87 - 198 Varicella-Zoster Virus Infections

198 Varicella-Zoster Virus Infections

effective in the developing world, their clinical and virologic ben efits, especially in reducing the frequency of genital lesions among patients in Africa, seem reduced from those in European and U.S. populations. The mechanism of this phenomenon is uncertain. Acyclovir therapy does not reduce the rate of HIV acquisition; however, HIV load among MSM in the United States decreased by 1.3 log10 in contrast to 0.9 log10 among Peruvian MSM and 0.5 log10 among African women. Curiously, the anti-HIV drug tenofovir reduces HSV-2 acquisition among women in Africa, although it has no demonstrable clinical benefit or antiviral effects among persons with established HSV-2 infection in studies in the United States. The reasons for these disparate results are unclear.

■ ■PREVENTION Efforts to control HSV disease on a population basis through suppres sive antiviral therapy and/or educational programs have been limited. Barrier forms of contraception (especially condoms) decrease the like lihood of transmission of HSV infection, particularly during periods of asymptomatic viral excretion. When lesions are present, HSV infection may be transmitted by skin-to-skin contact despite the use of a condom. Nevertheless, the available data suggest that consistent condom use is an effective means of reducing the risk of genital HSV-2 transmission. Chronic daily antiviral therapy with valacyclovir can also be partially effective in reducing acquisition of HSV-2, especially among suscep tible women. There are no comparative efficacy studies of valacyclovir versus condom use. Most authorities suggest both approaches. The need for a vaccine to prevent acquisition of HSV infection is great, especially in light of the role HSV-2 plays in enhancing the acquisition and transmission of HIV-1. PART 5 Infectious Diseases A substantial portion of neonatal HSV cases could be prevented by reducing the acquisition of HSV by women in the third trimester of pregnancy. Neonatal HSV infection can result from either the acquisi tion of maternal infection near term or the reactivation of infection at delivery in the already-infected mother. Women without known genital herpes should be counseled to abstain from vaginal intercourse during the third trimester with partners known to have or suspected of hav ing genital herpes. Some authorities have recommended that antiviral therapy with acyclovir or valacyclovir be given to HSV-2-infected women in late pregnancy as a means of reducing reactivation of HSV-2 at term. Data are not available to support the efficacy of this approach, and the high treatment-to-prevention ratio makes this a difficult if not dubious public health strategy, even though it can reduce the frequency of HSV-associated cesarean delivery. ■ ■FURTHER READING Centers for Disease Control and Prevention: 2021 Sexually transmitted diseases treatment guidelines. Available at https://www

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Varicella-Zoster Virus

Infections ■ ■DEFINITION Varicella-zoster virus (VZV) causes two distinct clinical syndromes: varicella (chickenpox) and herpes zoster (shingles). Chickenpox, a ubiquitous and extremely contagious infection, is usually a benign ill ness of childhood characterized by an exanthematous vesicular rash. With reactivation of latent VZV (which is most common after the sixth decade of life), herpes zoster presents as a dermatomal vesicular rash and is usually associated with severe pain. ■ ■HISTORY AND ETIOLOGY Early in the twentieth century, similarities in the histopathologic fea tures of skin lesions resulting from varicella and herpes zoster were described. Viral isolates from patients with each of these diseases produced similar pathology in tissue culture—specifically, the appear ance of eosinophilic intranuclear inclusions and multinucleated giant cells. These results suggested that the viruses were biologically similar. Restriction endonuclease analyses of viral DNA from a patient with chickenpox who subsequently developed herpes zoster verified the molecular identity of the two viruses responsible for these different clinical presentations. VZV is a member of the family Herpesviridae, sharing with other members such structural characteristics as a lipid envelope surround ing a nucleocapsid with icosahedral symmetry, a total diameter of ~180–200 nm, and centrally located double-stranded DNA that is ~125,000 bp in length. ■ ■PATHOGENESIS AND PATHOLOGY Primary Infection Transmission occurs readily by the respiratory route; the subsequent localized replication of the virus at an undefined site (presumably the nasopharynx) leads to seeding of the lymphatic/ reticuloendothelial system and ultimately to the development of viremia. Viremia in patients with chickenpox manifests as a diffuse and scattered skin lesions that can be confirmed by the recovery of VZV from the blood (rarely) or routinely by the detection of viral DNA in either blood or lesions by polymerase chain reaction (PCR). Vesicles involve the corium or dermis, with degenerative changes characterized by balloon ing, the presence of multinucleated giant cells, and eosinophilic intranu clear inclusions. Infection may involve localized blood vessels of the skin, resulting in necrosis and epidermal hemorrhage. With the evolution of disease, the vesicular fluid becomes cloudy because of the recruitment of polymorphonuclear leukocytes and the presence of degenerated cells and fibrin. Ultimately, the vesicles either rupture and release their fluid (which includes infectious virus) or are gradually reabsorbed. Recurrent Infection The mechanism of reactivation of VZV that results in herpes zoster is unknown. The virus infects dorsal root ganglia during chickenpox, where it remains latent until reactivated. Histopathologic examination of representative dorsal root ganglia dur ing active herpes zoster demonstrates hemorrhage, edema, and lym phocytic infiltration. Latent virus has been detected in sensory

