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# Chickenpox

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Chickenpox is caused by varicella zoster virus (*Herpesvirus varicellae*), a unique double-stranded DNA virus that belongs to the subfamily of Alphaherpesvirinae.[1] This virus is capable of producing two different clinical disease syndromes: 1) varicella (chickenpox); and 2) zoster (shingles). The differences in the clinical presentation of the two are not attributable to distinct etiologic agents, but rather to variations in the affected host and circumstances of infection. Primary varicella infection is largely a disorder of childhood, with one study estimating that 90% of cases occur in children less than 10 years of age.[2] Primary varicella infection is highly contagious and thus a common disease of childhood. Exposure to varicella in a healthy child, generally as a rule, confers immunity to the host. Re-exposure at a later age rarely leads to clinical manifestations due to the heightened immune response of primed humoral and cell-mediated mechanisms. Recurrent primary varicella infection is extremely rare, and is mostly limited to immunosuppressed or immunocompromised populations.[3]

## Pathogenesis

Primary varicella, or chickenpox, is most commonly acquired by inhalation of respiratory droplets.[4-7] Vesicle fluid contains a large amount of the virus; viral transmission through contact with skin lesions also may occur. The virus initially infects the conjunctiva or mucosa of the upper respiratory tract. Then viral replication ensues in regional lymph nodes on days 2 to 4 postinfection. Primary viremia follows, which ensues on days 4 to 6. Varicella viremia is hypothesized to transpire within mononuclear monocytes; lymphocytes are suspected of being the primary carriers of viral particles. Secondary viral replication occurs in the body's internal organs, most notably the spleen and liver. Elevated serum hepatocellular enzymes are a common observation in the acute stage of primary varicella infection. A secondary viremia follows, during approximately days 14 to 16, in which viral particles progressively invade capillary endothelial cells, capillaries, and the epidermis diffusely throughout the body.

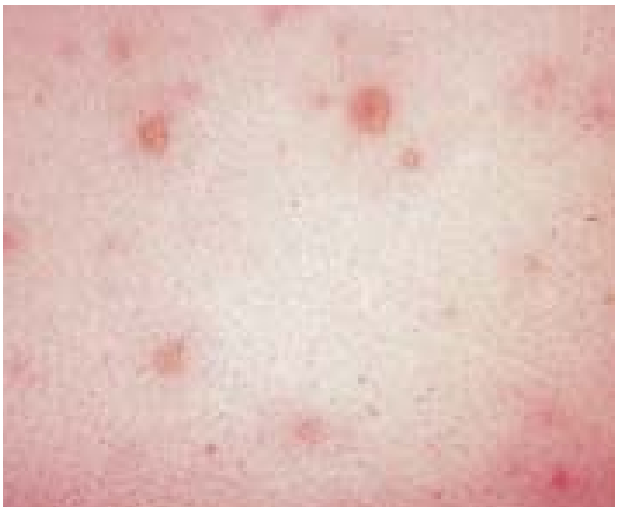

**FIGURE 1.** Dew drop on rose petal characteristic vesicle of chickenpox (courtesy of Emanuel G. Kuflik, MD, Clinical Professor, Dermatology, New Jersey Medical School).

Distinctive epidermal pathologic changes may be seen in varicella infection.[8,9] Cells of the malpighian layer demonstrate intracellular edema; characteristic nuclear changes consisting of eosinophilic inclusion bodies and marginated chromatin are also appreciated. Multinucleated giant cells, which are produced predominantly by cell fusion, are also typical of varicella infection. The clinical appearance of the vesicle in varicella is a result of both intracellular and intercellular edema within the malpighian layer.

Primary varicella infection, or chickenpox, is believed to spread from mucosal and epidermal lesions into sensory nerves. The varicella zoster virus (VZV) enters a latent state in the dorsal ganglion cells of sensory nerves; reactivating of the virus produces the clinically distinct syndrome of herpes zoster. The exact mechanisms of this process have not yet been fully elucidated.

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## Clinical Characteristics

In young, healthy children, the onset of chickenpox usually begins with the triad of rash, malaise, and low-grade fever. Varying degrees of pruritus accompany its onset, which is usually abrupt. A prodrome of myalgia, nausea, anorexia, headache, and vomiting is most commonly seen in older children and adults. The rash of primary varicella is characterized by small erythematous macules appearing on the face and trunk with rapid progression, over the course of 12 to 14 hours, to papules, clear unilocular vesicles (usually 2 to 3 mm in diameter), pustules, and crusts. A dew drop on a rose petal well describes the characteristic vesicle of chickenpox (Figure 1). The dry crust forms and separates from the skin over a time-course of 1 to 3 weeks, leaving behind a shallow, pink depression. These lesions, as a rule, commonly heal without scarring in the absence of secondary infection. The distribution of the vesicles is most numerous on the trunk, face, scalp, and proximal limbs (Figure 2). An identifying feature is the presence of lesions at different stages of development and healing in each site. In addition, the eruption is not only an exanthem, but also an enanthem, with oral vesicles often seen.

