Varicella Zoster Virus

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Varicella zoster virus (VZV), human herpesvirus 3, is a highly contagious virus found worldwide. Humans are the only known reservoir. Transmission is via respiratory droplets, aerosolized vesicular contents, or direct contact with skin lesions. After infection, VZV becomes latent in sensory ganglia, with reactivation possible even decades later.

Primary infection with VZV results in varicella (chickenpox), which is typically seen in school-age children in temperate climates in late winter and early spring. Before the varicella vaccine, there were approximately 4 million cases of varicella and 100 varicella-related deaths in the United States per year, whereas after vaccination, the incidence has declined 97%, with no reported pediatric deaths since 2010. Varicella disease presents as a diffuse, pruritic, vesicular rash, with fever and malaise appearing just before or on the day of the rash. The contagious period begins 1 to 2 days before the appearance of the rash and continues until all lesions are crusted, an average of 7 days. The incubation period lasts from 10 to 21 days, with an average of 14 to 16 days. Lesions begin as macules, progressing to papules, then vesicles. Initially, lesions are 2- to 4-mm, thin-walled, irregular vesicles with clear fluid over an erythematous base, classically described as “dewdrops on a rose petal.” The rash usually starts on the head, trunk, and then extremities but can appear anywhere, including mucous membranes. As they resolve, vesicles become umbilicated, fill with cloudy fluid, and develop crust. Lesions in varying stages of healing is a hallmark feature. Healthy, unvaccinated children have an average of 200 to 500 lesions. Lesions typically do not scar unless they become infected or excoriated. Once all lesions have crusted, children may return to school.

The most common complication of VZV in children is secondary bacterial skin infection with *Staphylococcus* or *Streptococcus*. Because infection with varicella usually includes a viremia, dissemination to other organs can occur. Acute cerebellar ataxia is the most common extracutaneous complication. Encephalitis can occur and may lead to seizure and coma. Pneumonia after varicella can be due to viruses but is more commonly bacterial in children less than 12 months old. Additional, but more rare, complications include aseptic meningitis, Guillain-Barré syndrome, hepatitis, myocarditis, hemorrhagic varicella, transverse myelitis, uveitis, and iritis. Immunocompromised children are at greater risk for severe disease from VZV as well as severe complications and even death.

Primary maternal VZV infection during the first or early second trimester of pregnancy results in congenital varicella syndrome in up to 25% of cases. Clinically, affected babies can have intrauterine growth retardation, contracted scarring, hypoplastic limbs and digits, and central nervous system abnormalities such as microcephaly, cortical atrophy, mental retardation, and hydrocephalus.

Reactivation of VZV manifests as herpes zoster (shingles), a painful vesicular eruption typically unilateral along a dermatomal distribution most commonly on...
the trunk or involving the fifth cranial nerve. The rash begins as macules and papules, progressing to vesicles that develop crust and resolve. Once lesions are crusted, they are no longer contagious. Pain and paresthesia usually occur several days before the appearance of the rash. The average rash duration is 10 days. Although rare in children, post-herpetic neuralgia may continue for months after rash resolution. If lesions can be covered, patients can return to school.

Treatment for primary VZV is supportive, with antipyretics, fluid, and control of itching. Aspirin should be avoided due to the risk of Reye syndrome. Antiviral therapy with acyclovir, an acyclic nucleoside analog, is generally not used for healthy children younger than 12 years. However, in patients with severe VZV infection in a high-risk group (individuals with chronic cutaneous or pulmonary disorders, those receiving long-term aspirin or corticosteroid therapy, and unvaccinated children older than 12 years), oral acyclovir may be considered. Initiation of acyclovir treatment within 24 hours of rash onset provides the greatest benefit. Immunocompromised patients with VZV infection should be treated with intravenous acyclovir within 24 hours of the appearance of the rash.

Active immunization against varicella with live-attenuated VZV was licensed as a single-antigen vaccine in the United States in 1995, and a quadrivalent measles, mumps, rubella, and varicella (MMRV) vaccine was licensed in 2005, both for healthy children age 12 months and older. Varicella vaccines found worldwide are based on the wild Oka strain of VZV, except for the vaccine licensed in South Korea. A single-dose 0.5-mL subcutaneous injection was recommended initially in the United States, which reduced the incidence of disease by 90% by 2008. The universal vaccination effort also resulted in herd immunity, reducing the incidence of disease in unvaccinated individuals. Despite these successes, varicella outbreaks in fully vaccinated children still occurred, in part due to an estimated 9% to 14% vaccine seroconversion failure.