(dorsal, cranial, and enteric) ganglia. Active replication of VZV in other organs, such as the lung or the brain, can occur during either chickenpox or herpes zoster but is uncommon in the immunocompetent host. Pulmonary involvement is characterized by interstitial pneumonitis, multinucleated giant cell formation, intranuclear inclusions, and pulmonary hemorrhage. Central nervous system (CNS) infection leads to histopathologic evidence of perivascular cuffing similar to that encountered in measles and other viral encephalitides. Focal hemorrhagic necrosis of the brain, characteristic of herpes simplex virus (HSV) encephalitis, develops infrequently in VZV infection.

■ ■EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS Chickenpox Humans are the only known reservoir for VZV. Chickenpox is highly contagious, with an attack rate of at least 90% among susceptible (seronegative) individuals. Persons of both sexes and all races are infected equally. The virus is endemic in the popula tion at large; however, it becomes epidemic among susceptible indi viduals during seasonal peaks—namely, late winter and early spring in the temperate zone. For the most part, our knowledge of the disease's natural history and incidence predates the licensure of the chicken pox vaccine in 1995. Historically, children 5–9 years old were most commonly affected, accounting for 50% of all cases. Most other cases involved children 1–4 and 10–14 years old. Approximately 10% of the population of the United States over the age of 15 was susceptible to infection. VZV vaccination during the second year of life and followed by a preschool booster has dramatically changed the epidemiology of infection, causing a significant decrease in the annualized incidence of chickenpox, as noted below. The incubation period of chickenpox ranges from 10 to 21 days but is usually 14–17 days. Secondary attack rates in susceptible siblings within a household are 70–90%. Patients are infectious ~48 h before the onset of the vesicular rash, during the period of vesicle formation (which generally lasts 4–5 days), and until all vesicles are crusted. Clinically, chickenpox presents as a rash, low-grade fever, and malaise, although a few patients develop a prodrome 1–2 days before onset of the exanthem. In the immunocompetent patient, chickenpox is usually a benign illness associated with lassitude and with body temperatures of 37.8°–39.4°C (100°–103°F) of 3–5 days' duration. The skin lesions—the hallmark of the infection—include maculopapules, vesicles, and scabs in various stages of evolution (Fig. 198-1; see also Fig. A1-30). These lesions, which evolve from maculopapules to vesi cles over hours to days, appear on the trunk and face and rapidly spread to involve other areas of the body. Most are small and have an ery thematous base with a diameter of 5–10 mm. Successive crops appear over a 2- to 4-day period. Lesions can also be found on the mucosa of the pharynx and/or the vagina. Their severity varies from one person to another. Some individuals have very few lesions, while others have as many as 2000. Younger children tend to have fewer vesicles than older individuals. Within families, secondary and tertiary cases are associ ated with a larger number of vesicles than the first family case. Immu nocompromised patients—both children and adults, particularly those FIGURE 198-1 Varicella lesions at various stages of evolution: vesicles on an erythematous base, umbilical vesicles, and crusts.

with leukemia—have lesions (often with a hemorrhagic base) that are more numerous and take longer to heal than those of immunocompe tent individuals. Immunocompromised individuals are also at greater risk for visceral complications, which occur in 30–50% of cases and are fatal 15% of the time in the absence of antiviral therapy.

