Varicella-Zoster Virus Infections
Anne A. Gershon
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Varicella–Zoster Virus Infections

Anne A. Gershon, MD*

Author Disclosure
Dr Gershon has disclosed that she occasionally is a consultant and lecturer for Merck and Company, Inc, and GlaxoSmithKline.

Objectives  After completing this article, readers should be able to:

1. Describe the natural history and pathogenesis of varicella and zoster and how these diseases are related.
2. Explain to patients and parents the complex role of this virus in causing disease and how the virus spreads.
3. Describe how best to manage patients who have these infections.
4. Discuss how varicella vaccine works, how effective it is in preventing disease, and why two doses of vaccine are now recommended.

The Pathogen
Varicella-zoster virus (VZV), a close but distinct relative of the other seven human herpesviruses, including herpes simplex virus (HSV), causes two diseases. Varicella (chickenpox), a generalized illness, is its primary infection, and zoster (shingles) is its secondary infection, caused by reactivation of VZV from latency. Varicella infection occurs in almost all people over their lifetimes. VZV becomes latent after varicella and usually persists silently and indefinitely. VZV reactivates, however, to cause zoster in roughly 20% of individuals, with higher reactivation rates in immunocompromised patients and the elderly.

Epidemiology
In the prevaccine era in the United States prior to 1995, approximately 4 million cases of varicella and 1 million cases of zoster occurred annually. Varicella was primarily a disease of children younger than age 10 years and zoster an illness of adulthood. Childhood varicella infection, however, is less common than adult infection in countries that have tropical climates. Varicella occurs in children who have no humoral or cellular immunity to VZV, termed “susceptibles.” Zoster occurs in individuals who previously have had varicella; they usually have detectable specific antibody titers, but have low or absent cell-mediated immunity (CMI) to VZV.

VZV spreads primarily from the skin vesicles of persons who have varicella or zoster to the respiratory tract of susceptible persons, who then become infected. Electron microscopic studies have shown a high concentration of well-formed, cell-free VZV in skin vesicles. (1) Respiratory spread is difficult to rule out entirely, but during disease, it is rare to isolate the virus from the throat, although it is common to isolate it from skin vesicles. VZV spreads as cell-free enveloped viral particles, or virions, which are present in skin vesicles and are small enough (approximately 200 nm in diameter) to be aerosolized. (2) The virus spreads by the airborne route and requires direct exposure to an infected individual for transmission.

Evidence for spread of VZV from skin is as follows. A 14% transmission rate of the vaccine (Oka) strain of VZV occurred when susceptible siblings were exposed to a recently immunized child who had leukemia and had a vaccine-associated rash. No transmission occurred if the vaccinee had no rash, and VZV could not be isolated from the throats of any of vaccinees, whether or not they had a vaccine-associated rash. Transmission rates were directly proportional to the number of skin lesions. Recent observations in otherwise healthy children who contracted wild-type breakthrough varicella after immunization also have indicated that VZV spreads from skin. (3) Another recent study indicated that

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children who had active varicella and were not excluded from school on day 1 after rash onset played a major role in spreading the virus in their classrooms. (4) Finally, spread of VZV to observers during an autopsy indicates that transmission by other means than the respiratory tract must occur. (5)

VZV is highly communicable, and subclinical infection is unusual; clinical infection develops in about 80% of susceptibles after family exposure. In contrast, in healthy vaccinees, the Oka strain very rarely spreads to others, even if a rash is present.

Patients who have zoster can transmit varicella to others because the vesicular lesions contain infectious VZV. About 100 years ago, during early attempts to develop a VZV vaccine, children were inoculated with vesicular fluid from zoster patients, and they developed mild chickenpox. Zoster, however, is less contagious than varicella.

