Varicella in the 21st Century

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EDUCATION GAPS

Neonatal clinicians may encounter only a few cases of varicella during their career because of the successful adoption of universal varicella vaccination in the United States. Immunity against varicella is not life-long; therefore, it is necessary for clinicians to be able to recognize varicella and determine those cases that would need isolation, chemoprophylaxis, and/or treatment.

OBJECTIVES *After completing this article, readers should be able to:*

1. Recognize the various clinical presentations of varicella-zoster virus infection in infants.
2. Provide guidance about isolation, chemoprophylaxis, and treatment of infants and pregnant persons exposed to varicella.

ABSTRACT

Varicella is a highly contagious disease caused by the varicella-zoster virus and has a wide range of clinical presentations. Varicella can cause mild disease in infants born to infected persons who are immunized as a result of previous vaccination or previous clinical or subclinical infection. However, varicella can also lead to severe life-threatening disease in infants, particularly for those born to nonimmunized persons. In this review, we will summarize the natural history of varicella-zoster infection in pregnant persons, infants with congenital varicella syndrome, and infants with postnatal varicella infection. We will also provide guidance about isolation recommendations and chemoprophylaxis for exposed hospitalized infants. Finally, we will describe risk factors for developing disseminated disease and review the approach to treatment of infected infants.

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ABBREVIATIONS

VariZIG	varicella-zoster immune globulin
VZV	varicella-zoster virus

INTRODUCTION

Varicella is an extremely contagious disease caused by the varicella-zoster virus (VZV) and has a wide range of clinical presentations. Varicella can cause mild disease in infants born to pregnant persons who are immunized (either from immunization or previous clinical or subclinical infection), and it can also lead to severe life-threatening disease in infants born to nonimmune pregnant patients. Although the first varicella vaccine was developed by Takahashi in 1972,

varicella vaccination was not adopted in the United States until 1995. (1) This delay was partly because varicella was not viewed as a high-risk infection, and the potential for development of a latent reactivation later in life with more severe symptoms was of concern. (1) After safety was demonstrated and the cost of hospitalized children with parental loss of work time became a societal burden, the United States adopted a vaccination program for varicella.

Significant decline in the incidence of varicella in children in the United States has followed the adoption of this vaccination program with vaccine hesitancy, leading to mild-to-severe outbreaks in some communities. Although varicella infection remains endemic, the risk of developing varicella infection is now lower in the United States than in most other parts of the world. (2) Life-long immunity to varicella is possible, but immunity can wane over time. (3) Breakthrough cases of varicella, although mild, can still occur in previously immunized individuals, and this can affect nonimmune persons. (2)(4) Diagnosis can be challenging when persons infected with varicella have mild and atypical symptoms.

This article will provide a summary of the natural history of varicella-zoster infection in pregnant persons, infants with congenital varicella syndrome, and infants with postnatal varicella infection. We will also provide guidance about isolation recommendations and chemoprophylaxis for exposed hospitalized infants. Finally, we will describe risk factors for developing disseminated disease and review the approach to treatment of infected infants.

CLINICAL PRESENTATION

VZV infection causes 2 clinically distinct forms of disease: varicella (chickenpox) and herpes zoster (shingles). The incubation period of varicella ranges from 8 to 21 days after exposure, but most patients develop the disease between days 14 and 16. (4) Individuals with varicella become infectious 24 to 48 hours before the onset of rash. (4) In adults and adolescents, prodromal symptoms such as headache, general malaise, myalgia, oral sores, and low-grade fever may precede the onset of a generalized pruritic rash. The rash appears on the face, scalp, and torso and later spreads to the upper and lower extremities. The typical rash begins as macules that progress rapidly to papules, pustules, and then vesicles. This rash typically appears in crops, and affected individuals usually present with the rash in different stages of development and resolution. (4) The vesicles occur on an erythematous base and can rupture or become purulent before crusting over with scab formation. The generalized distribution and appearance of the lesions distinguish varicella from the vesicular rash seen in neonatal herpes simplex, which is more likely to occur in clusters. (5)

Acute varicella infection is generally mild and self-limited in the pediatric population. A rash is typically the first sign of the disease in children, and other constitutional symptoms usually resolve within a few days. (6) Severe disease is more likely to develop in adults, immunocompromised individuals, infants younger than 1 year, and pregnant women. (7)

After varicella infection, the virus can become latent in the dorsal root ganglia and later reactivate as herpes zoster. Herpes zoster is also contagious and usually presents with a painful vesicular rash in a dermatomal distribution. However, it is rare in children. (8)