The most common infectious complication of varicella is secondary bacterial superinfection of the skin, which is usually caused by Strep tococcus pyogenes or Staphylococcus aureus, including strains that are methicillin-resistant. Skin infection results from excoriation of lesions after scratching. Gram stain of skin lesions may help clarify the etiology of unusually erythematous and pustulated lesions. The most common extracutaneous site of involvement in children is the CNS. The syndrome of acute cerebellar ataxia and meningeal inflammation generally appears ~21 days after onset of the rash and rarely develops in the pre-eruptive phase. The cerebrospinal fluid (CSF) contains lymphocytes and elevated levels of protein. CNS involvement is a benign complication of VZV infection in immunocompetent children and generally does not require hospitalization. Aseptic meningitis, encephalitis, transverse myelitis, and Guillain-Barré syn drome can also occur. Encephalitis is reported in 0.1–0.2% of children with chickenpox. Reye syndrome, an historical complication for the most part, can occur in children concomitantly treated with aspirin; therefore, aspirin is no longer utilized. Other than supportive care, no specific therapy (e.g., although acyclovir is administered by some physicians) has proved efficacious for patients with CNS involvement. Varicella pneumonia, the most serious complication following chickenpox, develops more often in adults (up to 20% of cases) than in children and is particularly severe in pregnant women. Pneumonia due to VZV usually has its onset 3–5 days into the illness and is associ ated with tachypnea, cough, dyspnea, and fever. Cyanosis, hypoxemia, pleuritic chest pain, and hemoptysis are frequently noted. Roentgeno graphic evidence of disease consists of nodular infiltrates and intersti tial pneumonitis. Resolution of pneumonitis parallels improvement of the skin rash; however, patients may have persistent fever and compro mised pulmonary function for weeks. CHAPTER 198 Varicella-Zoster Virus Infections Other complications of chickenpox include myocarditis, corneal lesions, nephritis, arthritis, bleeding diatheses, acute glomerulonephri tis, and hepatitis. Hepatic involvement, distinct from Reye syndrome and usually asymptomatic, is common in chickenpox and is generally characterized by elevated levels of liver enzymes, particularly aspartate and alanine aminotransferases. Perinatal varicella is associated with mortality rates as high as 30% when maternal disease develops within 5 days before delivery or within 48 h thereafter. Illness in this setting is unusually severe because the newborn does not receive protective transplacental antibodies and has an immature immune system. Congenital varicella, with clinical mani festations of limb hypoplasia, cicatricial skin lesions, and microcephaly at birth, is extremely uncommon. Herpes Zoster Herpes zoster (shingles) is a sporadic disease that results from reactivation of latent VZV from dorsal root ganglia. Most patients with shingles have no history of recent exposure to other individuals with VZV infection. Herpes zoster occurs at all ages, but its incidence is highest (5–10 cases per 1000 persons) among individu als in the sixth decade of life and beyond. Data suggest that at least 1.2 million cases occur annually in the United States. Vaccination has, likely, decreased the incidence of shingles. Recurrent herpes zoster is exceedingly rare except in immunocompromised hosts, especially those with AIDS. Herpes zoster is characterized by a unilateral vesicular dermatomal eruption, often associated with severe pain. The dermatomes from T3 to L3 are most frequently involved. If the ophthalmic branch of the trigeminal nerve is involved, zoster ophthalmicus results. The factors responsible for the reactivation of VZV are not known. In children, reactivation is usually benign; in adults, it can be debilitating because of pain. The onset of disease is heralded by pain within the dermatome, which may precede lesions by 48–72 h; an erythematous maculo papular rash evolves rapidly into vesicular lesions (Fig. 198-2). In the normal host, these lesions may remain few in number and continue to

