infection with HSV is usually acquired through contact with immediate family members who have symptomatic or asymptomatic oral-labial HSV type-1 infection or through nosocomial transmission.

**Associated Conditions**

Allergic cutaneous and mucous membrane disorders can accompany or follow acute HSV infection. Up to 75% of all cases of erythema multiforme are preceded by HSV infection;² HSV DNA and antigens often can be identified in skin biopsy specimens from erythema multiforme lesions,² and prophylactic systemic administration of ACV can prevent development of erythema multiforme. HSV also has been implicated in the pathogenesis of neurologic disorders of unknown etiology (including Bell’s palsy), atypical pain syndromes, ascending myelitis, trigeminal neuralgia, Mollaret’s recurrent aseptic meningitis, and focal lobar epilepsy.

**DIAGNOSIS**

The etiologic type of HSV often can be identified in 24 to 48 hours by isolation of the virus using tissue culture techniques; however, samples are typically held for 5 days before they are considered negative for HSV infection. Sensitivity is higher for samples from patients with vesicular lesions, primary infection, or an immunocompromised status. However, no laboratory...
detection methods might be useful with late ulcerative-stage lesions. Acute and convalescent serum can be useful in documenting seroconversion during primary HSV type-1 or type-2 infection. Immunofluorescent assays of specimens of the skin/vesicle base are rapid and approach the sensitivity of isolation techniques, except in cases of asymptomatic infection. Tzanck’s test—performed by scraping tissue from the base of the vesicle, fixing it with ethanol or methanol, and then staining it with a Giemsa or Wright’s preparation—can detect multinucleated giant cells characteristic of herpesviruses but does not distinguish between HSV and VZV. PCR used to detect infection of the CNS has a sensitivity of more than 95% and a specificity approaching 100%.5

**TREATMENT**

**Preventive Measures**

Prevention of infection is optimal and is directed at avoiding contact with lesions by using barriers such as gloves or condoms. Use of sunscreen can substantially reduce cases of ultraviolet light–induced recurrent herpes labialis. Counseling and education regarding transmission are important. Cesarean-section delivery is critical in prevention of perinatal infection if cervical infection is detected before membrane rupture.

**General Antiviral Therapy**

ACV is a synthetic acyclic purine nucleoside analogue. Viral thymidine kinase phosphorylates ACV to a monophosphate form, which is subsequently converted to ACV triphosphate by cellular enzymes. ACV is a potent inhibitor of HSV DNA polymerase and causes little cellular toxicity. Potential toxic effects, including neurotoxicity, seizures, disorientation, hallucinations, tremors, ataxia, and reversible renal dysfunction related to crystalluria, are seen primarily with high-dose intravenous therapy.6 Parenterally administered ACV (5–10 mg/kg body weight every 8 hours for 14 to 21 days) is the recommended therapy for CNS, visceral, or disseminated HSV virus infection.

ACV-resistant HSV primarily occurs in immunocompromised hosts and can be progressive, especially in patients with AIDS. The virus may have altered thymidine kinase and thus be unable to phosphorylate ACV, or it may be deficient in thymidine kinase. Intravenously administered foscarnet, which does not require phosphorylation for activity, is the treatment of choice for patients with ACV-resistant HSV, although intravenously administered cidofovir is an alternative. Topical regimens (eg, cidofovir 0.3%, trifluorothymidine 1%, foscarnet 1%) are considered investigational.

Valacyclovir for oral administration is the L-valyl ester of ACV and is more completely absorbed than is orally administered ACV. It is rapidly hydrolyzed to ACV, making it 3 to 5 times more bioavailable than is ACV. Its efficacy and safety for treatment of genital HSV is similar to those of ACV. The profile of adverse effects is similar to that of ACV but also can include thrombotic thrombocytopenia purpura or hemolytic uremic syndrome in severely immunocompromised patients treated with high doses (eg, 6 g/day). The recommended dose is 500 mg twice daily for 5 days (in cases of recurrent genital HSV) or 1000 mg twice daily for 10 days (in cases of primary HSV).9

Famciclovir is the orally administered prodrug of penciclovir, a guanosine analogue that has a mechanism of action similar to that of ACV. Famciclovir is well absorbed after oral administration (approximately 80% bioavailable) and is rapidly converted by deacetylation and oxidation to penciclovir, which is the active drug. Penciclovir is primarily renally excreted; dosage adjustment is required in cases of significant renal dysfunction. The antiviral spectrum and profile of adverse effects of famciclovir are similar to those of ACV. The recommended dosage of famciclovir is 125 mg twice daily for 5 days for recurrent infection or 250 mg twice daily for 5 to 10 days for primary infection.8,10 Penciclovir also is available as a topical therapy that will accelerate clinical healing of herpes labialis by approximately 1 day.

