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Varicella-Zoster Virus

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INTRODUCTION

Varicella-zoster virus (VZV) is a ubiquitous human alphaherpesvirus, which causes varicella (chicken pox) and herpes zoster (shingles). Varicella results from primary VZV infection; it is a common childhood illness associated with fever and a generalized pruritic vesicular rash. As is characteristic of the alphaherpesviruses, VZV establishes latency in cells of the dorsal root ganglia after primary infection. Herpes zoster is a localized, painful, vesicular rash involving one or adjacent dermatomes and caused by VZV reactivation. The incidence of herpes zoster increases with age or immunosuppression.

Historically, the relationship between the etiologies of varicella and herpes zoster was first suggested by von Bókay in 1892, from the observation that young children often developed varicella after exposure to an adult with herpes zoster (249). Transmissibility of the agent was demonstrated by inoculating children who had no history of varicella with fluid recovered from herpes zoster lesions; these children developed varicella, and secondary transmission was documented (158). Varicella lesions are scattered, whereas zoster lesions are localized, but early studies showed histopathologic similarities in skin biopsy specimens from patients with either clinical illness. Garland and Hope-Simpson first suggested that herpes zoster was caused by reactivation of latent virus acquired during varicella (132; reviewed in reference 258). Goodpasture and Anderson detected multinucleated giant cells in a human skin/chorioallantoic membrane culture system infected with herpes zoster lesion fluid in 1944 (107), and infectious VZV was isolated in tissue culture by Weller and Stoddard in 1953 (258). Knowledge about the molecular virology of VZV and mechanisms of pathogenicity has grown during the past two decades. The complete VZV genome has been sequenced, the infectivity of intact VZV DNA has been demonstrated (39, 53), and, most recently, infectious virus has been produced from cosmids spanning the genome (39). Antiviral agents that modify the severity of varicella and herpes zoster have been developed, and a live attenuated varicella vaccine that protects against primary VZV infection is now licensed for clinical use (3, 245, 260, 261).

THE VIRUS

The VZV virion consists of a nucleocapsid surrounding a core that contains the linear, double-stranded DNA genome; a protein tegument separates the capsid from the lipid envelope, which incorporates the major viral glycoproteins (reviewed in reference 41). VZV DNA consists of approximately 125,000 bp with at least 69 open reading frames (ORFs) (53). The viral DNA is arranged in long and short unique segments with terminal repeat regions; although four isomeric forms are possible, most full-length VZV DNA consists of two predominant

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isomers. The linear sequence of VZV genes is similar to that of herpes simplex virus type 1 (HSV-1), which is the prototype of the alphaherpesviruses, and complementation has been demonstrated for some genes. VZV is the smallest of the human herpesviruses and lacks genes for several proteins found in HSV, such as glycoprotein D. VZV produces six or more glycoproteins, now designated gB (gp II), gC (gp IV), gE (gp I), gH (gp III), and gL, which are also expressed on cell membranes during viral replication (52; reviewed in reference 111). The gE protein is produced most abundantly in VZV-infected cells; it is noncovalently linked to gI and has been shown to bind the Fc fragment of immunoglobulin G (IgG). The gB protein is the target of neutralizing antibodies and probably plays a role in virus entry. The amino acid sequence of gB is highly conserved between VZV and HSV-1, accounting for past observations of their antigenic relatedness (149). The gH protein appears to have fusion function, facilitating cell-to-cell spread of the virus; gH requires the presence of gL (the ORF 60 product) for glycosylation and transport to the cell surface (77). The gC protein is not essential for VZV replication; plaque-purified virus that does not express gC can be subcloned from VZV isolates, including the Oka vaccine strain.

Homologies between VZV and HSV ORFs do not always correlate directly with function, as illustrated by the observation that the ORF 10 protein of VZV, which is the HSV VP16 homolog is dispensable for VZV replication in vitro; the ORF 4 protein also fails to complement the HSV ICP27 homolog (40, 154, 191, 206). The VZV origin-binding protein can substitute for the HSV homolog (256). VZV proteins with gene regulation activities include the products of ORFs 4, 10, 61, 62, and 63. The IE62 protein is the major transactivator for VZV replication and is a major component of the tegument (152). A viral thymidine kinase (deoxypyrimidine kinase) is produced by most VZV strains, which is inhibited by acyclovir and other nucleoside analogs, but the enzyme is not essential for VZV infectivity. In addition to being found in HSV-1 and HSV-2, ORFs with homologies to VZV genes are present in the pseudorabies virus and simian varicella virus genomes (41, 109).

VZV replication is highly cell associated, and virus is not released at any phase of replication in cell culture (112). The limited cell-free virus stocks that can be produced preclude a precise analysis of VZV replication kinetics, but it is presumed to follow the cascade of alpha, beta, and gamma gene activation that characterizes HSV replication (41). VZV infects human fetal diploid cells and melanoma cells well in cell culture and also replicates in Vero cells and primary African green monkey kidney cells. Current evidence indicates that like HSV, VZV attaches to heparin sulfate proteoglycan on the cell surface and is then bound to a second, low-affinity receptor before entry (269). Replication is associated with expression of viral proteins within 4 to 10 h and formation of multinucleated giant cells and other cytopathic changes within 2 to 7 days. Electron microscopy studies show that most VZV virions are enclosed in cytoplasmic vacuoles; defective particles are numerous, and virions appear to disintegrate in the cytoplasm before reaching extracellular spaces. Degradation appears to occur as a result of virus entry into acidic prelysosomal vacuoles in the cytoplasm (85). VZV is highly temperature sensitive, with inactivation occurring at 56 to 60°C, and it is not infectious if the virion envelope is disrupted. Lyophilization provides the optimal preservation of VZV infectivity and is used in production of the live attenuated varicella vaccine.

Information about the genetic variability or effects of genetic mutations on VZV infectivity or virulence patterns is limited. Epidemiologically distinct VZV strains seem to exhibit very little antigenic variation, and no distinct subtypes of the virus have been identified. The annual epidemics of varicella do not suggest any differences in virulence associated with particular epidemic strains. VZV variants, including thymidine kinase-negative and gC-negative viruses, can be recovered from infected individuals, but these mutations do not alter replication in vitro (153).

VZV is highly species specific in its infectivity. Some nonhuman primates and small animals, including guinea pigs and rats, can be infected with the virus, but infection does not cause VZV disease (193, 226). The rat model has been particularly useful in studies of VZV latency (54, 226).

EPIDEMIOLOGY

VZV is found in a worldwide geographic distribution, but annual epidemics are more prevalent in temperate climates, occurring most often during late winter and spring (reviewed in references 8 and 260). Cases of herpes zoster provide a source of VZV transmission to susceptible close contacts, causing varicella; the virus then spreads rapidly to other susceptible individuals, in part because, in contrast to other herpesviruses, VZV is transmissible by the respiratory route (33, 116). Varicella attack rates among susceptible household contacts exposed to VZV are approximately 90%; more limited exposures, such as those occurring in school classrooms, result in transmission rates of about 10 to 35% (225). Varicella is a less common childhood disease in tropical areas. In temperate climates, children usually acquire varicella during the first 5 to 10 years of life. Since almost all children become infected, the annual incidence of varicella is equivalent to the birth rate; about 3.5 million cases occur in the United States every year. Susceptibility rates among individuals over 18 years old are about 5% in temperate climates, but as many as 50% of young adults in tropical regions have not had primary VZV infection (196). Second episodes of varicella are rare (92).

Restriction endonuclease analyses of viral DNA give identical results for VZV isolates that are closely related epidemiologically. Differences in restriction digest patterns are noted for unrelated isolates but do not appear to reflect clinically significant strain differences that might correlate with the variation in VZV prevalence or virulence. Most VZV isolates recovered from children with varicella in the United States can be distinguished from the Oka strain, a Japanese clinical isolate used to produce the live attenuated varicella vaccine (163). This technique is valuable for determining whether lesions in vaccine recipients are caused by the vaccine strain or by breakthrough infection with wild-type VZV.

Herpes zoster occurs only in individuals who have had primary VZV infection. Herpes zoster exhibits no seasonal pattern, indicating that disease results from the reactivation of latent virus rather than new exposures to VZV. Early studies defined the incidence of herpes zoster as 3.4 cases per 1,000 persons per year in the United Kingdom (132). The epidemiology of herpes zoster is affected by host factors that predispose to the reactivation of latent virus. Most cases of herpes zoster occur in individuals who are more than 45 years old; the incidence increases with advancing age, to more than 10 cases per 1,000 persons per year by 75 years. The possibility that genetic factors alter the risk of herpes zoster is suggested by a recent study showing that elderly black Americans were one-fourth as likely as elderly white Americans to have had herpes zoster, after controlling for age, cancer, and demographic factors (231). Herpes zoster is very unusual in children younger than 10 years old, with an incidence of 0.74 per 1,000 persons per year (114). Risk factors for herpes zoster in childhood include varicella acquired during the first year of life and VZV

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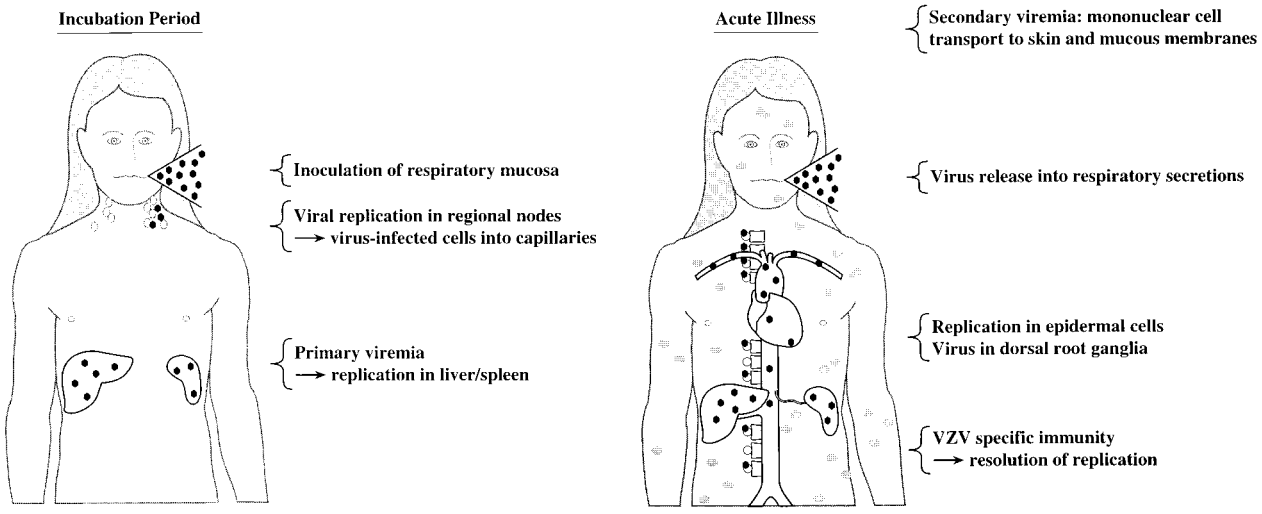

FIG. 1. Pathogenesis of primary infection with VZV. Reprinted from reference 8 with permission.

infection in utero as a result of maternal varicella during gestation (62, 65, 202).

Herpes zoster is common in patients treated with immunosuppressive drugs for malignant diseases or to prevent rejection of bone marrow or organ transplants and in individuals with human immunodeficiency virus (HIV) infection (42, 120, 177, 234, 260). VZV reactivation is particularly frequent among patients with leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, and oat cell carcinoma of the lung (58). Systemic steroid therapy for chronic diseases such as rheumatoid arthritis or systemic lupus erythematosus also predisposes to VZV reactivation. Although malignancy predisposes to herpes zoster, the occurrence of herpes zoster in otherwise healthy individuals does not predict a diagnosis of cancer in subsequent years (222). In contrast, herpes zoster suggests HIV infection in individuals with risk factors for this disease (46).