FIGURE 198-2 Close-up of lesions of disseminated zoster. Note lesions at different stages of evolution, including pustules and crusting. (Photo courtesy of Lindsey Baden; with permission.) FIGURE 198-3 Herpes zoster in an HIV-infected patient is seen as hemorrhagic vesicles and pustules on an erythematous base grouped in a dermatomal distribution. form for only 3–5 days. The total duration of disease is generally 7–10 days; however, it may take as long as 2–4 weeks for the skin to return to normal. Patients with herpes zoster can transmit infection to sero negative individuals, resulting in chickenpox. In a few patients, char acteristic localization of pain to a dermatome with serologic evidence of herpes zoster has been reported in the absence of skin lesions, an entity known as zoster sine herpetica. When branches of the trigeminal nerve are involved, lesions may appear on the face, particularly the tip of the nose (Hutchinson sign), in the mouth, in the eye, or on the tongue. Zoster ophthalmicus is usually a debilitating condition that can result in blindness in the absence of antiviral therapy. In Ramsay Hunt syndrome, pain and vesicles appear in the external auditory canal, and patients lose their sense of taste in the anterior two-thirds of the tongue while developing ipsilateral facial palsy. The geniculate ganglion of the sensory branch of the facial nerve is involved. PART 5 Infectious Diseases In both normal and immunocompromised hosts, the most debilitat ing complication of herpes zoster is pain associated with acute neuritis and postherpetic neuralgia. Postherpetic neuralgia is uncommon in young individuals; however, at least 50% of patients over age 50 report some degree of pain in the involved dermatome for months after the resolution of cutaneous disease. Changes in sensation in the derma tome, resulting in either hypo- or hyperesthesia, are common. CNS involvement may follow localized herpes zoster. Many patients without signs of meningeal irritation have CSF pleocytosis and mod erately elevated levels of CSF protein. Symptomatic meningoencepha litis is characterized by headache, fever, photophobia, meningitis, and vomiting. A rare manifestation of CNS involvement is granulomatous angiitis with contralateral hemiplegia, which can be diagnosed by cere bral arteriography. Other neurologic manifestations include transverse myelitis with or without motor paralysis. Like chickenpox, herpes zoster is more severe in immunocompro mised than immunocompetent individuals. Lesions continue to form for >1 week, and scabbing is not complete in most cases until 3 weeks into the illness. Patients with Hodgkin disease and non-Hodgkin lymphoma are at greatest risk for progressive herpes zoster. Cutaneous dissemination (Fig. 198-3) develops in ~40% of these patients in the absence of therapy. Among patients with cutaneous dissemination, the risk of pneumonitis, meningoencephalitis, hepatitis, and other serious complications is increased by 5–10%. However, even in immunocom promised patients, disseminated zoster is rarely fatal. Recipients of hematopoietic stem cell transplants are at particularly high risk of VZV infection. Of all cases of posttransplantation VZV infection, 30% occur within 1 year (50% of these within 9 months);

45% of the patients involved have cutaneous or visceral dissemination. The mortality rate in this situation is 10%. Postherpetic neuralgia, scarring, and bacterial superinfection are especially common in VZV infections occurring within 9 months of transplantation. Among infected patients, concomitant graft-versus-host disease increases the chance of dissemination and/or death. ■ ■DIFFERENTIAL DIAGNOSIS The diagnosis of chickenpox is usually based on clinical presentation and is not difficult. The characteristic rash and a history of recent exposure should lead to a prompt diagnosis. Other viral infections that can mimic chickenpox include disseminated HSV infection in patients with atopic dermatitis and the disseminated vesiculopapular lesions sometimes associated with coxsackievirus infection, echovirus infec tion, or atypical measles. However, these rashes are more commonly morbilliform with a hemorrhagic component rather than vesicular or