Finally, trifluorothymidine is used topically to treat HSV keratitis.

**Therapy for Oral-Facial HSV Infection**

ACV is effective in shortening the duration of symptoms and lesions of mucocutaneous oral-facial HSV infection in immunocompromised patients. Intravenous and oral administration of ACV prevents reactivation of HSV in seropositive immunocompromised patients who are undergoing induction chemotherapy for acute leukemia or who have undergone transplantation. Treatment is not recommended for immunocompetent persons who experience less frequent episodes of oral-facial HSV infection, because it has not been shown to affect pain or healing. However, one can consider using penciclovir cream, which is FDA-approved for herpes labialis and accelerates clinical healing by 1 day, or ACV 200 mg 5 times daily for 3 to 5 days, which reduces the time it takes crusts to resolve by 1 day; valacyclovir is currently under review for the latter indication. Some clinicians consider prophylactic treatment appropriate for herpes labialis–associated erythema multiforme, for periods of intense sun exposure or stress, for chemical or abrasive facial procedures, for selected health care
professionals, and for persons for whom professional appearance is critical.

**Therapy for Genital HSV Infection**

Orally administered ACV speeds the healing and resolution of symptoms of primary episodes of genital HSV type-1 and type-2 infections; however, its use does not influence the subsequent recurrence rate. Benefits of treating acute episodes of recurrent genital disease with orally administered ACV are moderate; it shortens the duration of viral shedding and the length of time to healing from 7 to 6 days, when initiated in the first 24 hours after onset of symptoms, but does not affect duration of symptoms and length of time to the next recurrence. Therefore, routine use for recurrent episodes is not recommended.

Antiviral treatment is useful for patients with severe recurrences or severe complications. An oral formulation of ACV is recommended for most uses, in a dose of 200 mg 5 times daily for 5 days or 400 mg twice daily for 5 days. Use of valacyclovir 500 mg twice daily for 5 days is more convenient and increases the frequency of aborted episodes of genital HSV infection from 21% to 28%, compared to ACV.9; famiciclovir 125 mg twice daily for 5 days is an alternative.

Suppressive therapy (ie, continual administration) also can be given (ACV 200 mg 3 to 4 times daily, or 400 mg twice daily, or the minimal dose required). Long-term daily suppressive therapy reduces the frequency of reactivation of the disease by 80% to 90% among patients with very frequent genital herpes.9 Daily ACV therapy reduces but might not suppress symptomatic/asymptomatic shedding of HSV type 2 in the genital tract. Treatment should be stopped annually to assess further need for therapy.4 Famciclovir and valacyclovir are alternatives for suppressive therapy. Latent virus remains susceptible to ACV. Cost comparison among available drugs (ie, ACV, famciclovir, valacyclovir) should be a factor when selecting a suppressive regimen, because the newer agents are significantly more costly than is ACV.

**FURTHER DISCUSSION OF CASE PATIENT 1**

- What is the most likely diagnosis for Case Patient 1?
- What is the most appropriate work-up and management?

The course of Patient 1’s illness appears consistent with aseptic meningitis secondary to primary genital HSV infection. Flexible sigmoidoscopy is performed, with findings of diffuse ulcerations on the posterior wall of the distal rectum that are consistent with HSV proctitis. A direct fluorescent antibody stain identifies HSV, confirmed by results of viral culture and by histologic findings of a rectal biopsy. ACV is administered intravenously, until clinical improvement is noted. The patient is counseled regarding primary HSV infection, methods of transmission, and risk for other sexually transmitted diseases. HIV testing is performed, with negative results; repeat testing in 6 months is recommended. She is discharged home to complete a 10-day course of ACV, taken orally. Results of PCR of a CSF specimen later come back as positive for HSV, type 2.