Varicella in Pregnant Persons

The incidence of varicella in pregnancy is not known; however, best estimates are calculated to be 1 to 5 per 10,000 pregnancies. (9) Women who develop varicella during pregnancy may experience miscarriage or fetal demise. Approximately 10% to 20% of cases of varicella in pregnancy are complicated by pneumonia, and morbidity and mortality are higher than in nonpregnant persons. (10) Pregnant persons with pneumonia from VZV should be admitted to the hospital for monitoring and be treated with antiviral medication, as up to 40% of pregnant patients may need respiratory support. (11)

Congenital Varicella Syndrome

Congenital varicella syndrome is a rare disorder that affects infants of pregnant persons who contracted zoster infection early in pregnancy. The risk of transmission to the fetus is 0.55% when the pregnant person is infected before the 12th week of gestation, and it is higher (1.4%) between the 13th and 20th weeks of gestation. (11) Affected infants have variable clinical presentations including the following:

- In utero fetal demise
- Severe growth restriction
- Central nervous system abnormalities, such as cortical atrophy and seizures, and developmental disability
- Various skin abnormalities that include scarring lesions, which may be depressed and pigmented across dermatomes
- Eye examination findings including microphthalmos, chorioretinitis, cataracts, and Horner syndrome
- Limb abnormalities

The range and severity of symptoms and physical findings in infants with congenital varicella syndrome is highly variable. Congenital varicella syndrome is fatal in ~30% of

affected infants within the first month of age. (12) Mortality is usually a result of aspiration pneumonia and respiratory failure.

Neonatal Varicella Infection

Neonatal varicella develops when a pregnant person contracts varicella near term or soon after birth and infects their newborn. Neonatal varicella infection from an infected birth parent occurs via transplacental viremia, ascending infection during birth, or contact with the birth parent's respiratory droplets or vesicles after birth. An infant typically presents with symptoms 9 to 15 days after onset of the birth parent's rash. (6) Postnatal neonatal infection may also occur from exposure to an infected person.

Neonatal varicella infection should be suspected when generalized vesicular skin lesions in various stages of development are seen in the neonate (Fig 1). Neonatal varicella is a mild disease, but serious complications can occur, particularly in preterm infants. (13)

Breakthrough Varicella

Breakthrough varicella is caused by an infection with wild-type VZV in a person who received at least 1 dose of varicella vaccine 42 days or more before the development of symptoms. (14) Affected persons usually have less than 50 lesions with few-to-no vesicles and less pruritis. Fever, when present, is very mild, and the illness is usually of a shorter duration than seen in unvaccinated persons. Diagnosis is best made using polymerase chain reaction testing of scrapings from skin lesions.

NOSOCOMIAL TRANSMISSION OF VSV

The VZV virus can be transmitted in hospitals by patients, staff, or visitors who are symptomatic or in the incubation phase of the disease when they are asymptomatic. As VZV is highly contagious, varicella or herpes zoster may be spread to vulnerable patients in hospitals. This group includes preterm infants, pregnant persons, immunocompromised individuals undergoing chemotherapy, immunodeficient individuals, and health-care workers. Transmission in hospital settings have been attributed to delayed reporting and failure to implement control measures. (5) It is therefore important for health-care facilities to make every effort to control and prevent the transmission of VZV infection.

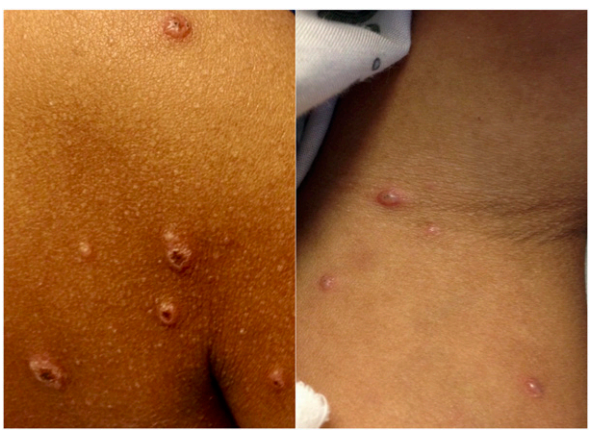

Figure 1. Papules, macules, and vesicles seen in varicella.