PATHOGENESIS

Varicella

The cell-associated nature of VZV has hampered virologic documentation of specific events in the pathogenesis of infection. Although VZV can be transmitted by the respiratory route, infectious virus has rarely been isolated from respiratory mucosal sites (90). However, viral DNA has now been detected by PCR in specimens obtained from these sites just before or after the onset of the rash (230). The PCR data are consistent with the epidemiologic evidence that VZV is transmissible for 24 to 48 h before the exanthem begins. VZV lesions in the oropharynx are common and may facilitate transfer of the virus in respiratory secretions (155). In the course of transmission, infectious virus present in respiratory droplets or vesicular fluid from an infected contact is presumed to be inoculated at mucous membrane sites. The virus is then thought to spread to regional lymph nodes, resulting in a primary viremic phase that carries the virus to the liver or other cells of the mononuclear phayocyte system during the incubation period (110). The incubation period usually lasts about 14 days (Fig. 1).

VZV viremia can be detected during the last 4 or 5 days before the onset of symptoms and for a few days after the appearance of the rash (14–16, 88, 156, 197, 198). VZV has been recovered from 11 to 24% of peripheral blood mononuclear cell (PBMC) samples taken within 24 h of onset of the rash from healthy individuals with acute varicella by using cell culture methods and in 67 to 74% of samples tested by in situ hybridization or PCR (155, 156, 230). In immunocompetent individuals with varicella, only 0.01 to 0.001% of PBMC contain VZV as detected by in situ hybridization and infected PBMC are usually eliminated by 24 to 72 h after the appearance of the rash (156). Viremia during primary VZV infection is cell associated, but it has been difficult to identify the PBMC subpopulations that become infected because of the low frequency of positive cells. Both lymphocytes and monocyte/macrophage cell types may harbor infectious virus. Our recent experiments with SCID-hu mice with human thymus or liver implants demonstrate that VZV is lymphotropic for $CD4^+$ as well as $CD8^+$ T lymphocytes (190). Activated T lymphocytes can be infected with VZV in vitro, and the IE62 protein was effective in transactivating all classes of VZV genes in a human T-lymphocyte cell line (156, 207).

Cell-associated viremia provides the virus with access to epidermal cells, and replication in these cells causes the typical varicella rash. Precise mechanisms for virus transfer to skin cells are not known, but infected PBMC may migrate out of the capillaries into cutaneous tissue or the virus may spread into endothelial cells forming the capillary walls, replicate, and spread to adjacent epithelial cells; alternatively, as suggested by experiments in the SCID-hu mouse model, infected T lymphocytes may migrate from capillaries and release infectious virus particles that enter cutaneous target cells (190). Viral inclusions are detected in capillary endothelial cells and in adjacent fibroblasts, as well as in epithelial cells. Varicella lesions evolve through maculopapular, vesicular, and crusting phases. The initial changes associated with the maculopapular stage include vasculitis involving small blood vessels and the fusion of epithelial cells to form multinucleated cells that often have eosinophilic intranuclear inclusions (139, 169). The cells lining the lymphatics of the superficial dermis are also affected, showing dilatation and intranuclear inclusions. The evolution to vesicles is associated with progressive "ballooning" degeneration of epithelial cells, the appearance of fluid-filled spaces between cells, and increased numbers of infected cells at the base of the lesion. Varicella lesions usually do not scar, because the infected epithelial cells are relatively superficial, but damage to the germinal layer of the epithelium may occur.

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Deep ulceration, which is characterized by necrosis through the whole dermal layer, is observed with some lesions.

VZV virions are detected in capillary endothelial cells and keratinocytes by electron microscopy, and cell-free virus is released into vesicular fluid. Direct contact with the infectious virions present in cutaneous lesions provides another mechanism for VZV transmission. The histopathologic appearance of VZV and HSV lesions cannot be differentiated definitively in skin biopsy specimens unless virus-specific immunocytochemical stains are performed. VZV inoculation of human skin tissues implanted in SCID-hu mice produces the pathologic changes that resemble natural infection (190).

VZV has the potential to cause disseminated infection of the lungs, liver, central nervous system, and other organs if the host immune response is inadequate to terminate cell-associated viremia (192). Varicella pneumonia is characterized by active infection of the epithelial cells of the pulmonary alveoli, mononuclear cell infiltration, and edema of the alveolar septae (105, 157, 214, 215). The interstitial inflammatory process, along with accumulation of desquamated septal cells in the alveoli, leads to inadequate oxygen transfer from the alveoli to the pulmonary capillaries, severe hypoxemia, and respiratory failure. Transient hepatitis probably occurs in most healthy individuals with primary VZV infection, but extensive viral replication in the liver, with widespread hepatocellular destruction due to virus-induced cell lysis, is a complication of progressive varicella, causing fulminant hepatic failure (5).

Varicella encephalitis and cerebellar ataxia are the most common neurologic complications of varicella. Knowledge about the pathogenesis of these disorders is limited, because fatal disease is unusual and tissue specimens are rarely obtained for diagnosis (23, 146). The pathologic mechanism causing cerebellar ataxia is intriguing, because it is particularly associated with varicella in otherwise healthy children (210). Varicella encephalitis may be infectious, caused by direct spread of the virus (147). VZV can infect vascular endothelial cells and may cause central nervous system disease by inducing vasculitis. An alternative hypothesis is that some central nervous system manifestations of varicella reflect immune system-mediated damage. The rare cases of hemiparesis reported after varicella are associated with vasculopathy and focal ischemia; the delayed onset of vasculitis in these cases may indicate an immunologic mechanism, perhaps triggered by circulating immune complexes (23, 146).

Other pathologic complications of VZV infection include thrombocytopenia, which causes coagulopathy and hemorrhage, particularly when associated with severe hepatitis (75). Thrombocytopenia may be caused by reduced production and survival of platelets; vasculitis, transient hypersplenism, or intravascular coagulopathy may contribute to lower platelet counts. Thrombocytopenia may be related to antibody-mediated destruction of platelets (75). Necrosis of the adrenal glands is common with fulminant, disseminated varicella (192). Primary VZV infection can cause glomerulonephritis, viral arthritis, uveitis, retinal necrosis, myocarditis, pancreatitis, and orchitis, but these complications are unusual (reviewed in references 8 and 260).

Varicella acquired by the mother during early pregnancy can be associated with transplacental transfer of VZV and the occurrence of the congenital varicella syndrome (65, 202, 203; reviewed in reference 34). Varicella embryopathy is characterized by microcephaly with cortical atrophy and calcifications due to intrauterine encephalitis, limb hypoplasia, unusual cicatricial skin scars, cutaneous defects and hypopigmented skin areas, and damage to the autonomic nervous system.

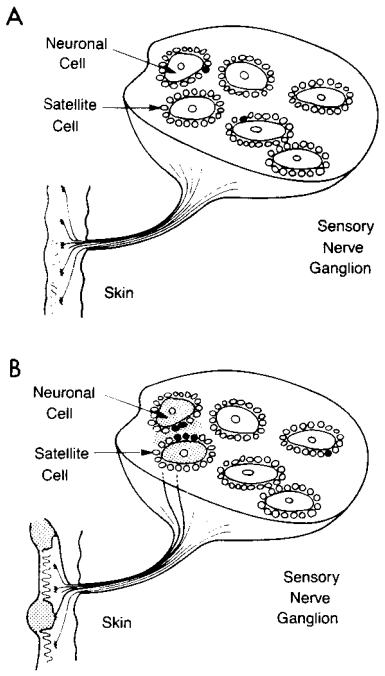

FIG. 2. Pathogenesis of latency and reactivation of VZV. (A) Hypothetical site of latent VZV within a sensory ganglion; (B) pattern of infection during reactivation. Large cells are neurons; small cells are nonneuronal cells, including satellite, endothelial, and fibroblast-like cells. Blackened cells contain latent virus; stippling indicates active viral replication. Reprinted from reference 242a with permission.

Herpes Zoster

VZV infection of cells in the dorsal root ganglia is probably a consequence of all primary VZV infections (80, 96, 243, 258). VZV DNA is detected by in situ hybridization and PCR in these tissues obtained at autopsy from individuals who have serologic evidence of prior VZV infection but no signs of VZV disease (50, 80, 100, 181, 182, 186). VZV may reach dorsal root ganglia from mucocutaneous lesions by an ascending route along neuronal cell axons, or it may be carried to these sites by infected PBMC before cutaneous lesions appear. In contrast to HSV, latent VZV cannot be reactivated by explanting human ganglia unless the patient has acute herpes zoster at autopsy. Transcription of ORF 63 has been detected in explanted ganglia in the rat model (54). The ganglion cell type(s) within which VZV persists is not certain. Some studies indicate that viral DNA is present in neuronal cells, whereas other experiments demonstrate the localization of VZV to the satellite cells that surround neurons in ganglia during latency, as illustrated in Fig. 2 (50, 102, 244). In vitro, VZV infects both neuronal and nonneuronal cells (Schwann cells and astrocytes) in cultures of fetal nervous system tissue (41). VZV lacks the antisense, latency-associated RNA transcripts of HSV-1 and HSV-2, but there is evidence that some production of polyadenylated transcripts of ORF 29, ORF 62, and other genes continues in latently infected dorsal root ganglion cells (43–45, 186).

Symptomatic VZV reactivation causes a vesicular rash, usually involving the dermatormal distribution of a single sensory nerve. Infectious virus may be carried by multiple axons, since clusters of lesions appear in scattered areas of the involved dermatome. The histopathologic changes in the skin resemble varicella lesions, except that vasculitis may be more pro-

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nounced (169). Histopathologic studies of ganglia during VZV reactivation show inflammation, necrosis, and disruption of the morphology of neuronal and nonneuronal cells (55, 68). The virus probably reaches the skin by transport along sensory neural axons (50, 101). Inflammation and necrosis from VZV reactivation sometimes extend into the anterior horn cells, producing myelitis and deficits of motor function (98, 130). VZV is detected within neurons and satellite cells during reactivation (68, 96). VZV reactivation often causes a postherpetic neuralgia syndrome (PHN). The etiology of PHN is poorly understood, but it is likely to be multifactorial (255). The death of primary neurons from virus infection, along with the inflammatory response that occurs in some patients, may result in chronic pain due to nociceptor-induced central hypersensitivity and spontaneous epileptiform discharge of deafferented neurons (24). However, continued viral gene transcription and translation may also occur, since VZV proteins have been detected in PBMC from some patients with PHN (247).

Other human herpesviruses, including HSV, Epstein-Barr virus, human cytomegalovirus, and human herpesvirus 6, cause frequent episodes of asymptomatic reactivation that can be detected by culturing samples taken from infected individuals. Latency, defined as persistence of viral DNA without production of infectious virus, is rarely maintained for prolonged periods. Reactivation, with shedding of infectious virus at mucocutaneous sites, is frequent, but immunity usually prevents symptomatic recurrences. Unless latency of VZV is maintained much more efficiently than that of other herpesviruses, periodic episodes of subclinical reactivation probably occur. In support of this hypothesis, subclinical VZV viremia was demonstrated by PCR in 19% of bone marrow transplant recipients who had no clinical signs of herpes zoster, and elderly adults have episodes of transient, asymptomatic VZV viremia (56, 262).

VZV reactivation in the immunocompromised host is usually associated with a more extensive local rash than in immunocompetent individuals and is often accompanied by cell-associated viremia (20, 58). VZV viremia can result in progressive varicella, with spread of the virus to the lungs, liver, central nervous system, and other organs (177, 232). Visceral dissemination may follow VZV reactivation in some immunocompromised patients who have no signs of cutaneous herpes zoster (177). Chronic VZV reactivation may occur in severely immunocompromised patients with persistent viral replication at skin sites and episodes of viremia lasting for several months. Recurrent VZV lesions in patients with AIDS are characterized by epidermal hyperplasia and massive hyperkeratosis with multinucleated giant cells and necrotic acantholytic keratinocytes (1, 42). VZV reactivation is also a cause of retinitis in HIV-infected patients (79, 127).