**VARICELLA-ZOSTER VIRUS**

**PATHOGENESIS**

VZV is a typical herpes-like particle measuring 150 to 200 nm in diameter, with a lipid envelope bearing glycoprotein spikes.11 The central region contains an icosahedral nucleocapsid, within which is the viral genome (double-stranded linear DNA of approximately 125,000 base pairs).12 The virus infects a host through the conjunctivae and/or mucosa of the upper respiratory tract.11 Over the next 2 to 3 days, it replicates in regional lymph nodes, and primary viremia occurs on days 4 to 6 after infection. The virus then replicates in the liver and spleen, with a secondary viremia occurring 10 to 14 days after initial infection. The secondary viremia coincides with the appearance of the vesicular rash characteristic of varicella (more commonly referred to as chickenpox).13

**VARICELLA**

**Epidemiology and Transmission**

Humans are the only known reservoir of VZV; primary infection nearly always results in varicella. Approximately 3 to 4 million cases of varicella occur each year in the United States, mostly (90%) in children age 1 to 14 years, and result in approximately 9300 hospitalizations and 100 deaths.11 Risk of death is greatest in infants, adults, and immunosuppressed persons.

VZV is highly communicable, with a secondary attack rate of more than 90% among household contacts.13 The incidence of infection peaks sharply in March, April, and May in temperate climates. The median incubation period is 14 days, with a range of 9 to 21 days; the shorter times are typical of immunosuppressed hosts.11 Asymptomatic viremia occurs 1 to 11 days before the appearance of a rash.11 Acquisition of the virus occurs by inhalation of infectious respiratory secretions or by direct contact with varicella or herpes zoster lesions. Patients are considered contagious from 2 days before the onset of rash until all lesions have crusted.11 Varicella occurs in children worldwide but, in
adults, occurs more frequently in persons residing in tropical regions.

**Natural History**

The first manifestation of varicella is usually a pruritic, vesicular rash occurring on the face, scalp, or trunk. Systemic symptoms such as fever, chills, myalgia, and arthralgia can occur before the onset of rash. Skin manifestations include maculopapules, vesicles, and scabs; lesions initially contain clear vesicular fluid but, over a short period of time, pustulate and scab. Classically described as appearing like dew drops on a rose-petal, varicella lesions of different stages are present simultaneously. Lesions appear over the face and trunk and spread centripetally; they are less commonly found on mucosal surfaces. The median number of lesions is 300; new lesion formation usually ceases by day 4 after first appearance of a rash, and most crustng occurs by day 6. These processes persist longer in immunocompromised patients. Differential diagnosis includes disseminated herpes zoster, disseminated herpes simplex, eczema vaccinatum, generalized vaccinia, hand-foot-and-mouth disease, atypical measles, rickettsialpox, and smallpox.

An episode of varicella infection generally confers lifelong protection against the disease, but subclinical reinfection has been documented. Symptomatic reinfection can occur in immunosuppressed patients, vaccine recipients, and (possibly) persons whose initial infections were mild or subclinical. Latency results in lifelong infection of the sensory nerve ganglia and can occur either via contiguous spread of virus from infected skin cells to sensory nerve endings (with subsequent ascent to ganglia) or hematogenously during the viremic phase.

**Complications**

Varicella generally follows a benign course in children. The most common cutaneous complication in children younger than age 5 is bacterial superinfection of skin with staphylococci or group A β-hemolytic streptococci. However, purpura fulminans, necrotizing fasciitis secondary to group A β-hemolytic streptococcal superinfection, and hemorrhagic or bullous varicella also can occur.

Possible neurologic complications include encephalitis, transient focal neurologic changes, aseptic meningitis, transverse myelitis, and Guillain-Barré syndrome. There are two forms of encephalitis that occur. The first involves cerebellar ataxia in children and typically presents with nystagmus, ataxic gait, headache, nausea, vomiting, and nuchal rigidity. This disease usually follows a self-limited course, with full recovery in 2 to 4 weeks. Conversely, the second type of encephalitis involves adults and presents with altered sensorium, seizures, and focal neurologic signs; the mortality rate is as high as 35%.

Encephalitis must be distinguished from Reye’s syndrome, which occurs most often in children age 5 to 14 years. Reye’s syndrome is an acute noninflammatory encephalopathy associated with hepatitis or fatty metamorphosis of the liver; it has a case-fatality rate of 20%. In children in the late stages of varicella, vomiting, restlessness, irritability, progressively decreased level of consciousness, and cerebral edema are typical of Reye’s syndrome. It is associated with elevated serum ammonia and transaminase levels, bleeding diathesis, and hyperglycemia. Of the 250 to 550 cases of Reye’s syndrome reported in the United States each year, 20% to 30% are preceded by varicella, with the remainder following episodes of respiratory infection (often influenza) or gastroenteritis. Use of salicylates increases the risk of Reye’s syndrome and, therefore, should be avoided in management of varicella.