APPROACH TO VZV EXPOSURE

Isolation of Infants in the Newborn Nursery

If an infant is born to a birth parent with VZV, the infant needs to be isolated from the birth parent until the parent's lesions are dry and crusted. (5) The infected mother who is breastfeeding can provide expressed or pumped human milk to the infant as long as she does not have any breast lesions. If the infant is discharged during the incubation period, the infant must continue to isolate from the infected mother for 21 days. (13)

Infants who develop varicella infection in the nursery should be isolated from other infants with airborne precautions, when available. (15) If the infant does not require admission to the intensive care unit and acquired the infection from the birth parent, the infant and birth parent can isolate together in a hospital room. If the infant acquired the infection from another source and the birth parent is seronegative, the infant needs to be isolated from the birth parent as well.

The birth parent who is seronegative with a history of VZV exposure 6 to 21 days before hospitalization may develop varicella and must be isolated from other patients in the hospital until discharge. Any parent or infant who has been exposed to varicella or is already infected should be discharged from the hospital as soon as possible. During outpatient appointments, contact and airborne precautions are needed for the infant and parents who require isolation. (13)(16) Mothers may continue to provide expressed breast milk and should be instructed on appropriate handwashing before pumping. (17)

Isolation of Infants in the NICU

Preterm infants in the NICU are at high risk for developing health-care–associated infections because of their immunologic immaturity. Many viral infections may be easily transmitted in the NICU as a result of the close proximity of patients in the open-pod NICU design, as well as the close and prolonged exposure to visitors as neonatal units adopt

family-centered care. (18) Identifying viral exposures may be difficult when staffing challenges prompt the frequent movement of infants to multiple bed-spaces within the NICU. Isolation precautions should be initiated while the hospital infection control team is consulted. (19)

A preterm infant born to a birth parent with varicella lesions 5 days before and up to 2 days after birth must be isolated using standard contact and airborne precautions for at least 21 days; this isolation period is extended to 28 days if the infant requires immunoprophylaxis. (20) The affected parent may not visit in the NICU until they are no longer considered infectious (ie, all the lesions are dry and crusted). Other family members need to be monitored closely for symptoms.

Airborne Precautions

Negative pressure rooms are a common solution in infection control efforts and are used by hospitals to prevent the spread of airborne infectious diseases throughout the hospital via the heating ventilation and air conditioning systems. (21) Negative pressure rooms are equipped with an exhaust system that removes air from the room and moves it through special high-efficiency particulate air filters before being released outside (Fig 2). Some negative pressure rooms also have higher infection control precautions, such as alarms, to alert staff to loss of pressure within the room and self-closing doors.

The challenge of providing proper isolation in hospitals was evident during the recent COVID-19 pandemic. In the United States, only 2% to 4% of all hospital rooms are equipped for negative pressure. (22) Although more negative-pressure rooms are needed in hospitals, the cost and process of creating more of these rooms can be a challenge to hospital systems.

Individuals requiring hospitalization and who are suspected to have VZV infection should be removed from waiting rooms or public areas and placed in a negative-pressure room. Patients are also considered exposed to an index varicella case if the patients 1) were admitted in the same room with 2 to 4 other patients, 2) were present in adjacent areas in the same pod, or 3) had face-to-face contact with the index varicella case. (20) Only health-care workers with documented immunity to varicella should be allowed to care for exposed or infected patients. Standard contact and airborne precautions must be used when caring for patients with varicella.

Figure 2. Negative-pressure room with anteroom.

Approach to Multiple Infants with Varicella Exposure within the NICU

Example Case. The mother of a 5-day-old preterm infant in the NICU developed a rash for which she was referred to the emergency department for evaluation. Varicella infection was suspected, and testing of vesicular fluid lesion confirmed the diagnosis. The hospital infection control team was contacted. Eight infants who resided in the same pod with this infant were identified, but only 6 infants remained hospitalized. The neonatologist caring for this infant at the time contacted every family by telephone to inform them of the exposure. Information was also provided on the anticipated length of isolation. The primary care physicians for the 2 discharged infants were also contacted to ensure that family members were being monitored closely for symptoms. For the nonhospitalized infants, families were given instructions to isolate their infant as much as possible for the next 21 days and to contact the hospital infection control group if they became ill and/or developed skin lesions.

The index case was placed in the single negative pressure room available in the NICU. The remaining 5 infants were moved into individual private rooms after the installation of air scrubbers with high-efficiency particulate air filters in each room (Fig 3). Infants were placed in NICU rooms with windows to reduce recirculation of air within the NICU. Installation in internal rooms would have added more cost and delays and also required a dedicated ventilation system to move air directly outside the NICU.

Guidelines for chemoprophylaxis were followed and the appropriate infants received the varicella immune globulin. Only nursing staff with documented evidence of varicella immunity or who had received 2 doses of varicella vaccine were permitted to care for these infants for the entire period. These infants remained hospitalized with airborne isolation for 28 days. Neither the hospitalized infants nor the discharged infants developed varicella.