The incubation period of varicella ranges from 10 to 23 days (average, 14 days). During the incubation period, VZV multiplies, spreads to regional lymph nodes, and causes viremia. Wild-type VZV has been isolated from blood cultures just before and during very early chickenpox in immunocompetent children. An attractive, recently proposed pathogenetic mechanism is that VZV reaches keratinocytes soon after infection by way of VZV-infected CD4 memory T cells from infected tonsillar cells. These lymphocytes normally circulate through the skin, engaged in immune surveillance; some also become infected with VZV as they circulate, spreading the virus in the body. In this model, overcoming innate immunity in skin accounts for the 2- to 3-week incubation period following infection, as reviewed by Gershon and associates. (6)

Second attacks of varicella are uncommon but may occur. Asymptomatic immunologic boosting of VZV immunity occurs after re-exposure to VZV in varicella-immune individuals and may play a role in long-term maintenance of immunity to VZV.

Patients who develop zoster usually have a history of previous varicella. Zoster can occur in childhood; the incidence is increased by a factor of as much as 20 in those who had varicella in utero or before age 2 years, possibly because the immune response to VZV in young infants is immature. Infants afflicted with the congenital varicella syndrome are at even greater risk for developing zoster.

The incidence of zoster is age-related and begins to increase sharply at 50 years of age. (7) Loss of VZV CMI, which occurs during normal aging, is related to development of zoster. In keeping with this observation, zoster can be prevented by immunization. Zoster also develops commonly in patients treated for cancer and after organ transplantation. Spinal trauma, irradiation, and corticosteroid therapy are other precipitating factors for zoster. Children infected with human immunodeficiency virus (HIV) are at increased risk for developing zoster. Children who develop zoster should be screened (usually by history) for possible risk factors such as HIV infection and underlying immunodeficiency; most often, however, no predisposing factors are identified.

On occasion, zoster occurs in healthy children or young adults. Presumably, such infection is the result of a transient decrease in CMI to VZV, perhaps caused by another inapparent viral infection. Low CMI to VZV is a necessary, but not sufficient, requirement for the development of zoster.

The Diseases
Clinical Manifestations
Varicella usually is a mild-to-moderate illness in children. It often is more severe in adults. Even in children, however, varicella cannot be counted on to be entirely benign. After a short or absent prodrome, skin lesions appear. These start as macules and progress rapidly to papules, vesicles, pustules, and scabs. The rash is concentrated on the trunk and head rather than on the extremities; it normally evolves as a series of successive “crops” over 3 to 4 days. Most children have 250 to 500 superficial skin lesions, many of which are vesicular. Subclinical elevations of hepatic transaminase concentrations are a common, self-limited occurrence during varicella.

Zoster usually appears as a unilateral vesicular skin eruption involving one to three dermatomes. Skin vesicles may be painful or pruritic, especially in adults. Zoster generally is a milder disease in children than in adults. From 25% to 50% of persons older than 50 years of age and the same proportion of immunocompromised patients who acquire zoster experience serious pain, termed post-herpetic neuralgia (PHN), after the rash has healed. The cause of PHN is unknown.

Complications
The most common complication of varicella is bacterial superinfection of the skin, lungs, or bones, most often by Staphylococcus aureus or group A beta-hemolytic streptococci (GAS). Such infections may be severe and even fatal. Whether treatment with ibuprofen is associated with increased severity of GAS after varicella remains unresolved. Therefore, this drug is not recommended for treatment of fever accompanying varicella.

Central nervous system (CNS) complications, which
may precede or follow varicella, include transient cerebellar ataxia, encephalitis, aseptic meningitis, and transverse myelitis. Most CNS complications are self-limited, except for encephalitis, which frequently is associated with severe sequelae if the patient survives. Other less frequent complications of chickenpox include arthritis, glomerulonephritis, myocarditis, and purpura fulminans.

**Immunocompromised Patients**

Varicella may be severe and even fatal in immunocompromised patients, particularly those who have malignancy or congenital deficits in CMI, as well as in those who have undergone organ transplantation, have underlying HIV infection, or are receiving high doses of corticosteroids. Immunocompromised children who have severe varicella tend to have high fevers, extensive rashes lasting for more than 1 week, hepatitis, and primary viral pneumonia, which may be fatal despite antiviral therapy. Children who have leukemia have a 30% rate of disseminated varicella, with a 7% mortality rate. Severe varicella may occur in HIV-infected children, especially in those who have acquired immunodeficiency syndrome (AIDS). In most of these children, however, mild-to-moderate varicella occurs, although the illness often is more severe than occurs in healthy hosts.