Pneumonia is the commonest serious complication of varicella in adults, occurring in 1/400 cases; pregnant women are at highest risk. This complication most often develops 1 to 6 days after onset of rash. Physical findings can be minimal, with patchy or diffuse bilateral nodular infiltrates with prominent peribronchial distribution on chest radiographs. Up to 10% of fetuses acquire intrauterine infection with VZV, as evidenced by subsequent cases of congenital varicella syndrome or neonatal varicella. Congenital varicella syndrome is associated with first-trimester varicella in the mother and is characterized by limb hypoplasia, cutaneous scars, cortical atrophy, chorioretinitis, and other anomalies. Neonatal varicella is associated with frequent visceral complications, particularly pneumonia, and has a case-fatality rate of up to 31%. The risk is greatest when evidence of maternal infection appears 5 days or fewer before or up to 2 days after delivery, because it is then too late for the fetus/neonate to receive transplacental antibodies and because the immune system is still immature at that point.

Immunosuppressed patients with varicella have a 15% to 18% mortality rate. The risk is greatest for patients with impaired cell-mediated immune responses, because they are more likely to have extensive skin lesions, pneumonia, hepatitis, or encephalitis.

Notably, the incidence of VZV infection is 30% in bone-marrow transplant recipients during the first year after transplantation if they do not receive ACV prophylaxis. Graft-versus-host disease increases the probability of visceral dissemination. HIV-infected children can develop recurrent or progressive varicella.
varicella also can cause hepatitis, thrombocytopenia, arthritis, uveitis, conjunctivitis, carditis, inappropriate antidiuretic hormone syndrome, nephritis, and orchitis.

HERPES ZOSTER

Epidemiology

Herpes zoster, which results from reactivation of latent VZV in sensory nerve ganglia, occurs sporadically during the lifetime of 10% to 20% of all persons.\(^{11}\) Incidence correlates with increasing age and is believed to reflect the gradual senescence of cell-mediated immune containment of the virus.\(^{11,14}\)

Approximately 50% of persons age 85 years and older have had herpes zoster.\(^{11}\) Approximately 4% of persons with herpes zoster will later have a second episode.\(^{12}\) Exogenous acquisition is unlikely. In children, herpes zoster occurs within the first 2 years of life in infants born to women who had varicella during pregnancy, most likely reflecting in utero varicella with early reactivation.

Natural History

A prodrome of fever, malaise, headache, and dysesthesias often occurs 1 to 4 days before development of cutaneous lesions. Usually 1 but occasionally 3 dermatomes are affected in cases of herpes zoster; affected dermatomes are generally unilateral, with thoracic and lumbar areas most commonly involved. The characteristic rash consists of grouped vesicles on an erythematous base, in contrast to the more discrete and widely scattered lesions typical of varicella.\(^{11}\) Lesions become pustular and, occasionally, hemorrhagic by day 3 to 4 after onset, then collapse to form crusts by day 7 to 10 when they no longer contain viable virus.\(^{11}\) The lesions usually resolve in 2 to 3 weeks but, because of a greater propensity for dermal involvement in herpes zoster than in varicella, scarring is common.\(^{11}\) Zosteriform HSV infection should be considered in patients with maxillary (V\(_2\)) or sacral nerve root involvement or with histories of previous vesicular eruptions in the same distribution.\(^{11}\)

Complications

Postherpetic neuralgia. Postherpetic neuralgia, or pain that persists after resolution of the skin lesions in herpes zoster, increases in prevalence and duration with age, occurring in 25% to 50% of patients older than age 50.\(^{4}\) This pain resolves within 2 months in 50% of all patients with herpes zoster and within 1 year in 70% to 80% of patients.\(^{11}\)

Cranial nerve involvement. Ramsay-Hunt syndrome accounts for more than half of cephalic motor neuropathies.\(^{11}\) Characterized by geniculate ganglion involvement, this syndrome presents with cutaneous lesions of the external auditory canal. Involvement of the ipsilateral facial (V\(_7\)) and auditory (V\(_8\)) nerves results in hearing deficits, vertigo, loss of taste in the anterior two thirds of the tongue, and ipsilateral facial palsy. Involvement of the maxillary or mandibular branch of the trigeminal (V) nerve results in intraoral involvement, with possible lesions of the palate, tonsillar fossa, floor of the mouth, and tongue.