Variations may be noteworthy. Rarely, lesions may be bullous or hemorrhagic (see below).[10] In addition, the live attenuated varicella vaccine, produced from the Oka strain of the virus, may cause a limited cutaneous eruption of chickenpox with transmission to susceptible household contacts.[11]

## Complications

In the healthy pediatric population, chickenpox is usually a self-limited disease. The most frequent complication of primary varicella infection in children is secondary bacterial infection of skin lesions. Staphylococci and streptococci are the most common bacterial pathogens, with clinical manifestations including impetigo, cellulitis, and erysipelas. Local bacterial infection significantly increases predisposition to scarring. These local infections rarely lead to septicemia with a bacterial pneumonia or otitis media. Primary varicella pneumonia is a common complication of infection in adults, but is rare in children. Ninety percent of reported cases of varicella pneumonia occur in adults.[12-14]

There are more than 100 cases described of thrombocytopenia and purpura secondary to primary varicella infection.[15] These manifestations have been subclassified into five major clinical syndromes: 1) febrile purpura (most benign syndrome with an uncomplicated outcome); 2) malignant chickenpox with purpura (associated with widespread systemic infection and a greater than 70% mortality rate); 3) postinfectious purpura; 4) purpura fulminans; and 5) anaphylactoid purpura.[16] Hemorrhagic complications are more common in immunocompromised or immunosuppressed populations, although healthy children are also susceptible to these syndromes, including malignant chickenpox with purpura.[17] The etiology of these rare hemorrhagic varicella syndromes is not clear, although an autoimmune hypothesis has been proposed. Other rare complications of varicella include hepatitis, myocarditis, and glomerulonephritis.

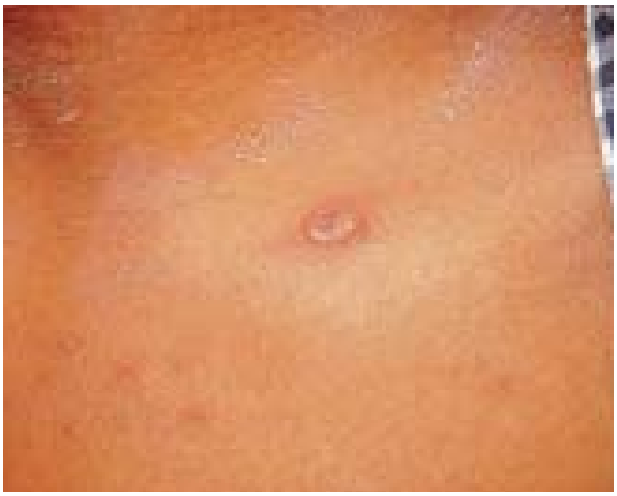

**FIGURE 2.** Vesicular eruption on trunk (courtesy of Emanuel G. Kuflik, MD, Clinical Professor, Dermatology, New Jersey Medical School).

Central nervous system complications of primary varicella infection are extremely rare. Reye's syndrome, acute cerebellar ataxia, encephalitis, and the Guillain-Barré syndrome have all been documented to occur with primary varicella infection. Reye's syndrome occurs in highest incidence secondary to varicella infection in comparison to other viral infections; this syndrome is most commonly associated with concomitant aspirin ingestion.[18,19]

Chickenpox in pregnancy may produce congenital disease ranging from asymptomatic latency to severe defects or fetal wastage.[20] Infection in the first trimester is the most dangerous, associated with cortical atrophy, psychomotor retardation, ocular abnormalities, and other findings.

## Diagnosis

Primary varicella infection in children is usually diagnosed clinically. The characteristic papulovesicular rash, described above, accompanied by fever with or without malaise, is one characteristic of varicella infection. The presence of lesions in varying stages of evolution and healing in one body site is also an integral clinical identifier of primary varicella infection. Diagnostic techniques of identifying varicella infections include Tzanck smears of vesicular fluid, although

this technique cannot distinguish varicella from herpes simplex virus infection. Culture of VZV (*ie*, through the use of vesicular fluid) is technically difficult to accomplish, but provides a distinction between VZV and herpes simplex virus infection. Direct immunofluorescence from skin lesions allows rapid diagnosis with greater sensitivity than the aforementioned tests.[5] Recent progress in varicella zoster identification by polymerase chain reaction techniques provides even greater specificity/sensitivity.[21,22] Much research is being devoted to this laboratory technique, which should gain much more clinical use in the future.[6,23]