**Congenital and Neonatal Varicella**

After maternal VZV infection in the first or second trimester of pregnancy, approximately 2% of infants develop the congenital varicella syndrome. (8) Approximately 100 affected infants have been described since 1947; more than 95% of cases occurred after maternal varicella and the remainder after possible maternal zoster. In the prevaccine era, an estimated 40 affected infants were born annually in the United States. Cicatricial skin scars (in >60% of cases) are the most prominent abnormalities. Other common manifestations include hypoplastic limbs, chorioretinitis, microphthalmos, Horner syndrome, cataract, nystagmus, cortical atrophy or mental retardation, zoster, and early death.

**Diagnosis**

Chickenpox generally is diagnosed clinically because of the characteristic vesicular rash and its distribution, as well as through epidemiologic information such as history of exposure and absence of prior varicella. Zoster also presents with a distinct unilateral, dermatomal, vesicular rash that is diagnosed clinically. Laboratory diagnosis can be used in questionable instances and is facilitated by the accessibility of the virus in superficial skin lesions. (9) The diagnosis is made most definitively by demonstration of specific viral antigens in skin scrapings by immunofluorescence (DFA) using a commercial monoclonal antibody to VZV conjugated to fluorescein or by polymerase chain reaction (PCR). These diagnostic methods are highly sensitive and rapid.

Diagnosis also may be made by isolating the virus from skin lesions, but this technique is more complicated and expensive, is less sensitive, and takes longer than DFA or PCR. VZV rarely can be isolated from cerebrospinal fluid (CSF) and respiratory secretions. The presence of VZV or antigens in secretions or tissues is diagnostic of acute VZV infection because this virus is not shed by asymptomatic persons. The Tzanck test is not recommended by this author because it lacks sensitivity and specificity.

Testing of skin scrapings, vesicular fluid, respiratory secretions, and CSF by PCR is useful for diagnosing VZV, and PCR is replacing culture in many laboratories. PCR is available widely in commercial laboratories and can distinguish between vaccine and wild-type VZV.

Many serologic tests measure antibodies to VZV, including fluorescent antibody to membrane antigen, latex agglutination, and enzyme-linked immunosorbent assay (ELISA). Antibody to VZV develops rapidly after the onset of varicella and persists indefinitely. Peak antibody concentrations occur after 4 to 8 weeks. VZV infections may be proven by a fourfold or greater rise in VZV antibody titer in acute and convalescent serum specimens. Specific immunoglobulin M in one serum specimen suggests recent VZV infection. Persistence of VZV antibody in infants older than 8 months of age suggests intrauterine varicella. Immunity to varicella is highly likely if there is a positive antibody titer to VZV in a single serum sample in a healthy patient. Commercial ELISAs, however, usually are not sufficiently sensitive to identify the level of immunity that develops in vaccinees. After active immunization against VZV, antibody titers are significantly lower than after natural infection.

Serologic procedures for diagnosing zoster are limited because of the nonspecific increases in antibody titer against VZV in some patients who have active HSV infection. These viruses also share minor antigens, which can lead to an increase in VZV titer with HSV infection. Zoster occurs in the presence of serum VZV antibodies; elevations in titer, therefore, can be missed.

CMI responses play the major role in host defense against the virus. CMI to VZV can be demonstrated in vitro most practically by stimulation of lymphocytes with VZV antigens and by an interferon-gamma enzyme-linked immunosorbent spot (ELISPOT) assay. CMI re-
actions remain positive for years, although CMI often wanes in individuals older than 50 years of age.