CNS involvement. Involvement of the CNS in cases of herpes zoster is more common than is recognized clinically. Results of lumbar puncture in patients with herpes zoster who have CNS involvement often show pleocytosis. Many neurologic complications, including encephalitis, are thought to be immunologically mediated. Myelitis is an unusual complication.

Ophthalmic involvement. Herpes zoster can involve the eyelids when the first or second branch of the trigeminal (V) nerve is affected, but keratitis heralds a sight-threatening condition referred to as herpes zoster ophthalmicus. Although lesions at the tip of the nose possibly presage corneal lesions, the absence of such skin lesions does not guarantee corneal sparing. Keratitis can be followed by severe iridocyclitis, secondary glaucoma, or neuropsyarteral keratitis, and ophthalmologic consultation is required.\(^{15}\) Cerebral angiitis can follow herpes zoster ophthalmicus.

Reactivation of VZV within the eye has been suggested as a cause of acute retinal necrosis, which is characterized by retinal arteritis, necrotizing retinitis, vitreitis, and retinal detachment.\(^{11}\) Approximately 64% of patients with acute retinal necrosis have a poor outcome, becoming legally blind.\(^{11}\)

Cutaneous dissemination. When herpes zoster occurs in immunosuppressed patients, it is more likely not only to be severe and prolonged but to disseminate. Cutaneous dissemination of herpes zoster indicates the presence of viremia and can be defined, arbitrarily, as more than 20 lesions outside the primary and adjacent dermatomes. Dissemination typically appears 4 to 11 days after onset of localized herpes zoster.\(^{11}\) Cutaneous dissemination is not associated with increased morbidity but is likely to be accompanied by visceral, ocular, or neurologic infection.

Chronic herpes zoster. Chronic cutaneous herpes zoster is the term used to describe the condition of patients who have sustained periods of new lesion formation without healing of their existing lesions. Chronic persistent infection of the CNS with progressive encephalopathy has also been described, particularly in patients with AIDS.\(^{11}\) Herpes zoster is a frequent infection in HIV-infected persons. Although cutaneous dissemination is infrequent in HIV-infected persons, complications such
as VZV retinitis, acute retinal necrosis, progressive outer retinal necrosis, and chronic progressive encephalitis can occur. Atypical, scattered, verrucous or eschar-like lesions can be seen in immunocompromised patients with chronic cutaneous herpes zoster and might result from ACV-resistant virus.

**DIAGNOSIS OF VARICELLA-ZOSTER VIRUS INFECTION**

Diagnosis of VZV infection usually is based on patient history and examination. Results of a Tzanck’s test will be positive for herpesvirus infection in 50% to 60% of patients with varicella or herpes zoster, but—as mentioned previously—the test does not distinguish HSV from VZV. Direct fluorescent antibody staining of smears obtained from scrapings of fresh lesions is a more rapid and sensitive test than is viral culture. PCR has been used to detect VZV DNA in CSF of patients with neurologic disease and in biopsy specimens of verrucous lesions of patients with AIDS, when cultures from the same patients are often negative for infection. Serology of acute and convalescent serum is also an available technique but provides only a retrospective diagnosis.

**TREATMENT OF VARICELLA-ZOSTER VIRUS INFECTION**

Supportive and symptomatic treatment of varicella in children consists of administering nonaspirin antipyretics, analgesics, and antipruritics. Appropriate hygiene includes gentle cleansing and drying of lesions, astringent soaks, and trimming of fingernails. Aluminum acetate topical solution (ie, Burow’s solution) can be soothing and cleansing. Antibiotics are indicated if bacterial superinfection occurs.

ACV is approved in the United States for treatment of varicella and herpes zoster. However, treatment of immunocompetent children with varicella remains controversial. Orally administered ACV shortens duration of lesion formation by approximately 1 day, reduces the total number of new lesions by approximately 25%, and improves constitutional symptoms in a third of patients who receive it. Treatment of high-risk patients is recommended within 24 hours of onset of disease (20 mg/kg 4 times daily for 5 days for children; 800 mg 5 times daily for adults). Most physicians do treat older adolescents and adults with varicella. Postexposure prophylaxis with ACV is not recommended.

