Varicella-zoster virus (VZV) is the etiologic agent of varicella (primary infection) and herpes zoster (reactivation of latent infection). Although varicella is most often a relatively benign and self-limited childhood illness, the disease can be associated with a variety of serious and potentially lethal complications in both immunocompetent and immunocompromised persons. One complication of varicella that appears to be increasing in frequency is serious bacterial soft tissue infections caused by group A streptococci. Issues related to management of varicella become especially complex when varicella involves pregnant women or susceptible neonates. Herpes zoster can be associated with a variety of neurologic complications, including a syndrome of delayed contralateral hemiparesis. Neurologic complications of herpes zoster, including chronic encephalitis, occur with increased frequency in AIDS patients. VZV retinitis is a potentially sight-threatening complication that occurs in both immunocompetent and immunocompromised persons. Current knowledge regarding pathogenesis and antiviral therapy is reviewed.

Varicella-zoster virus (VZV) causes two clinically distinct diseases. Primary infection results in varicella (chickenpox), a common and extremely contagious acute infection that occurs in epidemics among preschool and school-aged children, is characterized by generalized vesicular rash. Like other α-herpesviruses, VZV establishes latency in neural tissue following primary infection. Reactivation of latent VZV from dorsal root ganglia results in herpes zoster (shingles), a localized cutaneous eruption accompanied by neuralgic pain that occurs most commonly in older persons. The typical clinical presentations of varicella and herpes zoster are distinctive and readily recognized by most experienced clinicians. However, atypical clinical presentations and uncommon complications of these diseases can pose diagnostic and therapeutic challenges. This review will address some less common manifestations of VZV infection that can occur in otherwise healthy immunocompetent persons and in special populations.

Varicella

Pulmonary Complications

Pneumonitis as a complication of varicella is rare in healthy children but occurs with increased frequency in immunocompromised persons of all ages and in immunocompetent adolescents and adults [1, 2]. Among otherwise healthy adults with varicella, 2.7%–16.3% will have radiographic evidence of VZV pneumonitis, but only about one-third of those with abnormal chest radiographs will have respiratory symptoms [3–6]. As discussed below, varicella pneumonia appears to be more frequent and more severe in pregnant women [7]. The onset of respiratory symptoms (including cough, dyspnea, and sometimes hemoptysis) usually occurs within a few days of development of the varicella rash. The chest radiograph reveals a diffuse interstitial nodular infiltrate [2, 8]. Prior to the availability of antiviral therapy, mortality rates of up to 30% were reported for varicella pneumonia. However, with the advent of antiviral treatment and intensive supportive care, the mortality rate is now probably less than 10%. Although intravenous acyclovir has not been evaluated in controlled trials for treatment of varicella pneumonia, abundant clinical experience and anecdotal reports indicate the drug is effective in this setting [9–11].

Neurologic Complications

The incidence of neurologic complications associated with varicella is estimated to be 1–3 per 10,000 cases [12]. The central nervous system (CNS) manifestations that occur most frequently with varicella are cerebellar ataxia and encephalitis [13–15]. Other rare neurologic complications include transverse myelitis, aseptic meningitis, and Guillain-Barré syndrome [16–18]. Few data exist to help define the role of antiviral therapy for neurologic complications of varicella.

Varicella with cerebellar ataxia. Symptomatic cerebellar ataxia occurs in about 1 in 4000 varicella cases [12]. The pathogenesis of this syndrome is incompletely understood, partly because the illness is rarely fatal and few pathologic studies have been reported. Possible mechanisms are direct viral infection of the cerebellum or a parainfectious immunologically mediated demyelinating process. VZV-specific antibodies and
antigens have been found in cerebrospinal fluid (CSF) of patients with varicella-associated cerebellar ataxia, suggesting that VZV replicates within the CNS [19–21].

Ataxia may develop from several days before to 2 weeks after the onset of varicella, although the neurologic symptoms most often occur simultaneously with rash [16]. Ataxia is usually accompanied by vomiting, headache, and lethargy; nuchal rigidity and nystagmus occur in about 25% of patients. When rash and ataxia occur together, the clinical presentation is sufficient to establish a diagnosis. The CSF is most often normal but may show moderate lymphocytic pleocytosis (<100 cells/μL) with mildly elevated protein in 20%–30% of cases. The cerebellar dysfunction associated with varicella is self-limited. The vast majority of patients recover without apparent sequelae within 1–3 weeks. Although there is no substantial evidence that antiviral therapy alters the natural history of the cerebellar ataxia syndrome, it is probably appropriate.