Treatment
Nonspecific treatment for varicella includes oral antihistamines, frequent bathing, calamine lotion, oatmeal baths, and the trimming of fingernails to discourage scratching. Fever should be controlled with acetaminophen. Use of aspirin for this purpose may predispose to Reye syndrome, and ibuprofen may predispose to GAS infection.

Indications for Specific Treatment
Because most varicella infections are not serious and the illness usually is self-limited in otherwise healthy children, oral acyclovir (ACV) is not administered routinely. Further, the drug is not well absorbed from the gastrointestinal tract. Specific therapy is reserved for those at higher risk for developing severe varicella or those who already have severe disease. Because controlled studies in children and adolescents given oral ACV for 5 days, starting within 24 hours of the rash of varicella, have shown a modest benefit, prompt oral ACV therapy usually is recommended for adolescents and young adults, who are at moderately high risk for developing severe illness. (10)(11)(12) The oral dose is 20 mg/kg qid for children and 1 g qid for adolescents. The antiviral activity of ACV depends on its phosphorylation by virus-induced thymidine kinases.

Patients at serious risk for or who have severe or potentially severe VZV infections should be treated with intravenous (IV) ACV (10 mg/kg per dose tid for adults and adolescents and 500 mg/m² per dose tid for children). Patients whose creatinine clearance is less than 50 mL/min per 1.73 m² are given one half to one third of this dosage, with slow infusion, making sure that hydration is adequate. ACV usually is tolerated very well, but adverse effects include phlebitis, rash, nausea, and neurologic symptoms. Children who are relatively immunocompromised, such as those who have early, seemingly mild varicella and those who have early HIV infection (not AIDS), may be given a closely monitored treatment trial of oral ACV and switched to IV ACV if clinically necessary. In those who have zoster, IV or oral ACV heals skin lesions rapidly and resolves pain.

Prevention
Control Measures
It virtually is impossible to protect susceptible individuals from infection with VZV by avoidance because the agent is highly communicable. Transmission is expected to decrease, however, when VZV infection occurs in populations that are highly vaccinated.

Children who have chickenpox should be excluded from school or child care from the time the diagnosis is made until the lesions are crusted. Those who have zoster may attend school if the lesions can be covered or when they are crusted. The Table lists facts that can be helpful in advising parents whose children are exposed to chickenpox. Patients who have active VZV infection and are hospitalized should be isolated, preferably in a room that has negative pressure ventilation, to minimize viral transmission.

Vaccination of individuals is particularly important if there are family members who cannot be vaccinated, such as a pregnant woman or immunocompromised children. Transmission of the Oka strain from vaccinated individuals, even if they develop a rash, is extremely rare and has been reported after approximately 1 in 10 million vaccinations.

Passive Immunization
Passive immunization is used to protect exposed high-risk persons from developing severe VZV. Treatment is given to persons who have no history of previous VZV disease, are at high risk for developing severe varicella,
and have had an intimate exposure to VZV within the preceding 5 days. Formerly, passive immunization was accomplished by injection of varicella-zoster immune globulin (VZIG). VZIG is no longer being produced, however, because there was little demand for it after 1995. A similar product is available from Canada (VariZIG™, Cangene Corporation, Winnipeg, Canada) and is recommended for neonates whose mothers have active varicella at or soon after delivery and for exposed susceptible high-risk patients. (13) The product is available in the United States under an investigational new drug application expanded access protocol, with central institutional review board approval. IV immune globulin 400 mg/kg is an alternative should neither VZIG nor VariZIG™ be available. (13)(14)

Active Immunization

Live attenuated varicella vaccine was developed in Japan in 1974. (15) Since 1995, universal immunization of healthy children and adults in the United States who are susceptible to varicella has been recommended by the Centers for Disease Control and Prevention (CDC). This vaccine is extremely safe and well-tolerated. About 5% of healthy children develop a mild rash approximately 4 to 6 weeks after immunization. Serious neurologic events have not been related causally to varicella vaccine. Vaccinees who develop VZV rash within 2 to 3 weeks after immunization are likely to have wild-type infection and should be regarded so.