## Differential Diagnosis

Chickenpox must be distinguished from a number of other viral and bacterial exanthems, insect bites, drug eruptions, and primary vesiculobullous disorders such as vesicular pemphigoid and dermatitis herpetiformis. The latter is particularly true with bullous chickenpox.[10]

## Treatment

As alluded to above, varicella infection in healthy children is a relatively self-limited disease. Symptomatic treatment in this population group is the standard of care. Pruritus may be alleviated with calamine lotion, warm baths with baking soda, or oral antihistamines. Analgesics and antipyretics may be used in healthy children, but care should be taken to avoid salicylates due to their association with Reye's syndrome. Children also naturally tend to scratch pruritic lesions, necessitating the trimming and cleaning of fingernails in order to minimize secondary bacterial infection and/or permanent scarring. Acyclovir therapy has been shown to decrease the duration and severity of primary varicella infection in the healthy pediatric population.[24] This therapy is not as of yet widely implemented due to the cost of acyclovir treatment, rapidity with which treatment must be initiated, and the relative paucity of secondary complications in healthy children.[5] Acyclovir therapy may be indicated in adults suffering from primary varicella infection due to increased incidence of complications such as varicella pneumonia. Immunosuppressed and immunocompromised individuals are much more commonly treated with acyclovir.[25]

## Prophylactic Vaccination

In March 1995 the United States Food and Drug Administration approved the use of the live attenuated varicella Oka vaccine for use in susceptible healthy children and adults. Recommendation outlines for vaccination include one-dose vaccination for healthy children 12 to 18 months of age and two-dose vaccination, in a 4- to 8-week interval, in adolescents aged 13 years or older who are at high risk for varicella exposure.[26] Prophylactic immunization for all susceptible children and adolescents for varicella is recommended.[27] Universal varicella vaccination in healthy children would have a profound effect on cost-effectiveness of medical/nonmedical dollars attributed to chickenpox. It has been estimated that a universal vaccination program would prevent 94% of all potential cases of chickenpox.[27] Long-term immunity of children having received the varicella Oka strain have been documented to persist 10 years after vaccination.[28] Nonetheless, the duration of immunity to varicella after childhood vaccination is yet to be determined. Similarly, the risk of herpes zoster after vaccination needs to be established. Allergic reactions to gelatin have been reported with the use of the varicella Oka vaccine.[29] The possibility, albeit small, of vaccine-induced primary varicella or herpes zoster infection in healthy children is also a concern.

Vaccinations of susceptible adults is important, too. Groups of particular importance include health care workers, international travelers, persons at high risk such as day care workers, family contacts of immunocompromised persons, and nonpregnant women of childbearing age (who should avoid pregnancy for 3 months after each dose).

Determination of susceptibility requires serologic assay. In one study of recruits, almost all gave a positive history, but more than 20% lacked the serologic evidence.[30] Two highly sensitive techniques that measure humoral responses to VZV include an immunofluorescence assay for antibody to VZV-induced membrane antigens (FAMA) and a latex agglutination test.[31,32] The latex agglutination test has comparable sensitivity to the FAMA assay but has the added benefit of being much simpler to perform; the latex agglutination test is currently the most popular commercial test for determining immunity to VZV.[32]

## REFERENCES


1. Roizman B, Carmichael LE, Deinhardt F, de The G, Nahmias AJ, *et al*: Herpes viridae: definition, provisional nomenclature and taxonomy. *Intervirology* 16: 201-217, 1981.
2. Choo PW, Donahue JG, Manson JE, Platt R: The epidemiology of varicella and its complications. *J Infect Dis* 172: 706-712, 1995.
3. Arvin AM, Koropchak CM, Wittek AE: Immunologic evidence of reinfection with varicella-zoster virus. *J Infect Dis* 148: 200-205, 1983.
4. Grose C: Variation on a theme by Fenner: the pathogenesis of chickenpox. *Pediatrics* 68: 735-737, 1981.
5. McCrary ML, Severson J, Tyring SK: Varicella zoster virus. *J Am Acad Dermatol* 41: 1-16, 1999.