**Varicella encephalitis.** Encephalitis, the most serious CNS complication of varicella, has an incidence of 1–2 episodes per 10,000 varicella cases, with the highest incidence in adults and infants [22, 23]. The role of active VZV replication in the pathogenesis of varicella encephalitis remains uncertain [24]. Some histopathologic studies have had features suggestive of a postinfectious demyelinating process, while other findings have been more consistent with direct viral cytopathology [25–27].

Neurologic symptoms (headache, fever, vomiting, and altered sensorium) most often occur about 1 week after the onset of the varicella rash [13, 14]. The onset of symptoms may be abrupt or gradual and is accompanied by seizures in 29%–52% of cases [28, 29]. Abnormalities detected by neurologic examination can include ataxia, hypertonia or hypotonia, hyperreflexia or hyporeflexia, positive plantar reflexes, hemiparesis, and sensory changes. The CSF findings are usually abnormal with elevated opening pressure, a mild-to-moderate lymphocytic pleocytosis (usually <100 cells/μL), mildly elevated protein (50–100 mg/dL), and normal glucose levels. Electroencephalography shows slow wave activity consistent with diffuse encephalitis. CNS imaging studies may show edema and areas of low attenuation consistent with demyelination [25, 30, 31].

The mortality for varicella encephalitis is 5%–10%, but the majority of cases have complete or nearly complete recovery [32]. Higher mortality rates cited in older literature probably reflect a significant number of cases of Reye’s syndrome. Long-term sequelae, including seizure disorders, may be present in 10%–20% of survivors. The value of antiviral therapy for patients with varicella encephalitis has not been established by prospective clinical trials. However, since no other treatment is available and because acyclovir is extremely safe and well tolerated, therapy with intravenous acyclovir is warranted in persons with varicella encephalitis.

**Cutaneous Complications**

The most common complication of varicella is bacterial superinfection of skin lesions, caused most often by *Staphylococcus aureus* or *Streptococcus pyogenes* [33]. Bacterial cellulitis can accentuate the scarring associated with varicella and can be minimized by keeping the patient’s fingernails trimmed and by using antibacterial soaps. More serious complications, including staphylococcal and streptococcal toxic shock syndromes, have been reported [34, 35]. Other cutaneous complications of varicella include bullous or hemorrhagic varicella (more commonly seen in immunocompromised children) or purpura fulminans, which is associated with thrombocytopenia and disseminated intravascular coagulation.

A severe form of necrotizing soft tissue infection has been described following varicella [36, 37]. Although “varicella gangrenosa” was first described by Hutchison in 1882, several investigators recently reported an increased frequency of severe soft tissue infections caused by strains of group A β-hemolytic streptococci, which can elaborate exotoxins and cause extensive local tissue destruction [38, 39]. Therapy of varicella-associated necrotizing fasciitis consists of early and aggressive surgical debridement, appropriate antibiotic therapy, and intensive supportive care [40]. Adjunctive therapy with intravenous immunoglobulin may also be beneficial in patients with streptococcal toxic shock syndrome and necrotizing fasciitis, although this remains controversial [41, 42]. Some authors have suggested a possible association between the use of nonsteroidal antiinflammatory drugs (NSAIDs; e.g., ibuprofen) and increased risk of varicella-associated necrotizing fasciitis, although this remains controversial [43, 44]. Nonetheless, it seems prudent to avoid NSAIDs and to use alternative drugs (e.g., acetaminophen) for relief of pain and fever in patients with varicella.

**Maternal and Fetal Varicella Syndromes**

Pregnant women, developing fetuses, and neonates are at risk for mortality and serious morbidity from varicella. Perinatal transmission of varicella can occur either vertically or horizontally. Vaccinating VZV-susceptible women prior to pregnancy could prevent all of these scenarios.

**Maternal varicella.** Although based more on case reports than on prospectively acquired data, the evidence that varicella in pregnancy is associated with enhanced morbidity is compelling [7, 45]. Women who contract varicella while pregnant have an estimated 10% risk for developing severe VZV pneumonia [46]. The risk of varicella during pregnancy is relatively low in temperate climates, where only about 5% of young women are VZV seronegative. In the United States, where over 95% of adults are VZV seropositive, varicella is estimated to occur in about 5 of 10,000 pregnancies [47–49]. The risk may be higher in tropical regions where the incidence of childhood varicella is lower and thus more young women are susceptible to primary VZV infection [50, 51].

Aggressive antiviral therapy is recommended for a pregnant woman with varicella who develops any evidence of pulmonary involvement (including cough, shortness of breath, or abnormal chest radiograph). Data from clinical trials are lacking, but
several case series have reported clinical improvement with intravenous acyclovir given to pregnant women with varicella pneumonia [52, 53]. Although acyclovir is not approved for use during pregnancy for any indication, no fetal toxicity attributable to acyclovir has been documented and the risk-benefit ratio clearly supports use of acyclovir in the setting of maternal varicella pneumonia [7, 45, 54].