Live attenuated varicella vaccine is highly effective in healthy children and adults. Universal vaccination has decreased the incidence, complications, morbidity, and mortality of varicella by roughly 80% in the United States.

Although varicella vaccine is highly effective, approximately 20% of children develop mild chickenpox after exposure to wild VZV if they have received only one dose of vaccine. Severe varicella occurs only in about 3% of those who develop breakthrough varicella after vaccination. The vaccine is also 80% effective in adults after two doses. Severe wild-type varicella in vaccinated adults is rare. (6)(14)(16)(17)

It is unclear whether breakthrough varicella is the result more from primary or secondary vaccine failure, but primary vaccine failure seems to be the major factor. Loss of VZV antibodies occurs rarely in healthy vaccinated children, even after a follow-up for as long as 20 years. Between years 1 and 8 after immunization, there has not been a decrease in protection of healthy children. There have been, however, numerous recent reports of outbreaks of varicella among immunized children in child care facilities and schools. Most investigations of outbreaks have shown 80% to 85% vaccine effectiveness, but some show effectiveness as low as 45% to 55%. (6)(14) The children included in these studies had, for the most part, received only one dose of vaccine.

A recent investigation indicated a significant degree of primary vaccine failure (24%) in young children who received only one dose of vaccine. (18) To decrease virus transmission, improve vaccine effectiveness, and prevent accumulation of susceptible young adults, two doses of vaccine—previously recommended only for those older than 13 years of age—were recommended for all children by the CDC in June 2006. Catch-up varicella vaccination also is recommended for all children who received only one dose of varicella vaccine in the past. After a second dose of varicella vaccine, there is a marked boost in both humoral and cellular immunity, and the second dose is tolerated very well without significant complications. One small study indicated improved protection after two doses compared with one dose over 10 years of follow-up. (19)

Another important recent advance for varicella immunization was the development of the combined measles-mumps-rubella-varicella (MMRV) vaccine, which was approved by the United States Food and Drug Administration in 2005. MMRV contains about 10 times the amount of VZV as the monovalent formulation and is

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<th>Table. Information for Parents Who Ask What to Do If Their Child Is Exposed to Chickenpox</th>
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<tr>
<td>1. Some 80% of children who received one dose of vaccine are completely protected from chickenpox.</td>
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<tr>
<td>2. Only 3% to 4% of vaccinated children who received one dose of vaccine develop full-blown chickenpox.</td>
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<tr>
<td>3. Breakthrough chickenpox is just as contagious as chickenpox in unvaccinated children unless the child has fewer than 50 skin lesions (very mild infection).</td>
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<tr>
<td>4. All children should receive two doses of vaccine; the second dose can be administered as soon as 3 months after the first and even after an exposure occurs, in which case it might offer additional protection.</td>
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<td>5. Rashes caused by the vaccine (Oka) strain (that appear in weeks 2 through 6 after immunization) can be infectious to others, but transmission is very rare (roughly 1/10 million vaccines), and contact cases uniformly are mild.</td>
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licensed only for children younger than 14 years of age. Currently, most infants and children will be immunized with two doses of MMRV after the shortage of this vaccine is corrected. (20) Varicella vaccine also is recommended for susceptible adults, especially for healthcare workers and persons whose varicella-susceptible family members are immunocompromised or pregnant. Varicella vaccine is recommended only for healthy persons. Zoster appears to be less of a problem after immunization than after natural infection. The CDC now recommends postexposure vaccination for healthy varicella-susceptible exposed individuals.