IMMUNE RESPONSE

Humoral Immunity

Primary VZV infection elicits IgG, IgM, and IgA antibodies that bind to many classes of viral proteins, including glycoproteins, regulatory and structural proteins, and viral enzymes (29, 30, 35, 95). Antibodies to VZV proteins have neutralizing activity against the virus, either directly or in the presence of complement, and lyse infected cells by antibody-mediated cellular cytotoxicity. Antibodies to gE and gI proteins neutralize VZV in the presence of complement, whereas antibodies to gB protein have complement-independent neutralizing activity against VZV, as is characteristic of the homologous glycoproteins made by other herpesviruses. The gH and gC proteins also induce complement-independent neutralizing antibodies. Recent evidence indicates that antibodies to gH can modulate cell-to-cell spread of the virus, potentially modifying viral pathogenesis even after virus entry into permissive cells.

The capacity of VZV IgG antibodies to inhibit VZV infection in vivo is proved by clinical studies of the efficacy of high-titer VZV immune globulin (VZIG) given to immunocompromised patients within 72 h after exposure (267). Passively administered antibodies present during the early incubation period can limit the infectivity and replication of the virus, as shown by the reduction in severity of varicella and in the risk of varicella pneumonitis among high-risk patients given VZIG. Transplacentally acquired IgG antibodies to VZV also prevent or modify the severity of varicella during the first 6 months of life (34).

Viral replication during the incubation period of primary VZV infection does not stimulate humoral immunity in most individuals, but some have low concentrations of IgM and IgG antibodies by the time the varicella exanthem develops (95). Antibody production is usually detectable within 3 days after the onset of symptoms in healthy subjects. However, the role of humoral immunity in controlling primary VZV infection appears to be limited. In early studies, children with agammaglobulinemia were found to have uncomplicated varicella and did not become reinfected with the virus even though replacement Ig therapy was not available. Early production of IgG or IgM antibodies to VZV does not predict milder infection in healthy children, and some immunocompromised children develop progressive varicella despite adequate production of VZV antibodies (10). The administration of immune globulin to children with acute varicella has no effect on the clinical course.

IgM antibodies decline within a few months, but IgG antibodies to many viral proteins persist for years after primary VZV infection as part of the long-term immune response to VZV. These antibodies may help to protect against reinfection by neutralizing any infectious virus at mucosal sites of inoculation (29). Antibodies to viral glycoproteins may be particularly effective for this purpose. Antibodies to other proteins, such as the IE62 protein, which is required to initiate viral replication, also persist after the primary infection (9). These antibodies may be useful for blocking early stages of VZV reactivation from latency, assuming that antibodies to VZV proteins can interfere with intracellular events in replication. Healthy and immunocompromised individuals with herpes zoster have a rapid and substantial increase in the level of IgG antibodies to VZV proteins of various classes, including the glycoproteins, IE62 protein, and others, such as the viral thymidine kinase (reviewed in reference 8).

Cell-Mediated Immunity

Cell-mediated responses to VZV are nonspecific in the naive host or are mediated by antigen-specific T lymphocytes that are elicited during primary exposure to the virus (Table 1). In vitro studies show that VZV-infected fibroblasts are lysed by natural killer cells from nonimmune individuals (reviewed in reference 7). Alpha interferon (IFN-α) is produced by stimulation of PBMC with VZV antigen from susceptible subjects; its potential role in the early host response is suggested by the effect of IFN-α administration on the severity of varicella in immunocompromised children (12).

Studies of healthy and immunocompromised patients with primary or recurrent VZV infections demonstrate the importance of virus-specific cellular immunity for controlling viral replication (reviewed in references 7 and 89). T-lymphocyte-

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TABLE 1. Correlations between cell-mediated immunity and VZV disease[a]

Host	Clinical status	VZV-specific T-cell proliferation	Correlations
Healthy susceptible	Varicella	Early acquisition	Mild infection
Immunodeficient susceptible	Varicella	Delayed or no acquisition	Risk of dissemination
Healthy immune	Varicella exposure	Enhanced (booster) response	No disease
Healthy immune	Age >65 years	Low or absent response	Risk of herpes zoster
Immunodeficient immune		Low or absent response	Risk of herpes zoster and dissemination

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mediated responses act to eliminate virus-infected PBMC and to restrict virus replication in skin lesions. Varicella is mild in healthy children who develop T lymphocytes that recognize VZV antigens within 72 h after the onset of signs (10). Sensitized T lymphocytes produce cytokines of the Th1 type, including interleukin-2 and IFN-γ, which potentiates the clonal expansion of virus-specific T cells; IFN-γ has been detected in sera from healthy subjects with acute varicella (10, 268). Immunocompromised children who have an absolute lymphopenia of $<500/mm^3$ at the onset of varicella are at risk for severe varicella; failure to acquire T lymphocytes that recognize VZV antigens correlates with a risk of persistent viremia and life-threatening dissemination (10, 89) (Table 1).

As in the case of humoral immunity, T lymphocytes from healthy immune subjects recognize many proteins made by VZV (Table 2). While it has not been possible to examine responses to the 69 or more gene products of the virus, several glycoproteins and the IE62 major tegument/regulatory protein are known targets of the cell-mediated immune response to VZV (9, 13, 102, 123). T-lymphocyte responses to gE, gH, and the IE62 protein are elicited during primary VZV infection in the immunocompetent host, although the sequence in which T-lymphocyte recognition of these proteins develops is variable. VZV infection also elicits T lymphocytes that recognize gB and gC (87). T-lymphocyte proliferation and cytokine assays demonstrate that memory immunity to IE62 protein and to the glycoproteins gB, gC, gE, and gH is maintained for years after primary VZV infection (Table 2) (9, 102). Studies of T-lymphocyte responses to synthetic peptides that correspond to residues of the IE62 protein and gE demonstrate that several regions of each of these proteins can be recognized by most VZV-immune donors (25). IE62 protein and gE epitopes are immunogenic in individuals of diverse major histocompatibility complex (MHC) class II phenotypes. T-lymphocyte recognition of amphipathic regions of gB and gI, some of which exhibit helper B-cell function, have also been detected with VZV-specific $CD4^+$ T-lymphocyte clones from immune individuals (123).

TABLE 2. VZV proteins and peptides recognized by T lymphocytes from immune individuals[a]

Assay	T-cell subset	Viral proteins
T-cell proliferation		
Proteins		gE, gB, gH, gI, IE62
Peptides		gE, gB, gH, IE62
T-cell cytotoxicity		
Induction of clonal expansion by secondary stimulation	$CD4^+$	gE, gB, gI
Recognition of target cells expressing VZV proteins	$CD4^+$, $CD8^+$	gE, gI, gC, IE62

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Lysis of virus-infected cells by cytotoxic T lymphocytes is an important component of the host response to many viral pathogens. Cytotoxic T lymphocytes recognize viral peptides complexed with class I or II MHC antigens. $CD8^+$ T lymphocytes were first recognized as having cytotoxic function against infected cells that express class I MHC markers; in the case of VZV and other herpesviruses, cytotoxic T-lymphocyte function is also mediated by $CD4^+$ T lymphocytes that recognize viral peptides associated with class II MHC proteins (13, 125, 128). Primary VZV infection elicits cytotoxic T lymphocytes that recognize VZV glycoproteins and the IE62 protein (13). The VZV glycoproteins gE, gI, and gC are targets for cytotoxic T lymphocytes derived from PBMC of VZV-immune donors, and VZV-specific $CD4^+$ T-cell clones that recognize gE, gB, gH or gI have been generated (123, 235). In subjects immune to VZV, cytotoxic T lymphocytes that recognize the IE62 protein or gE are present in both the $CD4^+$ and $CD8^+$ memory T-cell populations and the precursor frequencies of cytotoxic T lymphocytes specific for the IE62 protein and gE are equivalent within both the $CD4^+$ and $CD8^+$ subpopulations (13).

Memory T lymphocytes that recognize VZV antigens are maintained at frequencies of approximately 1 in 40,000 PBMC in immune adults (124). These responses may persist because of periodic reexposures of immune individuals to VZV during the annual varicella epidemics. VZV T-cell proliferation responses, as well as IgG antibodies, are boosted in mothers of children with varicella (11). This mechanism of exogenous reexposure is supported by the observation that VZV is detected by PCR in oropharygeal secretions of close contacts of patients with varicella (48). VZV immunity may also be maintained by subclinical reactivations of latent virus associated with endogenous reexposure to viral antigens. This mechanism is difficult to document in healthy individuals, but it is suggested by the reestablishment of cell-mediated immunity to VZV in bone marrow transplant recipients with no clinical signs of herpes zoster in whom viral reactivation can be detected by PCR (262).

Viral virulence factors are likely to be important for the establishment of latent VZV infection in dorsal root ganglia. However, the clinical evidence demonstrates that host factors determine whether the individual with latent infection develops symptomatic VZV reactivation. T-lymphocyte-mediated immunity is critical in preserving the balance between the host and the virus, as demonstrated by the relationship between diminished recognition of VZV antigens by T lymphocytes in elderly adults and patients receiving immunosuppressive therapy and the increased risk of herpes zoster in these patients (89, 124, 187, 188). In contrast, the susceptibility of immunocompromised and elderly individuals to VZV reactivation does not correlate with decreasing titers of VZV IgG antibodies. Decreased VZV-specific cellular immunity appears to be a necessary but not sufficient condition for herpes zoster. Nevertheless, severe, prolonged suppression of cellular immunity is accompanied by a high incidence of symptomatic VZV reac-

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tivation, and cell-associated VZV viremia, with life-threatening dissemination, is frequent. Immunosenescence that occurs with aging correlates with impaired T-lymphocyte responses to VZV antigen, demonstrated by a decrease in delayed-type hypersensitivity responses to VZV skin test antigen and a decrease in the numbers of circulating T cells that recognize VZV antigen (26, 124, 188). Healthy and immunocompromised individuals who develop herpes zoster usually have a significant recovery of VZV-specific T-lymphocyte responses; the number of circulating T lymphocytes that recognize VZV antigens increases immediately as a consequence of the reexposure to viral antigens in vivo. Enhanced cell-mediated immunity to VZV following herpes zoster usually persists for a prolonged period and may explain why second episodes of herpes zoster are rare (122).

CLINICAL FEATURES

Varicella

Primary VZV infection is characterized by a relatively prolonged incubation period, ranging from 10 to 21 days, with the usual duration being 14 to 16 days (8, 260). About half of the cases begin with a prodrome of fever, malaise, headache, and abdominal pain; prodromal symptoms last about 24 to 48 h before the first skin lesions appear and are more common in older children and adults. Systemic symptoms, including fever, fatigue, and anorexia, persist or appear during the early exanthematous phase of the illness; severe respiratory symptoms and vomiting are unusual. Fever associated with uncomplicated varicella is usually less than 38.6°C (101.5°F) but may be as high as 41°C (106°F). The initial cutaneous lesions of varicella often involve the scalp, face, or trunk and are pruritic, erythematous macules; the maculopapular phase evolves to a vesicular phase, during which small, fluid-filled vesicles appear in existing or new erythematous lesions. The irregular zone of erythema surrounding these clear blisters leads to their "dewdrop on a rose petal" appearance. Ulcerative and often painful lesions appear on mucous membranes, including the oropharynx, conjunctivae, and vagina. The period of continued new-lesion formation ranges from 1 to 7 days in healthy children, with new lesions appearing in most children for 3 to 5 days. The crusting phase begins with clouding of the vesicular fluid, within about 24 to 48 h after the appearance of each lesion; umbilication of some lesions is evident as crusting begins. Most patients with primary VZV experience several "crops" of new lesion formation. The later crops are usually on the extremities and may not progress to the vesicular stage. The total number of varicella lesions is quite variable, from as few as 10 to more than 1,500 in healthy children; the usual range is 100 to 300 lesions. The varicella rash is more extensive in older children and in secondary household contacts who contract the disease. Patients with skin trauma, such as sunburn or eczema, may develop a more severe varicella exanthem (97). Lesions heal as new epithelial cells form at the base of the lesion; hypopigmentation is common during healing. Scarring is rare except where the first lesions appeared, usually along the hairline or eyebrows.