Oral antiviral therapy in patients with herpes zoster accelerates cutaneous healing and reduces the severity of acute neuritis but has only a marginal effect on postherpetic neuralgia. Famciclovir (500 mg 3–5 times daily for 7 days, administered orally) and valacyclovir (1000 mg 3 times daily for 7 days, administered orally) are used to treat herpes zoster within 3 days of onset of rash and have comparable efficacy. Antiviral therapy is most effective if used early (ie, within 24 to 48 hours of onset of rash). Intravenously administered ACV is recommended for immunocompromised patients with severe disease; this therapy accelerates healing of localized disease and decreases visceral complications. Administration of corticosteroids might be useful for decreasing both the severity of acute neuritis and the frequency of postherpetic neuralgia. Improved quality of life measurements resulted from use of a tapered dose of prednisone (30 mg twice daily, tapered over 21 days) in adults older than age 50 who were screened to exclude patients at high risk for corticosteroid complications. Controlled studies of corticosteroid use as an adjunct to antiviral therapy provide conflicting results.

**PROPHYLAXIS**

**Varicella-Zoster Immunoglobulin**

Varicella-zoster immunoglobulin should be administered to immunodeficient patients who have no or an unknown history of varicella (unless titers can be measured expeditiously), are not vaccinated, and have had significant exposure (eg, close contact for more than 1 hour with someone who has VZV infection). Administration of varicella-zoster immunoglobulin is indicated for pregnant women known to be seronegative who have had a significant exposure and for neonates whose mothers had onset of varicella 5 days or fewer before delivery or up to 48 hours postpartum to prevent neonatal varicella.

**VZV Vaccine**

A VZV vaccine was licensed in the United States in March of 1995; it was the first live herpesvirus vaccine to be licensed by the Food and Drug Administration (FDA). Although VZV vaccine has been shown to protect children with leukemia against severe varicella with an efficacy approaching 100% and to lower the rate of herpes zoster occurrence from 15% to 3%, it is FDA-approved only for use in immunocompetent individuals. It has a 95% 7-year efficacy rate, and 95% of those who receive it develop cellular and humoral immune responses that persist for 6 to 10 years postvaccination. It is anticipated that most vaccine recipients will have lifelong immunity.

The most common adverse effects of VZV vaccine are mild tenderness and redness at injection site, mild varicelliform rash (generalized maculopapular rash with < 10 lesions in 4% of recipients; rash at injection site with 2–4 lesions in 4% of recipients), and fever. A higher incidence of rash occurs in immunocompromised patients. The likelihood of transmission of vaccine virus to healthy contacts is low but becomes higher.
if either recipient or contact is immunocompromised. Vaccine failure results in a mild varicella-like syndrome, involving fewer than 50 lesions and no fever, after significant exposure to wild-type varicella.

Routine use of the vaccine has been calculated to be cost-effective from a societal perspective, in light of the work-loss and medical costs associated with varicella. A 0.5-mL dose is recommended for persons older than 12 months who have not had varicella; 2 doses are recommended for persons older than 13 years. The vaccine is contraindicated in women who are pregnant or plan to become pregnant and in persons on high-dose (ie, ≥ 20 mg daily) corticosteroid therapy. Persons receiving VZV vaccine should avoid salicylates for 1 month postvaccination, unless the drugs are being used therapeutically to treat rheumatoid arthritis.13,17,18

FURTHER DISCUSSION OF CASE PATIENT 2

• How can the diagnosis be confirmed in Case Patient 2?
• What is the appropriate management for mother and infant?

Based on results of a Tzanck’s test, the presence of herpesvirus infection is established in Patient 2. Direct fluorescent antibody staining of a specimen obtained on skin lesion scraping is then performed and identifies VZV; a subsequent viral culture provides confirmation of the suspected diagnosis of varicella. Because varicella is not endemic in her native Puerto Rico, a tropical region, most adults there remain susceptible to disease when traveling or moving to areas of endemicity, such as the United States.

Results of Patient 2’s work-up do not suggest a complicated course, because no evidence of hepatitis or pneumonia is detected. However, initial therapy with intravenous ACV is deemed appropriate in this peripartum woman while she is hospitalized and her clinical course can be easily followed. Oral therapy can be considered if she remains clinically stable. The neonate should receive varicella-zoster immunoglobulin, as is recommended for infants born to mothers with onset of varicella 5 days or fewer before delivery and up to 48 hours postpartum, to prevent neonatal varicella.

REFERENCES