In 2006, the Advisory Committee for Immunization Practices recommended routine varicella vaccination using a 2-dose series, with the first dose at 12 to 15 months and a second dose at 4 to 6 years of age. A 2016 meta-analysis of global varicella effectiveness noted a 10% overall increase in protection with the 2-dose series and a significantly higher seroconversion rate, close to 100%. Another recent 2017 meta-analysis found that the 2-dose varicella vaccine series was more effective in preventing breakthrough varicella in healthy children compared with the single-dose regimen. It was also suggested that the effectiveness of protection against breakthrough varicella was higher when the vaccines were given 3 to 4 years apart. Further studies are needed to evaluate the impact of vaccine spacing, as well as to determine the duration of protection after varicella vaccination.

The varicella vaccine has been found to be safe, with minimal adverse effects. Minor adverse effects, such as pain, swelling, or redness at the injection site, occur in approximately 20% of patients. Rash develops in 1% to 3% of those vaccinated, and 3% may develop a benign varicella-like rash 5 to 26 days after vaccination.

Caution should be used when vaccinating patients with moderate-to-severe illness with or without fever because postvaccine fever can obscure treatment of the concurrent illness. Patients with mild illness, such as upper respiratory tract infection, should be vaccinated. In children with a personal or family history of seizure, MMRV should not be used. Contraindications to varicella vaccination include anaphylaxis to a vaccine component (varicella vaccine contains trace neomycin and hydrolyzed gelatin); congenital or acquired T-lymphocyte immunodeficiency, including leukemia and lymphoma; and children taking long-term immunosuppressant therapy, including high-dose corticosteroid treatment (22 mg/kg per day). Children with moderate to severe human immunodeficiency virus (HIV) and those with AIDS should not receive the varicella vaccine. However, children with HIV and CD4 T-lymphocytes of at least 15% may be vaccinated with single-antigen varicella vaccine.

Varicella postexposure management depends on the immune status of the exposed individual and the level of exposure. Significant exposure to varicella includes household contacts, face-to-face contact, or at least 1 hour of exposure in the same room. For healthy, nonimmune patients older than 12 months, varicella vaccine should be administered within 3 days. Prophylaxis with varicella immunoglobulin (VariZIG), or intravenous immunoglobulin if VariZIG is not available, is recommended for populations at risk for severe disease within 96 hours of exposure (and up to 10 days). These high-risk patients include immunocompromised children and pregnant women without evidence of immunity, newborns with maternal varicella exposure within 5 days before and up to 2 days after delivery, preterm infants at least 28 weeks’ gestational age born to a nonimmune mother, and infants less than 28 weeks’ gestational age or less than 1,000 g at birth regardless of
maternal immunity. Patients with bone marrow transplant should receive VariZIG after exposure, regardless of their varicella history. Attention to airborne and contact precautions in hospitalized patients with varicella is critical to prevent spread of infection.

COMMENT: Reviewing this In Brief reminded me of the time before vaccine development when varicella was a common illness and most children developed natural immunity from disease. Parents would notify neighbors when their child contracted varicella, and some would have “varicella parties.” Parents would bring their children to these parties to purposefully expose their children. Due to the high level of contagion, parents could predict (within 1–2 weeks) the timing of development of the disease. During this period when varicella was so prevalent, both health-care providers and parents were skilled at correctly diagnosing chickenpox in their children by visual inspection, so many questions and cases were handled over the telephone. But since vaccine implementation and a marked decrease in disease, both parents and health-care providers are less familiar with the presentation of varicella and the ability to correctly diagnose it by visual inspection. When in doubt, it makes sense to send a polymerase chain reaction to make a definitive diagnosis (especially for patients who are immunocompromised) both for the benefit of the individual child and for the community and resultant exposure risks.

Another consideration for primary care providers is to remember that because the varicella vaccine is a live attenuated vaccine, children who have received blood products should have administration of this vaccine delayed to develop maximal immunity. The Red Book and the Centers for Disease Control and Prevention (CDC) website provide specific information about the time frame for delay, which ranges from 3 to 11 months and is specific to different blood products. The effectiveness of the varicella vaccine is a remarkable example of how immunizations have markedly changed the infectious disease landscape and practice for pediatricians.

– Janet R. Serwint, MD
Associate Editor, In Brief

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