In contrast to other herpesviruses, primary VZV infection almost always causes signs of disease, although varicella may not be diagnosed in children who have only a few lesions and no known exposure. The differential diagnosis of varicella includes vesicular rashes associated with infections caused by other common pathogens, such as enteroviruses or *Staphylococcus aureus*, rashes due to drug reactions, and contact dermatitis and insect bites.

Uncomplicated varicella is usually associated with lymphopenia and granulocytopenia (131). Mild, subclinical hepatitis, diagnosed by slightly elevated liver function tests, is common (70). The resolution of viremia and new-lesion formation is accompanied by lymphocytosis and the presence of activated T lymphocytes in the circulation (10).

Complications of varicella. The complications of varicella identified by Fleisher et al. in 1981 (76) are essentially the same as those described by Bullowa and Wishik 61 years ago (37). The most common cause of varicella-related morbidity in otherwise healthy children is secondary bacterial infection, usually due to *S. aureus* or *Streptococcus pyogenes* (group A beta-hemolytic streptococcus) (37, 76, 115, 142, 263). Antibiotic therapy reduces the risk of life-threatening bacterial superinfection, but fatal sepsis or necrotizing fasciitis may still occur (142). Secondary bacterial infection of varicella lesions is most obvious as bullous progression or cellulitis surrounding one or more lesions (76). Regional lymphadenitis and subcutaneous abscesses may occur. Varicella gangrenosa, which is usually due to *S. pyogenes*, is diagnosed when an area of rapidly extending erythema with pain and induration appears around a single lesion, often on the trunk or an extremity (49). Bacterial infection, usually caused by *S. aureus* or *S. pyogenes*, at deep tissue sites may follow subclinical bacteremia in children with varicella. The common manifestations include staphylococcal or streptococcal pneumonia, arthritis, or osteomyelitis. Varicella lesions often involve the eyelids and bulbar conjunctivae, but serious ocular complications are rare; unilateral anterior uveitis or corneal lesions occur occasionally but usually resolve without sequelae (64).

Varicella appears to involve transient hepatitis in most children. Liver involvement is usually asymptomatic, but children with the highest elevation of liver function tests may have severe vomiting (70). The differential diagnosis of varicella hepatitis is Reye's syndrome, a noninflammatory acute encephalopathy with fatty degeneration of the liver, characterized by vomiting, signs of increased intracranial pressure, and progressive neurologic deterioration. Children with varicella should not be given aspirin, because it increases the risk of developing Reye's syndrome (138).

VZV dissemination to the lungs is a rare complication of varicella in healthy children, but the increased morbidity and mortality associated with varicella in adults is due primarily to the higher risk of varicella pneumonia in these patients (105, 157, 214, 215). Most patients with this complication develop cough and dyspnea 1 to 6 days after the onset of the rash. Varicella pneumonia can be diagnosed by chest X ray in as many as 10% of adults (250). Varicella pneumonia can be mild and transient, improving within 48 h without therapy, but may also progress to cause hypoxemia, which is often much more severe than is suggested by the physical examination. Physical abnormalities may be limited to fever and tachypnea, with few rales; the chest X ray usually shows interstitial pneumonitis with diffuse bilateral infiltrates and perihilar, nodular densities. Fulminant respiratory failure, requiring assisted ventilation, occurs in patients with severe cases (117).

Neurologic complications are the second most frequent indication for hospitalization of otherwise healthy children with varicella (76, 115, 175). Meningoencephalitis and cerebellar ataxia are the major clinical manifestations of central nervous system involvement, with some patients having signs of both cerebral and cerebellar disease (23, 146, 210). VZV was the cause of encephalitis in 13% of cases with defined etiology in surveillance studies by the Centers for Disease Control from 1972 and 1977 (217). Central nervous system complications are most common in patients younger than 5 years and older than

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20 years (214, 215, 217). Before the relationship between Reye syndrome and salicylates was understood, Reye syndrome complicated varicella in about 2.5 per 10,000 cases in healthy children (138). Neurologic complications usually occur 2 to 6 days after the onset of the rash, although there are case reports of encephalitis and ataxia preceding the rash (175, 260). Encephalitis begins with sudden changes in the level of consciousness, often accompanied by generalized seizures; signs of meningitis without altered sensorium may predominate in some patients. Cerebellar involvement, with irritability, ataxia, nystagmus, and speech disturbances, progresses more gradually. Patients with varicella encephalitis or cerebellar ataxia usually have a mild lymphocytic pleocytosis in the cerebrospinal fluid, a slight to moderate elevation of protein levels (<200 mg), and normal glucose levels; the cerebrospinal fluid may be normal (23). Varicella encephalitis is usually transient, resolving within 24 to 72 hours. Cerebellar ataxia often persists for days or weeks but usually resolves completely over time. The risk of fatal neurologic complications of varicella is difficult to determine; estimates range from 5 to 18%, but most mortality appears to be related to encephalitis rather than cerebellar ataxia (23, 146). No precise data concerning the risk of long-term sequelae among survivors of varicella encephalitis are available; most patients recover fully, but recurrent seizures and neurologic deficits persist in some cases (215). Transverse myelitis, causing paraplegia and sensory deficits, and transient hemiplegia due to cerebral vasculitis are rare complications of varicella; optic neuritis can occur alone or with acute transverse myelitis (98, 130, 146). Guillain-Barré syndrome is rarely associated with varicella.

Hemorrhagic complications of varicella are rare in healthy children with varicella, but adults are at higher risk (215). Thrombocytopenia during acute varicella is associated with bleeding into skin lesions, petechiae, purpura, epistaxis, hematuria, and gastrointestinal hemorrhage. Hemorrhagic disease may progress to disseminated intravascular coagulopathy. Purpura fulminans (caused by arterial thrombosis) is a very rare but life-threatening complication of varicella. Thrombocytopenia may begin 1 to 2 weeks or more after varicella; although bleeding complications may last for several weeks, complete recovery can be expected (75).

Nephritis is an unusual, late complication in children and adults with varicella and may result from secondary group A streptococcal infection rather than from VZV infection of renal cells (49). Diffuse edema and hypertension, associated with proteinuria, hematuria, and abnormal renal function tests occur within 3 weeks after the appearance of the rash. Nephrotic syndrome and hemolytic-uremic syndrome have been reported in a few children with varicella. Viral arthritis, with isolation of VZV from joint fluid, has been described; viral joint infection resolves spontaneously within 3 to 5 days and has not been associated with residual damage. Myocarditis, pericarditis, pancreatitis, and orchitis are other very rare complications of varicella (reviewed in reference 8).

Varicella in high-risk populations. Before antiviral drugs were available for clinical use, 32 to 50% of children with lymphoproliferative malignancies or solid tumors developed disseminated varicella, 20% had varicella pneumonia, and infection was fatal in 7 to 17% (73). The risk of life-threatening progressive varicella increases when the exposure is not identified and chemotherapy is given inadvertently during the incubation period; the risk is also increased when the absolute lymphocyte count is below 500 cells per mm^3. Primary VZV infection is of particular concern in bone marrow transplant recipients (120, 177). Varicella in immunocompromised children is characterized by prolonged formation of new lesions, increased numbers of cutaneous lesions, and the risk of dissemination, with pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy (20). Many immunocompromised children with varicella have new lesions for at least 7 days, and the average time to crusting is 14 days (260). Children with malignancy who have granulocytopenia are likely to have increased susceptibility to secondary bacterial infections. Pneumonia develops within 3 to 7 days after the onset of skin lesions; in one large series, all varicella-related deaths in children with leukemia occurred within 3 days after the onset of varicella pneumonia (73). Immunocompromised children with disseminated varicella are at risk for severe hepatitis and disseminated intravascular coagulopathy. Hemorrhagic lesions are a hallmark of serious disease; severe abdominal or back pain also suggests severe varicella, although its pathogenesis is not known. Varicella encephalitis may accompany other signs of VZV dissemination, but it is rarely the direct cause of mortality. Myocarditis, nephritis, pancreatitis, necrotizing splenitis, esophagitis, and enterocolitis are less common complications of disseminated VZV infection (reviewed in reference 260).

Varicella in organ transplant recipients is associated with a risk of progressive infection (71, 137, 160, 179, 183). Hepatitis and thrombocytopenia are more common than is varicella pneumonitis in kidney transplant patients. Severe varicella may occur in children receiving steroid therapy for rheumatoid arthritis, nephrotic syndrome, or ulcerative colitis (83). Fatal varicella has been reported in patients with asthma who received high doses of prednisone during the incubation period, but children on long-term, low-dose steroid therapy usually have uncomplicated varicella (240). Children with congenital severe combined immunodeficiency disorder, adenosine deaminase deficiency, nucleoside phosphorylase deficiency, or cartilage hair hypoplasia/short-limbed dwarfism are at risk for fatal varicella. Varicella can also be severe in children with Wiskott-Aldrich syndrome and ataxia telangiectasia. Children with HIV infection and varicella have hyperkeratotic lesions and prolonged periods of new-lesion formation, lasting weeks or months; dissemination to visceral organs is less common than in other immunocompromised patients (139, 147, 151, 168, 204, 239).

Primary VZV infection can cause morbidity and mortality affecting the mother and the fetus or newborn infant. Varicella is a rare complication of pregnancy in the United States, because most adults are immune. In a study of 30,000 pregnancies, the incidence was 0.7 per 1,000 women (237). In rare cases, maternal varicella in early gestation results in the congenital varicella syndrome; varicella in late pregnancy may result in premature delivery (202). The risk of varicella pneumonia appears to be increased when varicella is acquired during pregnancy. In a series of 44 pregnancies, varicella pneumonia occurred in 9% of patients and was fatal in one patient (2%). In another series, one death from varicella pneumonia occurred in 150 pregnancies (0.7%) complicated by varicella (238). Varicella embryopathy is most often associated with maternal varicella during the first 20 weeks of gestation, but the risk of embryopathy is low, with an incidence of only about 2% on the basis of combined data from available studies (19, 65, 202, 203). VZV is transmitted to the fetus in later gestation, as shown by the detection of VZV-specific immunity in infancy and the occurrence of herpes zoster during the first few years of life (62, 202). The congenital varicella syndrome is characterized by unusual cutaneous defects, with cicatricial skin scars and atrophy of an extremity (reviewed in reference 34). Infants often have microcephaly and cortical atrophy, seizures, and mental retardation; chorioretinitis, microophthalmia, and cat-

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aracts also occur. Fetal sonography may reveal limb anomalies or microcephaly (218). Neurogenic bladder, hydroureter, hydronephrosis, and severe gastroesophageal reflux with recurrent aspiration pneumonia are common in severely affected infants. Infants whose mothers develop varicella close to term are at risk for neonatal varicella. Without passive antibody prophylaxis, the attack rate for infants is about 20% and the mortality rate is about 30% when the mother develops varicella from 4 days before to 2 days after delivery (216). The risk is much lower if maternal varicella precedes delivery long enough to allow the transfer of IgG antibodies to VZV across the placenta. Infants of these mothers may be born with cutaneous varicella lesions or may develop lesions within the first 5 days of life, but they are not at risk for serious complications. Infants exposed to varicella by nonmaternal contact rarely have neonatal disease, because most are born to seropositive mothers and have passively acquired antibodies to VZV. Herpes zoster in pregnancy does not appear to result in the congenital varicella syndrome.