vesiculopustular. Rickettsialpox (Chap. 192) is sometimes confused with chickenpox; however, rickettsialpox can be distinguished eas ily by detection of the “herald spot” at the site of the mite bite and the development of a more pronounced headache. Serologic testing is also useful in differentiating rickettsialpox from varicella and can confirm susceptibility in adults unsure of their chickenpox history. Mpox should be considered in travelers returning from endemic areas (Chap. 201) and has been a recent concern in HIV-infected individu als, leading to vaccination campaigns. Smallpox concern has increased because of the threat of bioterrorism (Chap. S4). The lesions of small pox are larger than those of chickenpox and are all at the same stage of evolution at any given time. Unilateral vesicular lesions in a dermatomal pattern should lead rapidly to the diagnosis of herpes zoster, although the occurrence of shingles without a rash has been reported. Both HSV and coxsacki evirus infections can cause dermatomal vesicular lesions. Supportive diagnostic virology and fluorescent staining of skin scrapings with monoclonal antibodies are helpful in ensuring the proper diagnosis. In the prodromal stage of herpes zoster, the diagnosis can be exceed ingly difficult and may be made only after lesions have appeared or by retrospective serologic assessment. ■ ■LABORATORY FINDINGS Unequivocal confirmation of the diagnosis is possible only through the isolation of VZV in susceptible tissue-culture cell lines, the

demonstration of either seroconversion or a fourfold or greater rise in antibody titer between acute-phase and convalescent-phase serum specimens, or the detection of VZV DNA by PCR. Specimens for detection of VZV DNA by PCR include lesions, blood, and saliva. A rapid impression can be obtained by a Tzanck smear, with scraping of the base of the lesions in an attempt to demonstrate multinucleated giant cells; however, the sensitivity of this method is low (~60%). PCR detection of viral DNA in vesicular fluid is available in many diagnostic laboratories and is the diagnostic method of choice. Direct immuno fluorescent staining of cells from the lesion base or detection of viral antigens by other assays (such as the immunoperoxidase assay) is also useful. The most frequently employed serologic tools for assessing host response are the immunofluorescent detection of antibodies to VZV membrane antigens, the fluorescent antibody to membrane antigen (FAMA) test, immune adherence hemagglutination, and enzymelinked immunosorbent assay (ELISA). The FAMA test and the ELISA appear to be most sensitive. TREATMENT Varicella-Zoster Virus Infections Medical management of chickenpox in the immunologically nor mal host is directed toward the prevention of avoidable com plications. Obviously, good hygiene includes daily bathing and soaks. Secondary bacterial infection of the skin can be avoided by meticulous skin care, particularly with close cropping of fin gernails. Pruritus can be decreased with topical dressings or the administration of antipruritic drugs. Tepid water baths and wet compresses are better than drying lotions for the relief of itching. Administration of aspirin to children with chickenpox should be avoided because of its association with the development of Reye syndrome. Acyclovir (800 mg by mouth five times daily), valacy clovir (1 g three times daily), or famciclovir (250 mg three times daily) for 5–7 days is recommended for adolescents and adults with chickenpox of ≤24 h in duration. (Valacyclovir is licensed for use in children and adolescents. Famciclovir is recommended but not licensed for varicella.) Likewise, acyclovir therapy may be of benefit to children <12 years of age if initiated early in the disease (<24 h) at a dose of 20 mg/kg every 6 h. The advantages (i.e., pharmacokinetics) of the second-generation agents valacyclovir and famciclovir are described in Chap. 196. Aluminum acetate soaks for the management of herpes zoster can be both soothing and cleansing. Patients with herpes zoster benefit from oral antiviral therapy, as evidenced by accelerated healing of lesions and resolution of zoster-associated pain with acyclovir, valacyclovir, or famciclovir. Acyclovir is administered at a dosage of

800 mg five times daily for 7–10 days. However, valacyclovir and famciclovir have superior pharmacokinetics and pharmacodynamics and should be used preferentially. Famciclovir, the prodrug of penciclovir, is at least as effective as acyclovir and perhaps more so; the dose is 500 mg by mouth three times daily for 7 days. Valacyclovir, the prodrug of acyclovir, accelerates heal ing and resolution of zoster-associated pain more promptly than acyclovir. The dose is 1 g by mouth three times daily for 5–7 days. Compared with acyclovir, both famciclovir and valacyclovir offer the advantage of less frequent administration. All three of these drugs are now available as generic products. In severely immunocompromised hosts (e.g., transplant recipients, patients with cancer, particularly lymphoproliferative malignancies), both chickenpox and herpes zoster (including dis seminated disease) should be treated, at least at the outset, with IV acyclovir, which reduces the occurrence of visceral complications but has little effect on healing of skin lesions or pain. The dose is 10 mg/kg every 8 h for 7 days. For low-risk immunocompromised hosts, oral therapy with valacyclovir or famciclovir appears ben eficial. If medically feasible, it is desirable to decrease immuno suppressive treatment concomitant with the administration of IV acyclovir.