This case presentation illustrates the challenges of staffing, space, and cost that may accompany 1 or more varicella

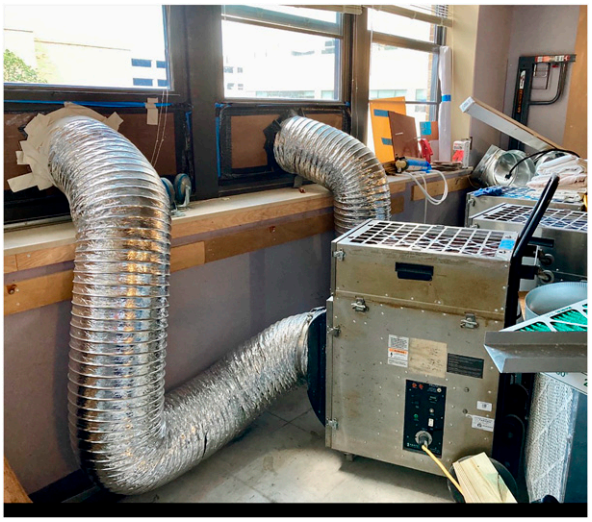

Figure 3. Air scrubbers used to provide negative pressure (units in patients room are usually smaller).

exposures in a NICU. A comprehensive infection control team approach is crucial to ensure that the varicella-exposed infants are identified in a timely fashion and that the necessary steps are taken to reduce nosocomial transmission and treat affected infants when indicated. (19)(23) In addition, it is critical to develop a system of early disclosure to families in the event of a varicella exposure within the hospital. The disclosure team may involve various members of the hospital organization; however, the primary physicians caring for the infant during the hospitalization may be best suited to inform families in these cases. The physician contacting the family should be able to provide families with accurate answers to their questions about anticipated symptoms and treatment and also provide information on how to isolate effectively at home. Notification of the primary care physician and social work would also be necessary for case-tracking, to maintain an open dialogue with affected families, and to provide ongoing support. (23)

POSTEXPOSURE CHEMOPROPHYLAXIS (FOR ALL CHILDREN AND ADULTS)

Chemoprophylaxis in patients exposed to varicella is considered based on the following 3 factors (24):

- Exposed patient's degree of immunity
- Exposed patient's likelihood of infection after the exposure
- Exposed patient's likelihood of complications if infected

Administration of varicella-zoster immune globulin (VariZIG) should be considered for individuals who are at a high risk of developing severe disease, lack evidence of immunity, or are ineligible for the vaccination. (25) VariZIG is the only preparation available in the United States for varicella prophylaxis. It is a purified compound from plasma with high levels of anti-varicella antibodies obtained from healthy donors with recent natural VSV infection or recurrent zoster infection (shingles). (26)

The recommended dose for VariZIG is 125 IU/10 kg of body weight, up to a maximum of 625 IU (5 vials). Infants weighing less than 2 kg should receive 62.5 IU (0.5 vial), and infants weighing between 2 and 10 kg should receive 125 IU (1 vial). (27) Exposed infants born at less than 28 weeks' gestation or weighing 1,000 g or less should be given VariZIG regardless of the birth parent's history of immunity, as these infants may not yet have acquired transplacental antibodies. (28) VariZIG should ideally be given within 96 hours of exposure for maximal effectiveness, but it can be given up to 10 days after exposure. (29) Exposed preterm infants born at more than 28 weeks' gestation to a birth parent without documented evidence of immunity to varicella should also receive VariZIG. The Table provides a summary of the recommended immunoprophylaxis in different clinical scenarios.

In 2012, the Advisory Committee on Immunization Practices recommended that neonates whose mothers have signs and symptoms of varicella around the time of delivery (5 days before to 2 days after delivery) receive VariZIG. (1) VariZIG is not recommended in healthy, full-term infants who are exposed postnatally 2 days after delivery, even if the mother has no documented history of immunity against varicella through vaccination or past varicella infection. This is because postnatally acquired varicella in term infants is usually mild. (31)

Infants who receive VariZIG should be observed closely for signs of varicella for 28 days after exposure as VariZIG may prolong the incubation period by 7 days or more.