Herpes Zoster

The reactivation of VZV from latency causes a localized, pruritic, vesicular rash that usually appears unilaterally in the distribution of one or more adjacent sensory nerves. The initial lesions in the affected dermatome are usually clustered at a few sites anteriorly and posteriorly; as the cutaneous disease evolves, the vesicles often coalesce into larger, fluid-filled lesions. The rash is often preceded by several days of localized neuropathic pain. Acute neuritic pain and hypersensitivity frequently accompany the appearance of the vesicular lesions. Herpes zoster most often involves the thoracic dermatomes, particularly T5 to T12; 14 to 20% of patients have disease in the distribution of a cranial nerve, and lumbosacral dermatomes, especially L1 to L2, are affected in 16% of patients (132). Scattered cutaneous lesions outside the primary dermatome are observed occasionally in the healthy host. About 40% of healthy individuals with herpes zoster have elevated leukocyte counts and protein levels in the cerebrospinal fluid; VZV has been isolated from the cerebrospinal fluid of these patients (106). New-lesion formation in the primary dermatome usually stops within 3 to 7 days, but it can progress to cover the complete dermatome. In the healthy individual, the affected dermatome usually heals within 2 weeks but may not resolve for 4 to 6 weeks (8, 260). Cutaneous hypersensitivity persists for several months in 5 to 10% of patients. Although the rash is the hallmark of herpes zoster, "zoster sine herpete" is diagnosed in patients who have acute unilateral neuropathic pain but no rash (43, 99, 101). In these patients, laboratory evidence of VZV reactivation is based on increased IgG antibody titers between acute- and convalescent-phase specimens (99). The occurrence of the syndrome has been correlated with VZV reactivation determined by PCR (101). Some cases of facial palsy without skin lesions may be due to VZV reactivation (74).

Complications of herpes zoster. The most common and debilitating complication of herpes zoster is PHN. In a population-based study, 9% of cases of herpes zoster were associated with PHN lasting 4 weeks to more than 10 years; pain persisted for more than 1 year in 22% of individuals who developed the syndrome (221). The risk of PHN increases in parallel with increasing age and is high among immunocompromised patients (23, 234, 255, 260). Other risk factors for PHN are less certain. Whether there is any correlation between the severity and duration of acute pain or the severity of cutaneous disease and the risk of PHN has not been established. When pain was assessed as a continuum, beginning with the onset of rash in placebo recipients of randomized studies of oral acyclovir, the median duration of zoster-associated pain was 62 days in the patients, whose mean age was 50 years (135). The risk of prolonged PHN is as high as 40 to 50% in individuals older than 60 years (255).

Herpes zoster can be complicated by extension to the central nervous system, causing encephalitis, but this event is rare, affecting only 0.2 to 0.5% of patients (143, 224). Older age and cranial nerve involvement are risk factors for zoster-associated encephalitis. The reported interval from the onset of cutaneous lesions to the occurrence of encephalitis is 9 days, with the range up to 6 weeks. The initial signs include altered sensorium, headache, photophobia, or meningismus; the electroencephalogram is usually diffusely abnormal (23, 143, 224). Cranial or peripheral nerve paresis occurs in some patients with central nervous system complications of herpes zoster. In one series, the mean duration of encephalitic symptoms was 16 days but symptoms persisted longer in patients with paresis (143).

The morbidity and mortality rates for encephalitis related to herpes zoster are low; most patients recover without any residual damage (23). Encephalitis, which may be associated with acute vasculitis, is distinguished clinically from cerebral angiitis. Cerebral angiitis is a syndrome of vasculitis, thrombosis, and microinfarcts which is associated with herpes zoster ophthalmicus or reactivation involving other cranial nerves in elderly individuals (129). Cerebral angiography demonstrates segmental constriction of the ipsilateral cerebral arteries, and computed tomographic brain scans usually show an infarct in areas perfused by the middle cerebral artery. In contrast to VZV-related encephalitis, the risk of fatal disease is as high as 20% in these patients. Transverse myelitis is a rare complication of herpes zoster, but the mortality rate is high when it occurs (98).

Although VZV reactivation involving the ophthalmic branch of the trigeminal nerve may be associated with conjunctivitis, dendritic keratitis, anterior uveitis, iridocyclitis, and panophthalmitis, blindness following herpes zoster ophthalmicus is rare (150, 172). Vision loss following herpes zoster is usually caused by retrobulbar neuritis and optic atrophy (67, 127). Facial palsy may accompany herpes zoster involving the third, fourth, and sixth cranial nerves. VZV reactivation involving the seventh cranial nerve produces facial palsy on the same side as the cutaneous lesions (224). Lesions on the tongue indicate seventh-nerve involvement and may be associated with loss of taste (55). Herpes zoster of the second or third branch of the fifth cranial nerve produces oral lesions. The Ramsey-Hunt syndrome (herpes zoster oticus and facial palsy) follows VZV reactivation in the geniculate ganglion of the seventh cranial nerve and the eighth nerve. Herpes zoster involving lumbosacral ganglia may be accompanied by bladder dysfunction or ileus (224).

The motor deficits that accompany some cases of herpes zoster, including facial palsies, usually resolve over time (143). Elderly patients are at highest risk for prolonged weakness, which may occur in 10 to 15% of cases.

Herpes zoster in high-risk populations. Immunosuppression increases the morbidity and mortality associated with herpes zoster, primarily because of the occurrence of pneumonia, but the overall risk of fatal recurrent VZV is less than 1% (20, 58, 72, 177, 260). Immunocompromised patients with herpes zoster usually have more severe local dermatomal disease; depending upon the degree of immunosuppression, these patients are also at increased risk for viremia and visceral dissemination (20, 187). The duration of untreated herpes zos-

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ter in patients with malignancy or organ transplantation is 2 to 4 weeks, compared with less than 2 weeks in otherwise healthy patients (20, 260). Some immunocompromised patients develop chronic VZV reactivation, which persists unless immunosuppressive therapy is reduced or antiviral therapy is given; AIDS patients are particularly susceptible to this complication. Cutaneous dissemination, defined as the appearance of lesions outside of the primary dermatome, is due to viremia; it occurs in 10 to 40% of immunocompromised patients with herpes zoster and provides a marker for possible visceral dissemination (58, 120). Dissemination following VZV reactivation can cause pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy (260). VZV reactivation in high-risk patients, especially bone marrow transplant recipients, may cause atypical nonlocalized herpes zoster (177). The diffuse vesicular rash caused by reactivation in these patients is indistinguishable clinically from varicella; this form of recurrent VZV has a higher mortality rate than does localized herpes zoster. Episodes of severe or fatal VZV reactivation, manifesting as a sepsis-like syndrome or as central nervous system disease, without any cutaneous lesions, have been reported (60, 177).

Herpes zoster is an early clinical sign of underlying HIV infection in high-risk populations. These patients are at risk for progressive, disseminated, or chronic VZV reactivation (1, 36, 42, 113, 165). Some episodes of retinitis in patients with AIDS are due to VZV rather than human cytomegalovirus (68, 79, 127). Progressive central nervous system infection due to VZV reactivation is extremely rare except in patients with AIDS. Unusual neurologic complications of VZV, such as vasculitis involving cerebral vessels or multifocal leukoencephalopathy, may occur without any signs of cutaneous infection or may progress after cutaneous lesions have disappeared (1, 4, 108).

LABORATORY DIAGNOSIS

The rapid laboratory confirmation of the diagnosis in cases of suspected varicella or herpes zoster can be an important clinical resource to guide the prescription of antiviral therapy; serologic tests are useful to identify individuals who may benefit from immunization with varicella vaccine (reviewed in reference 95).

Virologic Methods

Virologic methods for the laboratory diagnosis of VZV detect the presence of infectious virus, viral DNA, or viral protein in clinical specimens (51, 59, 78, 103, 140, 233). For maximum efficacy, antiviral therapy must be initiated as soon as possible after the onset of varicella or herpes zoster; therefore, it is important to make sensitive, specific, and rapid direct detection methods available to the clinician. Immunofluorescence or immunoperoxidase procedures with polyclonal or monoclonal antibodies to VZV antigens allow the rapid identification of VZV proteins in specimens of epithelial cells from suspected VZV lesions (59, 103, 208, 223, 233). The optimal sensitivity of these methods requires obtaining cells from the base of the lesion after unroofing a fresh vesicle or vesicles. Specific antibodies to HSV are usually used as a control reagent to stain a portion of the specimen, since the clinical differentiation of VZV and HSV lesions is often difficult. VZV proteins can also be detected in swab specimens from cutaneous VZV lesions by enzyme immunoassay methods (140). Direct and indirect immunofluorescence or immunoperoxidase methods are effective for detecting VZV-infected cells in tissue sections of lung, liver, brain, and other organs of patients with disseminated primary or recurrent VZV infection. Cytologic methods such as Tzanck smears were used before specific immunohistochemical stains were available, but these methods demonstrate only the presence of inclusion-containing or multinucleated giant cells in lesion specimens or tissue sections and do not distinguish VZV from other herpesviruses. Since the icosahedral structure of VZV virions is a morphologic characteristic of all herpesviruses on electron microscopy, electron microscopy is rarely useful for the clinical diagnosis of VZV infection.

The unequivocal diagnosis of VZV infection requires the detection of infectious virus in cell culture, but this method is less useful for VZV than for other viruses because of the relatively prolonged time required to detect cytopathic changes (95). Even under optimal conditions, cell culture methods for VZV isolation are substantially less sensitive than are those for HSV and human cytomegalovirus. Infectious VZV is most likely to be isolated from early vesicles with clear fluid rather than cloudy or crusted lesions. Infectious VZV is usually recoverable from varicella lesions for 2 to 3 days but can be isolated from herpes zoster lesions for a week or longer. Depending on the clinical circumstances, infectious VZV may be recovered from PBMCs, joint fluid, cerebrospinal fluid, or bronchial washings (107). The lungs are the most common organs from which VZV has been isolated at autopsy, but the virus has been recovered from many sites, including the heart, liver, pancreas, gastrointestinal tract, brain, and eyes.

VZV replication in vitro is optimal in primary human cells, particularly human embryo lung fibroblasts, but the virus also infects nonhuman cells, including primary monkey kidney cells, Vero cells, guinea pig embryo fibroblasts, and rabbit kidney cells (170; reviewed in references 8 and 95). Vesicular fluid of fresh cutaneous lesions, together with infected cells swabbed from the base of the lesion, is the best specimen for VZV culture. By using clinical specimens that are obtained carefully and well-maintained cell cultures, cytopathic changes are usually visible by phase-contrast microscopy within 2 to 7 days. If the sample contains a lower titer of virus, the interval may be 14 days or longer. If no cytopathic effect is observed by 7 days, VZV may be amplified by trypsinizing the inoculated cell monolayer and passaging to fresh cell cultures (95). Because the cytopathic effects produced by VZV, HSV, and human cytomegalovirus are similar, the identity of the virus isolate must be confirmed by staining with virus-specific antisera. Shell vial cultures combine centrifugation and staining with the use of fluorescein-conjugated monoclonal antibodies to detect synthesis of VZV proteins in infected cells before a cytopathic effect is visible; positive results may be available within 1 to 3 days after inoculation of the specimen (32). This method can improve the sensitivity of VZV culture and allows the more rapid identification of positive specimens.

Adverse conditions during transport may reduce the ability of the laboratory to recover infectious virus from clinical specimens (170). The specimen should be kept on dry ice or frozen at −70°C or below if storage for more than a few hours is required, because VZV is temperature sensitive; storing the specimen at −20°C for 24 h or longer usually inactivates the virus (95). Since infected-cell viral proteins persist after the cessation of viral replication, immunologic assays to detect infected cells or viral antigens may be positive when viral cultures are negative.