6. Koropchak CM, Graham G, Palmer J, Winsberg M, Ting SF, *et al*: Investigation of varicella-zoster virus infection by polymerase chain reaction in immunocompetent host with acute varicella. *J Infect Dis* 163: 1016-1022, 1991.
7. Myers MG: Hepatic cellular injury during varicella. *Arch Dis Child* 57: 317-319, 1982.
8. Barski G, Robineaux R: Evolution of herpes simplex lesions observed in vitro by phase contrast microcinematography. *Proc Soc Exp Biol Med* 101: 632, 1959.
9. Blank H, Burgoon CF, Baldridge CD, McCarthy PL, Urbach F: Cytologic smears in diagnosis of herpes simplex, herpes zoster and varicella. *J Am Med Assoc* 146: 1410–1412, 1951.
10. Schwartz RA, Jordan MC, Rubenstein DJ: Bullous chickenpox. *J Am Acad Dermatol* 9: 209-212, 1983.
11. LaRussa P, Steinberg S, Meurice F, Gershon A: Transmission of vaccine strain varicella-zoster virus from a healthy adult with vaccine associated rash to susceptible household contacts. *J Infect Dis* 176: 1072-1075, 1997.
12. Aebi C, Ahmed A, Ramilo O: Bacterial complications of primary varicella in children. *Clin Infect Dis* 23: 698-705, 1996.
13. Centers for Disease Control and Prevention: Varicella-related deaths among adults—United States, 1997. *JAMA* 277: 1754-1755, 1997.
14. Triebwasser JH, Harris RE, Bryant RE, Rhoades ER: Varicella pneumonia in adults. *Medicine* 46: 409-423, 1967.
15. Maness D, Rogers D: Hemorrhagic complications of varicella. *Am Fam Physician* 35: 151-155, 1987.
16. Charkes ND: Purpuric chickenpox: report of a case, review of the literature, and classification by clinical features. *Ann Intern Med* 54: 745-749, 1961.
17. Miller H, Stephan M: Hemorrhagic varicella: a case report and review of the complications of varicella in children. *Am J Emerg Med* 11: 633-638, 1993.
18. Centers for Disease Control: Reyes Syndrome-United States, 1984. *MMWR* 34: 13-16, 1985.
19. Liu GT, Urion DK: Pre-eruptive varicella encephalitis and cerebellar ataxia. *Pediatr Neurol* 8: 69-70, 1992.
20. Paryani SG, Arvin AM: Intrauterine infection with varicella-zoster virus after maternal varicella. *N Engl J Med* 314: 1542-1546, 1986.
21. Puchhammer-Stockl E, Popow-Kraupp T, Heinz FX, Mandl CW, Kunz C: Detection of varicella-zoster virus DNA by polymerase chain reaction in the cerebrospinal fluid of patients suffering from neurological complications associated with chicken pox or herpes zoster. *J Clin Microbiol* 29: 1513-1516, 1991.
22. Nahass GT, Goldstein BA, Zhu WY, Serfling U, Penneys NS, *et al*: Comparison of Tzanck smear, viral culture, and DNA diagnostic methods in detection of herpes simplex and varicella-zoster infection. JAMA 268: 2541-2544, 1992.
23. Schmidt NJ, Gallo D, Devlin V, Woodie JD, Emmons RW: Direct immunofluorescence staining for detection of herpes simplex and varicella zoster virus antigen in vesicular lesions and certain tissue specimens. *J Clin Microbiol* 12: 651-655, 1980.
24. Dunkle LM, Arvin AM, Whitley RJ, Rotbart HA, Feder HM Jr, *et al*: A controlled trial of acyclovir for chickenpox in normal children. *N Engl J Med* 325: 1539-1544, 1991.
25. Nyerges G, Meszner Z, Gyarmati E, Kerpel-Fronius S: Acyclovir prevents dissemination of varicella in immunocompromised children. *J Infect Dis* 157: 309-313, 1988.
26. Kamiya H, Ito M: Update on varicella vaccine. *Curr Opin Pediatr* 11: 3-8, 1999.
27. MacFarlane LL, Sanders ML, Carek PJ: Concerns regarding universal varicella immunization. Time will tell. *Arch Fam Med* 6: 537-541, 1997.
28. Asano Y, Nagai T, Miyata T, Yazaki T, Ito S, *et al*: Long-term protective immunity of recipients of the Oka strain of live varicella vaccine. *Pediatrics* 75: 667-671, 1985.
29. Kumagai T, Yamanaka T, Wataya Y, Umetsu A, Kawamura N, *et al*: Gelatin-specific humoral and cellular immune responses in children with immediate and nonimmediate-type reactions to live measles, mumps, rubella and varicella vaccines. *J Allergy Clin Immunol* 100: 130-134, 1997.
30. Strueiving JP, Hyams KC, Tuellar JE, Gray GC, *et al*: The risk of measles, mumps, and varicella among young adults: a serosurvey of US Navy and Marine Corps recruits. *Am J Public Health* 83: 1717-1720, 1993.
31. Larussa P, Steinberg S, Waithe E, Hanna B, Holzman R, *et al*: Comparison of five assays for antibody to varicella-zoster virus and the fluorescent-antibody-to-membrane-antigen test. *J Clin Microbiol* 25: 2059-2062, 1987.
32. Steinberg SP, Gershon AA: Measurement of antibodies to varicella-zoster virus by using a latex agglutination test. *J Clin Microbiol* 29: 1527-1529, 1991.