Pregnant persons who are exposed to a household contact with varicella infection should receive passive immunization with VariZIG within 96 hours of exposure to prevent severe varicella disease and/or reduce the risk of fetal infection. (15)(29) If a pregnant person develops varicella infection, treatment should be considered to decrease morbidity. (11) However, there are no randomized controlled trials on whether this treatment leads to a decreased risk or severity of congenital varicella. Options for treatment of pregnant persons with varicella include oral acyclovir or valacyclovir. (30) This regimen reduces the duration of fever and symptoms of varicella if begun within 24 hours of the rash. Intravenous acyclovir should be administered if severe complications such as pneumonia develop.

Table. Recommendation for Chemoprophylaxis after Varicella Exposure (13)

Involved Person	Patient Scenario	Immunoprophylaxis Recommended
Pregnant person	Pregnant person without evidence of immunity.	Yes, VariZIG recommended, and varicella vaccine should be given as soon as possible after delivery.
Hospitalized preterm infant	Hospitalized preterm infants ≥28 weeks' gestational age with exposure to VZV born to birth parent without documented immunization, serologic immunity, or previous varicella infection.[a]	Yes, VariZIG recommended.
	Hospitalized preterm infants ≥28 weeks' gestational age with significant exposure to VZV born to birth parent with documented immunization, serologic immunity, or previous varicella infection.	No
	Hospitalized preterm infants born <28 weeks' gestational age or birthweight <1,000 g with a significant exposure to VZV, independent of birth parent history of varicella or immunization.[a]	Yes, VariZIG recommended.
Hospitalized healthy term infant	Hospitalized healthy term infant with birth parent developing rash 5 days before and <48 hours after delivery.	Yes, VariZIG recommended.
	Hospitalized healthy term infant with postnatal VZV exposure or birth parent developing rash >48 hours after delivery.	No.[b]
Other	Immunocompromised individual without documented immunity to varicella.	Yes, VariZIG recommended. Select groups may receive the varicella vaccine.[c]
	Healthy persons 13 years and older without evidence of immunity,[d] who are exposed to varicella.	Yes, varicella vaccine is recommended within 3–5 days of exposure.

VariZIG = varicella-zoster immune globulin, VZV = varicella-zoster virus
[a]VariZIG should be given within 96 hours but up to 10 days after exposure.
[b]Some experts have recommended VariZIG in select cases.
[c]Severely immunocompromised children and adults should not receive varicella vaccine. Individuals in remission may receive vaccination at least 4 weeks before immunosuppressive therapy.
[d]Evidence of immunity includes the following: diagnosis of varicella or herpes zoster infection by a physician; documentation of age-appropriate vaccine in school age children, adolescents, and adults; or documented lab evidence of varicella immunity.

MANAGEMENT OF NEONATES WITH VARICELLA INFECTION

If a hospitalized infant presents with a rash that is consistent with VZV, infection can be confirmed with polymerase chain reaction testing of a polyester swab of the base of fluid-filled vesicle. (15) A complete evaluation of a newborn with vesicles should include testing for a bacterial and herpetic infection with initiation of broad-spectrum antibiotics and intravenous acyclovir. Newborns with severe disseminated varicella-zoster infection such as pneumonia and encephalitis should receive a 10-day course of intravenous acyclovir. Mothers should be encouraged to provide expressed breast milk, as there may be passive antibodies to varicella present in human breast milk that may be protective to the neonate.

PREVENTION

Many persons of child-bearing age born outside the United States are from countries without a universal varicella immunization program. All pregnant persons should have prenatal assessment for varicella evidence of immunity, and evidence of immunity should be documented in the electronic medical record during each pregnancy. There is no contraindication against breastfeeding in mothers who receive the varicella vaccine; therefore, susceptible women should receive postpartum vaccination. The Centers for Disease Control and Prevention strongly recommend against parents intentionally exposing their unimmunized children to varicella infection. Two doses of the vaccine are more than 95% effective against varicella and, thus, the most effective way of preventing chickenpox. (28)

CONCLUSION

Varicella infection is often a benign illness in adults and children but may be associated with severe disease in immunosuppressed individuals including preterm neonates. The incidence of varicella infection has decreased in the United States since universal vaccination was adopted, but varicella transmission can occur when immunity to varicella is not confirmed or documented in at-risk individuals or those not born in the United States. Early identification of at-risk or infected infants with varicella is critical to

prevent widespread infection among immunocompromised hospitalized infants. Birth parents and infants who are exposed to varicella infection require prompt chemoprophylaxis when appropriate. The hospital infection control team should also be involved in cases of exposure to varicella to ensure that patients are isolated appropriately and treated promptly, when indicated.

American Board of Pediatrics Neonatal-Perinatal Content Specification

- Plan the management of an exposure to varicella in the newborn nursery or newborn intensive care unit.

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