Advisory committees have recommended administration of varicella-zoster immune globulin (VZIG) to VZV-susceptible pregnant women who have been exposed to varicella [55]. For maximal efficacy, VZIG must be administered as soon as possible after exposure (and within 96 h). VZIG (as available in the United States) is administered by deep intramuscular injection at a dose of 125 U/10 kg of body weight, to a maximum of 625 U. Intravenous immunoglobulin also contains substantial VZV-specific IgG and may be substituted if VZIG is not available. Unfortunately, in this time-critical scenario, the true VZV serologic status of a pregnant woman with a negative history for varicella is often not known. The clinician may be faced with a decision to initiate passive immunoprophylaxis empirically or to wait for serologic testing [56]. The ideal time to determine VZV serologic status would be before pregnancy when vaccination could be offered to women confirmed to be seronegative [57]. Varicella vaccination of pregnant women is not currently recommended because of the theoretical risk of the live virus vaccine for both the fetus and mother. Prophylactic therapy with acyclovir for a pregnant woman after VZV exposure should be effective, but is an unproven approach.

**Congenital varicella.** A rare but well-defined fetal varicella syndrome may result when a woman acquires varicella during the first or second trimester of pregnancy [58, 59]. The embryo-pathy is characterized by limb hypoplasia, ocular and neurologic abnormalities, and distinctive cicatricial skin scarring in a dermatomal pattern [60]. The pathogenesis of the syndrome is thought to be invasion of the fetal nervous system by VZV during a critical stage of development [61]. Fortunately, fetal varicella syndrome is uncommon, arising in only 2% of cases of maternal varicella occurring during the first 20 weeks of gestation [62]. Due to the rarity of the syndrome, there are no data to indicate whether antiviral therapy given to a pregnant woman with varicella can reduce the risk of embryopathy.

A very small number of cases of congenital VZV syndrome have been reported after maternal herpes zoster [59]. However, because the mother has preexisting antibody and because herpes zoster results in only low-level viremia, the risk to a fetus from maternal herpes zoster is extremely low. Babies born to mothers who have varicella during pregnancy may develop herpes zoster during infancy [63].

**Perinatal varicella.** VZV infection of neonates may result from either vertical or horizontal transmission. If maternal varicella appears during a window of about 4 days before to 2 days after delivery, the neonate is at high risk (24%–48%) for developing varicella [64–66]. The period of greatest risk is when the infant is delivered after the onset of maternal viremia but before maternal antibody develops. These babies appear healthy at birth but develop signs and symptoms of varicella 5–10 days after delivery. In addition, infants born to VZV-seronegative mothers are at risk for severe varicella if infected during the first few days of life. Conversely, infants who have varicella lesions at birth or within the first 5 days of life (and who, thus, received transplacental maternal VZV antibody prior to delivery) are unlikely to have severe disease.

Perinatally acquired varicella is characterized by visceral organ involvement (including lung, liver, and CNS disease), with a mortality rate of 30% [67, 68]. Infants delivered during the high-risk window should receive prophylactic administration of VZIG [69]. VZIG administration, even when it does not prevent neonatal infection, appears to significantly reduce the risk of life-threatening neonatal varicella [70, 71]. Since instances of severe neonatal varicella have been described even in babies who received appropriate dosing with VZIG, intravenous acyclovir therapy should be immediately instituted for any perinatally exposed baby who develops characteristic skin lesions. The utility of other potential interventions, such as acyclovir therapy for maternal varicella late in pregnancy, preemptive acyclovir therapy of exposed newborns, or postexposure vaccination of infants, has not been adequately studied.

**Varicella in Human Immunodeficiency Virus (HIV)-Infected Persons**

The clinical presentation of varicella in HIV-seropositive children is usually similar to that seen in immunocompetent children, although some studies have reported a longer duration of new lesion formation and higher median lesion counts [72–74]. The most common complication of varicella in this population is cutaneous bacterial superinfection [75]. Cases of visceral dissemination of VZV (including pneumonia, hepatitis, and encephalitis) are uncommon.

After resolution of varicella, HIV-seropositive children are at high risk for recurrent episodes of cutaneous VZV infection. In some children with very low CD4 cell counts, the cutaneous lesions of primary varicella may fail to heal and remain VZV culture-positive, resulting in a syndrome of “chronic varicella” [76]. About half of HIV-seropositive children who develop varicella will have a VZV recurrence within 2 years [76]. Recurrent VZV infections may show as classic herpes zoster or as “recurrent varicella” characterized by a diffuse vesicular rash.