Hybridization and PCR methods are sensitive and specific for the detection of VZV in clinical specimens from patients with primary or recurrent VZV infections. Methods used include radiolabeled or biotinylated nucleic acid probes that hybridize to VZV DNA or RNA in Southern blot or in situ hybridization procedures or PCR amplification of conserved

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sequences of VZV DNA (51, 78, 80, 101, 156, 195). These methods are usually more sensitive than viral culture, but precise standardization of hybridization and PCR methods is essential to avoid false-positive results. In addition, positive results with these methods do not prove that infectious virus is present. The application of highly sensitive methods for VZV detection also requires careful consideration of the patient's clinical condition before an etiologic role or potential pathologic effect is assumed. For example, the use of PCR to detect fetal infection after maternal varicella during pregnancy is problematic because VZV infection can occur without harm to the fetus (167, 202). Whenever possible, correlation of PCR results with viral culture results is important for the reliable laboratory diagnosis of VZV infection. As is true of other herpesviruses, detection of VZV by PCR may be an accurate but incidental finding in many clinical circumstances.

Molecular epidemiologic characterization of VZV isolates can be accomplished by restriction endonuclease digestion of viral DNA, but this information is not necessary to guide the clinical management of patients (164, 244).

Serologic Methods

Serologic methods for the diagnosis of primary VZV infection require testing of acute- and convalescent-phase serum specimens for IgG or IgM antibodies to VZV. While many methods can be used to detect VZV antibodies, serologic approaches to the diagnosis of acute varicella or herpes zoster are of limited value because rapid confirmation of VZV infection is usually required. Testing for VZV IgM antibodies is not useful clinically, because the methods lack specificity and sensitivity; false-positive results are common in the presence of high IgG titers to the virus, which are expected in individuals with acute VZV infection. VZV reactivation induces IgM antibodies to VZV in many patients, so that their presence does not differentiate primary from recurrent VZV infection (148). A substantial VZV IgA antibody response is also elicited during both primary and recurrent VZV infections (29). Interpreting results of fetal blood tests for VZV IgM antibodies when a pregnancy is complicated by maternal varicella is difficult, because functional humoral immunity may not be present in the fetus during early gestation and intrauterine infection does not damage the fetus in every case (202). Local production of IgG antibodies, with a rise in VZV IgG titers in cerebrospinal fluid, occurs in patients with VZV-related encephalitis but provides only a retrospective diagnosis (87). A rise in VZV IgG titers in paired serum samples may help to identify the etiology of pain syndromes due to zoster sine herpete or to indicate a possible etiologic role of the virus in facial palsies not associated with cutaneous signs of VZV infection (99). VZV PCR may be more useful when specimens are tested in laboratories with experience in diagnosis of this clinical entity (101). In any case, the relationship of these clinical syndromes to VZV must be considered tentative in individual cases, and other etiologies should be sought as well.

The most important value of assays for IgG antibodies to VZV is to determine the immune status of individuals whose history of varicella is unknown or uncertain. Many clinical circumstances arise in which is necessary to know whether an individual remains susceptible to VZV, because passive antibody or active vaccine prophylaxis is available for them. In addition to defining susceptibility to primary VZV infection, testing for IgG antibodies to VZV defines whether immunocompromised patients are at risk for reactivation. The presence of IgG antibodies to VZV is a marker of latent infection unless the patient has received passive antibodies through recent administration of immune globulin or a blood product for other indications. The fluorescent-antibody membrane antigen assay, which detects binding of antibodies in sera to membranes of unfixed VZV-infected cells, is a highly sensitive and specific test, as is testing for antibodies to purified VZV proteins by enzyme immunoassay or immunoblotting. VZV neutralization and radioimmunoassay methods are sensitive and specific but not practical for clinical diagnostic virology laboratories. Commercial enzyme immunoassay methods to assess the presence of VZV antibodies are highly specific, generating few false-positive results, but they are not as sensitive as the fluorescent-antibody membrane antigen assay or other research methods; 10 to 15% of individuals who are immune to VZV may be identified as susceptible in these commercial tests (161, 241). VZV IgG antibodies are not detected consistently by complement fixation, especially several years after primary infection; this method should be used only to document the humoral immune response to primary or recurrent VZV infections and is now rarely relied upon in clinical practice. New latex agglutination methods are sensitive as well as specific for determining VZV immune status and are a useful alternative to more complex methods such as the fluorescent-antibody membrane antigen assay (162, 241). Enzyme immunoassays may be used for general screening purposes because many specimens can be tested at once, but if the serologic result seems inconsistent with the clinical history, confirmatory testing by latex agglutination may be helpful (241).

ANTIVIRAL THERAPY

Acyclovir, famciclovir, and valacyclovir are the antiviral agents that are licensed for the treatment of VZV infections (Tables 3 and 4). These nucleoside analogs have replaced vidarabine and IFN-α, which were the first antiviral agents shown to have clinical efficacy for treating life-threatening primary and recurrent VZV infections in immunocompromised patients (12, 20, 58, 261). Since acyclovir is phosphorylated initially only by the viral thymidine kinase (deoxypyrimidine kinase), the drug is inactive except within VZV-infected cells that contain the viral enzyme. Cellular kinases metabolize the monophosphate to the triphosphate form of the compound, which acts as a competitive inhibitor and chain terminator of viral DNA polymerase. Acyclovir inhibits HSV by the same pathway, but its specific activity is significantly lower against clinical isolates of VZV. The usual concentrations required for VZV inhibition are about 1.0 to 2.0 mg/ml (range, 0.3 to 10.8 mg/ml) (28). In contrast, HSV-1 and HSV-2 isolates are usually inhibited by 0.1 to 0.2 mg of acyclovir per ml. Famciclovir is the diacetyl, 6-deoxy ester of penciclovir, which is a guanosine nucleoside analog (63, 248). Metabolism of the drug to penciclovir begins with uptake by intestinal cells and is completed in the liver. The phosphorylation of penciclovir, like acyclovir, is mediated by the viral thymidine kinase followed by cellular kinases; high concentrations of the triphosphate form accumulate within VZV-infected cells. Valacyclovir is a valine ester derivative of acyclovir with improved oral absorption; it is modified to acyclovir immediately after absorption and has the same mode of action against VZV as the parent compound does (220). BVaraU (1-β-D-arabinofuranosyl-E-5-[2-bromovinyl]uracil) (sorivudine) is another nucleoside compound that is distinctive for its very high inhibitory activity against VZV in vitro (50% infective dose 0.0003 μg/ml) (180).

The pharmacokinetics of acyclovir given intravenously result in prolonged concentrations in plasma that are well above the VZV inhibitory range when given at doses of 10 mg/kg of body

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TABLE 3. Use of acyclovir for the treatment of varicella

Use of acyclovir
Acyclovir indicated
Patients
Malignancy, bone marrow or organ transplantation, high-dose steroid therapy
Congenital T-cell immunodeficiencies
HIV infection
Neonatal varicella after maternal varicella beginning within 5 days before or 2 days after delivery
Associated pneumonia or encephalitis
Administration
Initiate as soon as possible after initial lesions appear
Intravenous route[a]
Children < 1 yr, 10 mg/kg/dose given every 8 h as 1-h infusion
Children > 1 yr, 500 mg/m^2/dose given every 8 h as 1-h infusion
Adults, 10 mg/kg/dose given every 8 h as 1-h infusion
Duration, 7 days or until no new lesions have appeared for 48 h
Acyclovir optional
Patients
Chronic cutaneous disorders
Chronic diseases that may be exacerbated by acute VZV infection such as cystic fibrosis or other pulmonary disorders, diabetes mellitus, disorders requiring chronic salicylate therapy or intermittent steroid therapy
Otherwise healthy children, especially those >12 yr or secondary household contacts, and adults
Administration
Initiate within 24 h after initial lesions appear
Oral route
Children, 20 mg/kg/dose (maximum 800 mg/dose) given as four doses a day
Adults, 800 mg/dose given as five doses a day
Duration, 5 days

[a] Selected patients who are considered at relatively low risk for VZV dissemination may be treated with oral acyclovir and carefully monitored for disease progression. Famciclovir and valacylovir provide higher concentrations in plasma but are not yet approved for use in immunocompromised patients.

weight or 500 mg/m^2 every 8 h (260). Drug concentrations of 15 to 25 μg/ml in plasma are achieved with this regimen. Peak concentrations in plasma after oral administration of acyclovir are only about 1.0 to 1.5 μg/ml even when the drug is given at high doses of 800 mg every 4 h. In contrast, approximately 75% of the oral dose of famiciclovir is absorbed and the active form of the drug persists for several hours within infected cells. Valacyclovir, given as 2 g four times a day, yields concentrations in plasma and area-under-the-curve kinetics that are equivalent to those following intravenous administration of acyclovir. BVaraU (sorivudine) is well absorbed after oral administration, with pharmacokinetics that permit a once- or twice-daily dosage regimen.

TABLE 4. Antiviral agents for treatment of herpes zoster

Drug	Current status	Comment
Acyclovir	Licensed	Extensive clinical experience
Famciclovir	Licensed	Enhanced oral absorption
Valacyclovir	Licensed	Enhanced oral absorption
BVaraU (sorivudine)	Clinical trials in progress	High in vitro activity against VZV
Foscarnet	Licensed	May be useful for acyclovir-resistant strains
IFN-α	Licensed	May be useful for acyclovir-resistant strains

As in other herpesvirus infections, antiviral therapy does not eliminate VZV from the host, so that further episodes of reactivation can occur when treatment is stopped. The thymidine kinase gene is not essential for VZV replication; in vitro incubation of VZV isolates with acyclovir results in the selection of thymidine kinase-negative mutants. Prolonged administration of acyclovir, especially at low doses to patients whose limited host response allows persistent VZV replication, can select for thymidine kinase-negative VZV mutants (141, 201, 227). Emergence of resistant VZV strains is unusual but has been reported in severely immunocompromised patients, especially AIDS patients who have chronic VZV reactivation and do not recover cell-mediated immunity to the virus (21, 31). Newer agents, including famciclovir, valacyclovir, and BVaraU, inhibit VZV by mechanisms similar to those used by acyclovir and are therefore not effective against thymidine kinase-negative VZV strains. Foscarnet and IFN-α are unrelated drugs that have some clinical efficacy in high-risk patients and are the current alternative agents for treatment of acyclovir-resistant VZV infections (104, 227). Dihydroxypropoxymethylguanine (ganciclovir) has in vitro activity against VZV equivalent to that of acyclovir, but clinical studies of its efficacy have not been done because of its greater toxicity. Novel antiviral agents that inhibit VZV may be useful for patients with acyclovir-resistant VZV infections, since they are designed to interfere with genes that encode proteins other than thymidine kinase, such as ribonucleotide reductase (126, 227, 238).

Varicella

Antiviral therapy prevents progressive varicella and visceral dissemination and compensates for the diminished host response in immunocompromised children with varicella (Table 3). Varicella mortality is decreased primarily because VZV pneumonia does not occur or progressive pneumonia is prevented (20, 73, 219). Antiviral therapy has dramatically changed the prognosis for varicella in high-risk children, decreasing the mortality rate from 7 to 10% to few or no fatalities (Table 3). For optimal efficacy, acyclovir treatment for varicella in immunocompromised children should be initiated within 24 to 72 h after the onset of the rash. Because of poor oral absorption, the drug is given intravenously at a dose of 500 mg/m^2 per dose every 8 h; therapy is continued for 7 days or until no new lesions have appeared for at least 48 h (20, 261). If the diagnosis is uncertain, it can be confirmed within a few hours by rapid antigen detection methods. Treatment should not be delayed until severe cutaneous disease is evident, because visceral dissemination frequently occurs during the same period; varicella pneumonia develops within 4 to 8 days in immunodeficient patients. Early acyclovir therapy also reduces the severity of the cutaneous varicella exanthem, which may reduce the risk of secondary bacterial infections. Treatment with intravenous acyclovir is indicated for healthy as well as high-risk patients with varicella who have pneumonia, hepatitis, thrombocytopenia, or encephalitis (117). Supportive therapy, including assisted ventilation and other intensive care measures, improves survival, since damage to lungs, liver, and other organs caused by VZV is reversible in many cases.