Recently, a successful vaccine has been developed to prevent zoster in older adults; this vaccine is the Oka strain of VZV, given at a dose roughly 14 times greater than that in the monovalent formulation. One dose of this vaccine is recommended for healthy individuals older than age 60 years who have had varicella but not zoster. This vaccine is 50% to 60% protective against zoster and its major complication, PHN. (7)

Summary
As a herpesvirus, VZV causes acute varicella, latent infection, and zoster. The virus has the potential to cause serious infections, which may be difficult to treat. Complications include bacterial superinfections, CNS abnormalities, and a host of more unusual problems such as pneumonia and hepatitis. Immunocompromised patients, pregnant women and their infants, and the elderly are at highest risk of developing severe and even fatal illnesses. In modern times, successful specific drug therapy has been developed. More recently, medical emphasis has been on prevention of illness by vaccination. Due to the three-pronged approaches of passive immunization, active immunization, and antiviral therapy, the morbidity and mortality from VZV infections have decreased impressively in the past 20 years. With continued use and “fine tuning” of these modalities, particularly active immunization, additional progress should be made, resulting in the possibility of these infections becoming unusual in the developed world.

References
PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. Infections of susceptible persons with the wild-type varicella-zoster virus (VZV) are transmitted primarily through:
   A. Aerosols from skin lesions of infected individuals.
   B. Direct contact with a skin vesicle that has a damaged mucosal surface.
   C. Direct contact with a skin vesicle that has damaged skin.
   D. Respiratory droplets from individuals who have skin lesions.
   E. Respiratory droplets from subclinically infected individuals.

2. In a previously healthy 5-year-old child, the appearance of zoster most likely reflects a:
   A. Life-threatening defect in cellular immunity.
   B. Life-threatening defect in humoral immunity.
   C. Primary VZV vaccine failure.
   D. Temporary phagocytic dysfunction.
   E. Transient defect in cellular immunity.

3. A previously healthy 10-year-old boy develops uncomplicated varicella. As part of his initial management, evidence-based practice supports the regular use of an appropriate dose of oral:
   A. Acetaminophen.
   B. Acetylsalicylic acid.
   C. Acyclovir.
   D. Cephalexin.
   E. Ibuprofen.

4. An 11-month-old girl who has acute lymphoblastic leukemia in early remission was inadvertently exposed to varicella 1 day ago. To reduce the risk of life-threatening varicella, within 72 hours she should receive:
   A. An increase in her dose of prednisone.
   B. Intravenous acyclovir.
   C. Oral acyclovir.
   D. Subcutaneous VZV vaccine (Oka strain).
   E. VariZIG™.

5. You are asked to speak with a group of medical students about varicella vaccine. Your most appropriate statement is that after initial immunization:
   A. Breakthrough varicella generally is severe.
   B. Neurologic complications remain a serious concern.
   C. Primary vaccine failure is relatively common.
   D. Transmission of attenuated virus is common.
   E. Zoster incidence is unchanged.
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Clarification

In the article on varicella-zoster infections in the January issue (Pediatr Rev. 2008;29:5-11), the oral dose of acyclovir for children is given as 20 mg/kg qid. To clarify, the dose is 20 mg/kg per dose qid. The dose recommended in the article for adolescents is 4,000 mg/day and is based on the treatment for adults who have zoster. The American Academy of Pediatrics Red Book (27th ed. 2006:785) cites a dose of 800 mg qid (3,200 mg/day) for adolescents, and the author of the article in the January issue recommends using that dose, although there should be no significant clinical difference between the two regimens. Acyclovir is available in 800-mg tablets. Patients at serious risk for or who have severe or potentially severe infections should be treated with intravenous acyclovir.

PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. Mother–infant transmission of hepatitis B is most likely to occur:
   A. During delivery.
   B. In utero.
   C. Through breastfeeding.
   D. Through salivary transmission.
   E. Via the fecal–oral route.

2. Postnatal immunoprophylaxis is most effective against hepatitis B acquired:
   A. During delivery.
   B. In utero.
   C. Through breastfeeding.
   D. Through salivary transmission.
   E. Via the fecal–oral route.

   Match the serum HBV serologic marker with its correct interpretation.

3. HBeAb

4. HBeAg

5. HBsAb with negative HBeAb
   A. Acute infection.
   B. High viral replication rate.
   C. Immunity after immunization.
   D. Immunity after recovery from infection.
   E. Low viral replication rate.