Patients with varicella pneumonia typically require ventilatory support. Persons with zoster ophthalmicus should be referred immediately to an ophthalmologist. Therapy for this condition consists of the administration of analgesics for severe pain and the use of atropine. Acyclovir, valacyclovir, and famciclovir all acceler ate healing. Decisions regarding the use of corticosteroids should be made by the ophthalmologist.

The management of acute neuritis and/or postherpetic neuralgia can be particularly difficult. In addition to the judicious use of anal gesics ranging from nonnarcotics to narcotic derivatives, drugs such as gabapentin, pregabalin, amitriptyline hydrochloride, lidocaine (patches), and fluphenazine hydrochloride are reportedly beneficial for pain relief. In one study, glucocorticoid therapy administered early in the course of localized herpes zoster significantly acceler ated such quality-of-life improvements as a return to usual activity and termination of analgesic medications. The dose of prednisone administered orally was 60 mg/d on days 1–7, 30 mg/d on days 8–14, and 15 mg/d on days 15–21. This regimen is appropriate only for relatively healthy elderly persons with moderate or severe pain at presentation. Patients with osteoporosis, diabetes mellitus, glycosuria, or hypertension may not be appropriate candidates. Glucocorticoids should not be used without concomitant antiviral therapy. ■ ■PREVENTION Three methods are used for the prevention of VZV infections. First, a live attenuated varicella vaccine (Oka) is recommended for all children

> 1 year of age (up to 12 years of age) who have not had chickenpox and for adults known to be seronegative for VZV. Two doses are recommended for all children: the first at 12–15 months of age and the second at ~4–6 years of age. VZV-seronegative persons >13 years of age should receive two doses of vaccine at least 1 month apart. The vaccine is both safe and efficacious. Breakthrough cases are mild and may result in spread of the vaccine virus to susceptible con tacts. The universal vaccination of children has resulted in a decreased incidence of chickenpox in sentinel communities. Furthermore, the inactivated Oka vaccine, when administered to hematopoietic stem cell recipients, decreases the incidence of herpes zoster. CHAPTER 198 Varicella-Zoster Virus Infections In individuals >50 years of age, the shingles vaccine of choice is

> Shingrix. It is a subunit vaccine (HZ/su) that consists of VZV glyco protein E and the AS01B adjuvant. A randomized, placebo-controlled study administered two doses of vaccine or placebo 1 month apart to 15,411 participants aged 50 years or older. Overall vaccine efficacy for the prevention of herpes zoster virus was 97.2% (95% confidence interval, 93.7–99.0%; p <.001). Injection-site and systemic reactions were more frequent in vaccine recipients, but the proportions of participants who had serious adverse events were similar in the vaccine and placebo groups. The Advisory Committee on Immunization Practices recom mends that persons in this age group be offered this vaccine in order to reduce the frequency of shingles and the severity of postherpetic neu ralgia. Of note, vaccine immunity wanes over time, and reassessment of current recommendations or the use of a promising inactivated vaccine in development will be required. A second approach is to administer varicella-zoster immune globulin (VZIG) to individuals who are susceptible, are at high risk for developing complications of varicella, and have had a significant exposure. This product should be given within 96 h (preferably within 72 h) of the exposure but may be administered up to 10 days with some efficacy. Indications for administration of VZIG appear in Table 198-1, which has been adapted from the American Academy of Pediatrics Red Book. Lastly, antiviral therapy can be given as prophylaxis to individuals at high risk who are ineligible for vaccination or who are beyond the 96-h window after direct contact. While the initial studies have used acyclovir, similar benefit can be anticipated with either valacyclovir or famciclovir. Therapy is instituted 7 days after intense exposure. At this time, the host is midway into the incubation period. This approach significantly decreases disease severity, if not totally preventing disease.

Revision #1
Created 2026-01-06 16:33:27 UTC by Omar Ayman
Updated 2026-01-06 16:33:27 UTC by Omar Ayman