Oral acyclovir is licensed for the treatment of varicella in healthy children and adults on the basis of its clinical efficacy and its safety as demonstrated in large-scale, placebo-controlled clinical studies (2, 22, 61, 250). Acyclovir decreases the severity of primary VZV infection in otherwise healthy chil-

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dren, adolescents, and adults as long as treatment is started within 24 h after the appearance of the first cutaneous lesions (61). Oral acyclovir given at 20 mg/kg four times a day for 5 days reduced the occurrence and number of days of fever, the number of days of new-lesion formation, the total number of cutaneous lesions, and pruritus in healthy children aged 2 to 12 years (61). Acyclovir modifies the clinical course of varicella in all age groups, but the effect may be more important clinically in children who are 5 to 12 years old or are infected by being secondary household contacts, because the illness may be more severe in these groups. Oral acyclovir initiated within 24 h also alters the clinical course of varicella in adolescents, aged 13 to 18 years, and young adults, with a reduction in the number of days of fever and new-lesion formation as well as in the total number of varicella lesions (22, 250). The incidence of pneumonia in the placebo group was too low to show a reduction in the risk of this complication, but the general effect on viral replication suggests that treatment could limit virus spread to the lungs, as is observed in immunocompromised children (219). Acyclovir therapy does not diminish the acquisition of long-term immunity to VZV in children or adults (61, 66).

The efficacy of famciclovir and valacyclovir for varicella has not been evaluated in healthy or immunocompromised patients. BVaraU (sorivudine), given as a single dose of 40 mg/day for 5 days, is being studied in otherwise healthy young adults with varicella (251). The initial data analysis indicates that the drug reduces fever, the time to cessation of new-lesion formation, the time to complete crusting, and the total number of cutaneous lesions compared with placebo and that efficacy can be documented even when treatment is not initiated until 24 to 96 h after onset of the rash (251).

Herpes Zoster

Placebo-controlled studies of intravenous and oral acyclovir have demonstrated a clinical benefit in healthy and immunocompromised patients with herpes zoster who were treated within 72 h after onset (134, 184, 265, 266). Reductions in the number of days of new-lesion formation, the extent of involvement of the primary dermatome, and the time to crusting and healing were observed. The acute neuropathic pain that usually accompanies VZV reactivation in otherwise healthy individuals over 50 years of age was also less severe in acyclovir-treated patients in most of the clinical trials. Because of its limited absorption, oral acyclovir must be given as 800 mg five times a day. Clinical studies of famciclovir and valacyclovir indicate that these newer agents are as effective as acyclovir for the treatment of acute herpes zoster in immunocompetent individuals (27, 185, 228). Better oral absorption means that famciclovir and valacyclovir require less frequent administration and achieve levels in the blood that exceed those required to inhibit VZV in vitro. The superiority of these agents to acyclovir has not been established unequivocally, although the data from placebo-controlled trials suggest that these agents have more effect on the signs and symptoms of acute disease than acyclovir does. Whether the differences in clinical efficacy are important enough to justify the use of more expensive drug regimens is not yet certain. Valacyclovir is given as 2 g four times a day. The recommended dose of famciclovir is 500 mg three times a day in the United States and 250 mg three times a day in the United Kingdom.

Because of their greater risk of severe acute disease, elderly individuals (≥60 years old) are most likely to benefit significantly from antiviral therapy for herpes zoster. Ophthalmic zoster should be treated when possible because of the risk of acute uveitis and chronic keratitis; treatment of herpes zoster involving other cranial nerves is also indicated because of the frequency and severity of complications. Herpes zoster in healthy individuals does not always require antiviral treatment. Herpes zoster in healthy, younger individuals is often mild and may be treated symptomatically. Alternatively, antiviral therapy may have clinical benefit when administration of the drug can be started within 48 h after onset of symptoms or while new vesicles are appearing in the dermatome.

PHN causes serious morbidity in otherwise healthy elderly individuals. Although antiviral therapy reduces acute neuropathic pain, effects on PHN have been limited in most clinical studies (135). The apparent lack of correlation between effects on acute and chronic pain suggests that postherpetic pain is due to different mechanisms from those that cause acute pain (212). The failure of immediate antiviral therapy, even when it is given intravenously, to have a definitive impact on the occurrence of PHN suggests that extensive tissue destruction in sensory ganglia due to VZV reactivation may precede the cutaneous rash. The frequent occurrence of prodromal pain, which is especially common in elderly patients, may indicate that irreversible neuropathologic changes have occurred when the cutaneous process begins. In clinical practice, cutaneous lesions lead to the diagnosis of herpes zoster, but it is not clear whether improving antiviral drug concentrations in dorsal root ganglia at this point in the disease evolution can affect PHN. How the severity or duration of acute pain correlates with the risk of PHN is also uncertain; some patients who have little acute pain progress to severe PHN in spite of early antiviral therapy (135). Steroid therapy has been considered a potential adjunct to antiviral therapy for herpes zoster because some patients have an inflammatory response within the spinal cord (255). However, most clinical reports document little or no effect on the attack rate for PHN in patients given steroids for the acute disease (69). In a randomized comparison with a standard 7-day course of acyclovir without steroids, the frequency of PHN was not diminished by adding prednisolone or extending the course of acyclovir therapy to 21 days and adverse effects were more common in patients given steroids (264).

Acyclovir is given intravenously at 500 mg/m^2 or 10 mg/kg every 8 h to patients who are at high risk for disseminated disease; treatment is continued for 7 days or for 2 days after the cessation of new-lesion formation (20, 260). Prompt treatment with intravenous acyclovir decreases the duration of cutaneous VZV replication to an average of 4 days, reduces the duration of new-lesion formation to approximately 3 days, and prevents cutaneous and visceral dissemination. Acute pain is terminated within about 4 days, and lesions are crusted by 7 days and healed within 2 to 3 weeks (260). Immunocompromised patients may benefit even when antiviral therapy is not initiated until more than 72 h after symptoms develop, because of the increased clinical severity of recurrent VZV disease in these populations (20, 213, 260). Oral acyclovir is accepted for treatment of recurrent VZV in immunocompromised patients who are judged to be at low risk of visceral dissemination (176). Immunodeficient patients treated with oral antiviral drugs should be monitored carefully and switched to intravenous acyclovir if necessary.

Recurrent episodes of herpes zoster occur in some immunocompromised patients within a few days or weeks after acyclovir therapy is stopped, but most patients respond to treatment with a second course of acyclovir (176). These episodes are usually attributed to the poor host response rather than to acyclovir resistance.

Oral famciclovir and valacyclovir are not approved for treatment of herpes zoster in immunocompromised patients, but

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these new drugs will probably be effective on the basis of experience in immunocompetent patients. BVaraU, 50 mg three times a day, is being evaluated in healthy and immunocompromised patients with herpes zoster. It must not be given to patients who are receiving 5-fluorouracil because of the risk of serious hepatotoxicity with simultaneous treatment. Long-term, high-dose administration of BVaraU is associated with carcinogenicity in rats, but administration of the drug for clinical treatment of VZV infections requires only short-term exposure to low doses (104). Another new nucleoside agent, 882C87, exhibits high activity against VZV in vitro (205).

PREVENTION

VZV transmission to susceptible individuals is difficult to prevent because infected persons are contagious for 24 to 48 h before the clinical signs of varicella are obvious. As a result, restrictions on attendance, although a routine practice, do not alter varicella spread in schools (33). Susceptible health care workers who have had a close exposure to varicella should not care for high-risk patients for 10 to 21 days after the exposure. VZV is detected in air samples by PCR, and transmission through air flow systems within hospitals has been documented (166, 229). Infected patients must be cared for in isolation rooms with filtered air systems to limit spread to high-risk patients in the hospital environment.

Passive Antibody Prophylaxis

VZIG is a high-titer preparation of VZV IgG antibodies which is distributed by the American Red Cross Blood Services; the dosage is one vial per 10 kg of body weight given intramuscularly (Table 5) (38, 47). VZIG prophylaxis is indicated for susceptible high-risk individuals, including immunocompromised children and pregnant women, who have had a close exposure to an individual with varicella or herpes zoster and who can be given VZIG within 96 h (preferably within 48 h) after the exposure (86, 267). Newborn infants exposed to maternal varicella should also receive VZIG. Because of the high cost of VZIG, it is cost-effective to test pregnant women who are presumed susceptible for VZV IgG antibodies before giving VZIG, because most adults are immune to VZV regardless of the clinical history. VZIG is no longer recommended for healthy susceptible adults, because these individuals can be monitored and treated with oral acyclovir immediately if illness occurs. Although the risk of VZV transmission from an individual with herpes zoster is low, susceptible high-risk patients who have had close contact with a patient with VZV reactivation should receive VZIG (Table 5).

Some patients develop varicella despite VZIG prophylaxis at the time of exposure, particularly after household exposures (189). Although passive antibody prophylaxis lowered the risk of varicella pneumonia significantly compared with no intervention, 11% of children in one series developed this complication (73). VZIG prophylaxis is not necessary for immunocompromised patients who are receiving or have received high-dose intravenous VZIG (100 to 400 mg/kg) within 3 weeks before the exposure. A second dose of VZIG should be given if a new exposure to varicella occurs more than 2 weeks later. Passive antibody prophylaxis does not reduce the risk of VZV reactivation in high-risk populations, and administration after the appearance of symptoms does not alter the clinical course of herpes zoster (242).

TABLE 5. Use of VZIG as varicella prophylaxis in high-risk populations[a]

VZIG usage
Patients at risk
Immunocompromised children with no history of varicella
Pregnant women with no history of varicella and no antibodies to VZV[b]
Infants born to mothers with varicella beginning within 5 days before or 2 days after delivery
Premature infants <28 wk gestation or <1,000 g and hospitalized premature infants with no maternal history of varicella and/or no antibodies to VZV
Criteria for close exposure
Varicella
Household contact
Close indoor contact, defined as face-to-face exposure to playmate, schoolmate, or other infected individual
Hospital contact with an index case in the same room, ward, or nursery
Hospital contact by face-to-face exposure to an infected patient, staff member, visitor, or other individual
Newborn exposure to maternal varicella
Herpes zoster
Intimate, direct contact with infected individual
Administration of VZIG
VZIG must be given within 96 h and when possible within 48 h after exposure
Dose, one vial (125 U) per 10 kg of body weight by intramuscular injection[c]

[a] Further recommendations of the American Academy of Pediatrics are given in reference 38.
[b] Serologic testing is recommended when results can be obtained immediately, because most adult women with no history of varicella are immune.
[c] VZIG must not be given intravenously.

Antiviral Prophylaxis

Acyclovir prophylaxis to prevent reactivation is used rarely in clinical practice, because most recurrent VZV infections can be treated effectively with antiviral therapy when symptoms appear (234, 260). The efficacy of acyclovir prophylaxis for VZV suppression has been evaluated in bone marrow transplant recipients, who are at high risk for recurrent VZV infections. An inhibitory effect can be shown during treatment, but VZV reactivation occurs when the acyclovir treatment is discontinued (209). The net result is to lengthen the interval between transplantation and VZV recurrences, but the overall incidence of herpes zoster is unchanged. In general, prolonged administration of acyclovir should be avoided to prevent the selection of thymidine kinase-negative VZV strains that are resistant to the drug (22, 31). There is some clinical experience of using acyclovir prophylaxis for close contacts of children with varicella, but it is not recommended for this indication (2, 133).

Live Attenuated Varicella Vaccine

Takahashi et al. first developed and tested a live attenuated varicella vaccine during the 1970s (245). The vaccine contains the Oka strain of VZV, a clinical isolate that was passaged in guinea pig embryo fibroblasts and expanded for vaccine production in WI38 cells. The live attenuated varicella vaccine, made from the Oka strain, is the first human herpesvirus vaccine that has been licensed for clinical use in several countries (18, 94, 96). Using the Takahashi method and the Oka strain of VZV, Merck & Co., Inc., have evaluated a similar live atten-

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TABLE 6. Indications and contraindications for the administration of live attenuated varicella vaccine[a]

Indications and contraindications
Indications
Age 12 mo–13 yr
One dose[b] (susceptible by history)
Age 13 yr–young adult
Two doses, 4–8-wk interval (consider serologic testing to prove susceptibility)
Contraindications
Congenital immunodeficiency, blood dyscrasias
Leukemia, lymphoma, other malignancies except acute lymphocytic leukemia in remission[c]
Symptomatic HIV infection
High-dose systemic corticosteroids (≥2 mg of prednisone per kg per day for ≥1 mo, or equivalent)
Pregnancy
Exposure to varicella or herpes zoster within 21 days
Allergy to neomycin
Intercurrent illness
Immune globulin or other blood products within 5 mo
Salicylates within 6 wk[d]

[a] Further manufacturer's recommendations are provided in the product package insert.

[b] Simultaneous administration with the measles, mumps, and rubella vaccines is acceptable but requires the use of separate syringes and injection sites.

[c] Vaccine is available through a research protocol for children with acute lymphocytic leukemia in continuous remission for at least 1 year, lymphocyte count of >700/ml, and platelet count of >100,000/ml. Contact The Varivax Coordinating Center, Bio-Pharm Clinical Services, Inc., (215) 283-0891.

[d] Unless the risk of natural varicella is considered to outweigh the theoretical risk of Reye syndrome.

uated varicella vaccine (Varivax) in the United States. This vaccine was licensed by the Food and Drug Administration (82) in 1995. Indications and contraindications for administering varicella vaccine were established for licensure, and recommendations for the use of the vaccine in clinical practice have been developed by the American Academy of Pediatrics (3) (Table 6). The live attenuated varicella vaccine (Oka-Merck strain) was administered to more than 7,000 children and more than 1,600 healthy susceptible adults during prelicensure clinical trials in the United States. No clinical symptoms were elicited even when the vaccine preparation contained ≥9,000 PFU of infectious virus per dose (6). The vaccine induced protection against household exposure with an efficacy rate of more than 95% in an initial placebo-controlled study, and vaccine efficacy has been documented in open trials by comparison with the predicted annual attack rates (18, 84, 94, 144, 145, 159, 257). Subsequent open clinical investigations through sequential annual epidemics demonstrated protective efficacy against varicella in most children and adults. Universal immunization against VZV is expected to be worthwhile from an economic perspective, based on a recent cost-benefit analysis including the medical and other costs associated with the annual epidemics of varicella (173). A model of the effects of routine varicella immunization for preschool children indicates that universal immunization will reduce the number of patients with complications requiring hospitalization, but field studies of vaccine efficacy after widespread use will be required to confirm this prediction (118). Cost-effective use of the vaccine in adolescents and young adults with no history of varicella may be best achieved by serologic testing to document susceptibility, whereas presumptive immunization of younger children on the basis of a negative clinical history is appropriate (174). Varicella vaccine is immunogenic when administered concurrently with measles, mumps, and rubella vaccines, although it should be given in a separate syringe and at a different site (67). The safety of the varicella vaccine means that VZV may eventually be useful as a live virus vector to induce immunity to other pathogens; the expression of Epstein-Barr virus gp350 and hepatitis B surface antigen by recombinant VZV strains has been demonstrated in vitro (178, 236).

Immunologic studies of vaccinees given the current preparations of the live attenuated varicella vaccine have demonstrated consistently high seroconversion rates (above 95%), as well as persistence of VZV IgG antibodies 1 year after immunization (15, 81). The vaccine also elicits T lymphocytes that recognize VZV antigens or purified viral proteins (253). Circulating VZV-specific T lymphocytes are present in peripheral blood within 2 to 6 weeks after immunization in 98 to 100% of healthy children given the varicella vaccine. The evaluation of the kinetics of induction of VZV-specific T-cell proliferation indicates rapid expansion of these effector cells after immunization (235, 252). T-cell recognition of VZV is detected within 10 to 14 days in most individuals, whereas IgG antibodies to VZV are detected in only 40% of children tested at 2 weeks. Immunization with the varicella vaccine also induces cytotoxic T cells that can lyse cells expressing VZV proteins; the responder cell frequencies are comparable to those elicited by natural VZV infection (235). The early T-cell response may account for the apparent efficacy of the vaccine for varicella prevention when it is given immediately after the exposure of susceptible individuals (17).

Effective induction of persistent memory T-lymphocyte responses to VZV is important since cell-mediated immunity is fundamental to the host response to natural VZV infection. Persistence of T-lymphocyte proliferation to VZV antigens has been documented for up to 6 years in healthy children given varicella vaccine (253). Clinically effective immunity is elicited in children given one dose of varicella vaccine (84). However, comparison of cell-mediated immune responses to VZV antigen initially and at 1 year suggests that larger numbers of VZV-specific T lymphocytes are elicited by the administration of a two-dose regimen (194, 252). In our studies, the mean stimulation index at 1 year was 22.2 ± 6.42 (standard error) for the two-dose subgroup compared with 9.3 ± 1.39 for the one-dose subgroup ($P = 0.03$) (194). In addition to the infectious-virus component, the higher relative antigen content present in current vaccine lots may contribute to the high levels of cell-mediated immunity observed in healthy vaccine recipients. Immunization with varicella vaccine elicits memory T lymphocytes that proliferate and produce lymphokines in response to stimulation with the IE62 protein and the viral glycoproteins; these responses are comparable to those of subjects who have naturally acquired immunity to VZV. Adult vaccinees who were tested approximately 4 years after immunization for cytotoxic T-cell responses to IE62 protein, gI, and gC had mean effector cell frequencies equivalent to those of subjects with naturally induced memory T-cell responses to VZV (235).

Prolonged protective efficacy was shown among 95% of vaccine recipients from the original placebo-controlled trial who were monitored for 7 years (159). Some children and adults with vaccine-induced immunity develop mild breakthrough infections after exposure to natural virus, but the illness is characterized by fewer than 50 cutaneous lesions with no fever in most cases (144, 254). Compared with the expected clinical course of varicella in healthy children and adults, the symptoms of varicella are modified substantially by preexisting immunity due to vaccination. For example, among 2,163 vaccinees evaluated at one center, 114 children developed varicella at a median of 44 months after immunization but the median

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number of skin lesions was only 18 (254). The incidence of transmission to other vaccinated children in the household from these patients was 12%, compared with an anticipated transmission rate of 80% or higher for wild-type virus to susceptible immunized household contacts.

Adults respond less effectively to varicella vaccine than do children (91, 94). It is necessary to give two doses of vaccine, separated by at least 4 weeks, to achieve seroconversion rates of more than 95% in susceptible adults. Cell-mediated immune responses are also lower in healthy adult vaccinees (194). At 1 year, the mean stimulation index was 10.0 ± 1.13 for adult vaccinees compared with 15.6 ± 1.77 for children ($P = 0.03$). This difference was observed even though only 18% of the children were given two doses of varicella vaccine whereas all adults had received two doses of the vaccine. The decreased immunogenicity of the varicella vaccine is consistent with the observation that adults are more likely to have severe natural VZV infection (84, 91, 94). Adults have more episodes of transient local reactions and rash, and persistence of VZV antibodies may be less uniform. Only 70% of adult vaccinees had detectable VZV IgG antibodies 2 to 6 years after immunization in one study (91). Nevertheless, the varicella vaccine has significant clinical benefit for susceptible adults because of their enhanced risk of serious complications of varicella. Immunized adults with breakthrough infection have a much less severe illness than would be expected without preexisting immunity.

The Oka-Merck varicella vaccine has been given to children with acute leukemia in remission, reducing the attack rate following household exposure to 13% (93). Seroconversion in these patients is associated with a high degree of protection, but most children required two doses of the vaccine to elicit immunity (84, 90, 93). Children with leukemia who are immunized with varicella vaccine are less likely to have initial or persistent cell-mediated immunity to VZV, which is also true of immunocompromised children with naturally acquired immunity to VZV (93). Studies of vaccine-induced immunity in children with leukemia indicate the importance of cell-mediated immunity in reducing the risk of VZV reactivation, since VZV-specific T-cell proliferation was lower in 4 children who developed herpes zoster than in 29 vaccinees who did not have recurrent VZV infection (164). Varicella vaccine is available for administration to leukemic children who have been in remission for at least a year and who have absolute lymphocyte counts above 700 as participants in a manufacturer-sponsored protocol (3). The vaccine is not licensed for general use in immunocompromised patients, because vaccine-related rashes occurred at about 1 month after immunization in about 50% of children with leukemia in remission (93). Lesions were noted at the site of inoculation but were also widely scattered in some children, indicating that the vaccine virus has not lost the capacity to cause cell-associated viremia (139). Immunization of healthy siblings or other susceptible household contacts may be useful to reduce the risk of household exposure of immunocompromised children to varicella. No transmission of vaccine virus was observed in one study assessing this approach, whereas high rates of transmission of wild-type VZV would be expected (57).

While there is a theoretical risk of vaccine virus transmission from asymptomatic healthy vaccinees to susceptible contacts, the only episodes that have been observed followed exposure to vaccinees who had cutaneous lesions secondary to vaccine virus (136, 246). VZV was detected by PCR in oropharyngeal secretions from 7% of healthy children in Japan, but infectious virus was not recovered (199, 200). The vaccine virus was transmitted from about 15% of leukemic children with rash to their healthy susceptible siblings, but the contacts had mild clinical illness or asymptomatic seroconversion, providing clinical evidence for attenuation of the vaccine virus (84). The virus was transmitted to susceptible siblings only by leukemic children who had a rash. The fact that leukemic children without a rash did not transmit the virus suggests that even if vaccine virus replication occurred at respiratory sites, it was not sufficient to result in spread to close contacts (246).

Since the varicella vaccine contains infectious virus, it is important to assess the capacity of the vaccine virus to establish latency and to reactivate, causing herpes zoster. The vaccine virus can establish latency, as shown by its reactivation in immunized leukemic children, but the attack rate for herpes zoster in high-risk children given the vaccine was significantly lower than it was in leukemic children with natural VZV infection (121). The incidence of VZV reactivation among healthy children and adults enrolled in prelicensure studies was very low; only a few cases were identified (211). Episodes of herpes zoster caused by the vaccine virus are treatable with acyclovir if necessary, but the few reported cases were mild and did not warrant antiviral therapy. Some cases of herpes zoster in vaccine recipients may be due to infection with wild-type VZV. One healthy adult vaccine recipient has been described who remained asymptomatic after household exposure to varicella but later had an episode of herpes zoster caused by wild-type VZV (119).

Since the increased occurrence of herpes zoster with age is due to waning immunity to VZV, therapeutic vaccination with varicella vaccine may provide a strategy to prevent herpes zoster in otherwise healthy elderly patients (171). This approach has merit because fewer than 50% of patients seek medical care for herpes zoster in time to benefit from antiviral drug therapy. Prevention of reactivation rather than provision of antiviral treatment after cutaneous disease is recognized might also be a more effective way to eliminate the morbidity of PHN. Immunization with the live attenuated varicella vaccine significantly enhances VZV-specific IgG antibodies and cell-mediated immunity in older individuals; the frequency of VZV-specific T cells improved from 1 in 68,000 PBMC to 1 in 40,000 PBMC in healthy adults older than 55 years, which is equal to the numbers of VZV responder cells in younger individuals (111). Vaccination also led to increased production of IFN-γ by PBMC incubated with VZV antigen and to the recovery of skin test reactivity to VZV antigen in most vaccinees. Clinical studies are planned to determine whether the reversal of waning VZV immunity by immunization of seropositive elderly adults reduces the incidence of herpes zoster.

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