Because more than 95% of HIV-infected US adults are VZV seropositive, varicella is unusual in this population. However, when it occurs in HIV-infected adults, the infection may produce significant morbidity, including encephalitis and hepatitis [77]. For HIV-infected children or adults with varicella, most clinicians prescribe oral acyclovir or valacyclovir, reserving intravenous acyclovir for those with unusually severe or complicated infections [78]. No published studies have assessed the efficacy of famciclovir for varicella treatment, but the drug should theoretically be active.
Herpes Zoster

Neurologic Complications

Neurologic complications of herpes zoster can occur coincident with the acute eruption or appear weeks to months after the rash has resolved. The most common neurologic complication of herpes zoster is chronic pain (postherpetic neuralgia), which occurs with sufficient frequency that it should be considered a part of the natural history of the disease (reviewed elsewhere in this supplement). Distinct neurologic syndromes associated with herpes zoster include acute or chronic encephalitis, ophthalmic zoster with contralateral hemiparesis, myelitis, polyradiculitis, motor neuropathies, and a variety of cranial and peripheral nerve palsies, including Bell’s palsy and Ramsay Hunt syndrome [79].

Delayed contralateral hemiparesis. Hemiparesis is a rare but serious complication of herpes zoster that can occur weeks to months (mean, 7 weeks) after an episode of herpes zoster involving the first division of the trigeminal nerve [80–82]. The pathogenesis of this syndrome is thought to be direct VZV invasion of cerebral arteries by extension along intracranial branches of the trigeminal nerve, resulting in inflammation of the internal carotid artery or one of its branches on the side ipsilateral to the rash [83]. The typical presentation is headache and hemiplegia occurring in a patient with a recent history of herpes zoster ophthalmicus (HZO). Examination of CSF reveals mononuclear cell pleocytosis (usually 10–100 cells/μL) and increased protein [84]. Arteriography is usually diagnostic and demonstrates inflammation, narrowing, and thrombosis of the proximal branches of the anterior or middle cerebral artery [85, 86]. Both acyclovir and corticosteroids are used to treat this syndrome, although no interventions have been evaluated in controlled trials [87, 88]. Antiviral therapy is warranted because of the demonstrated presence of VZV in the inflamed arteries, but benefit of therapy is difficult to assess since irreversible cerebral infarction has often occurred by the time of diagnosis. The mortality rate is 20%–25% and there is a high probability of permanent neurologic sequelae among survivors [80, 84].

Chronic VZV encephalitis. This variant of VZV encephalitis is seen almost exclusively in patients with AIDS or other conditions with depressed cellular immunity. The onset of the encephalitis may occur months after an episode of herpes zoster, making the diagnosis more difficult [89]. Pathologic studies reveal multifocal lesions in the white matter near the gray-white junction, with small vessel vasculitis and demyelination [90, 91]. The clinical presentation is usually subacute with headache, fever, mental status changes, seizures, and focal neurologic defects, including aphasia, hemiplegia, and visual field cuts [92–94]. Magnetic resonance imaging studies demonstrate plaque-like lesions in deep white matter, changes consistent with demyelination, and late development of ischemic or hemorrhagic infarcts of cortical and subcortical gray and white matter [95, 96]. Examination of CSF reveals mild mononuclear pleocytosis. VZV DNA has been amplified from the CSF of encephalitis patients by polymerase chain reaction (PCR) techniques [79, 97]. The clinical course is often progressive deterioration and death, although anecdotal reports have suggested benefit with high-dose intravenous acyclovir therapy [90, 98].

Zoster sine herpete. Clinicians frequently encounter patients who present with zoster-like neuropathic pain but never develop the characteristic dermatomal rash. Recent detailed studies of a few patients presenting with dermatomal pain have established that some of these cases are due to VZV reactivation. Patients with this syndrome, termed zoster sine herpete, have rising titers of VZV-specific antibody in both serum and CSF and have VZV DNA in CSF and peripheral blood mononuclear cells detectable by PCR [99, 100]. Since there is no easy means for making the diagnosis, the incidence of zoster sine herpete is not known. In anecdotal reports, responses to antiviral therapy have been inconsistent.

Herpes Zoster in the Immunocompromised Host

The risks of cutaneous and visceral dissemination of VZV in severely immunocompromised patients (e.g., bone marrow transplant recipients) are well recognized [101]. Commonly reported complications include VZV pneumonia, encephalitis, and hepatitis. The mortality associated with disseminated zoster has been substantially reduced by the availability of effective antiviral therapy [102, 103]. An unusual presentation of herpes zoster in the immunocompromised host is “atypical generalized zoster.” These patients present with diffuse varicella-like skin lesions with no obvious primary dermatomal involvement [104] and are VZV seropositive prior to development of the rash, so the syndrome is not primary varicella. Risk factors for development of atypical generalized zoster appear to be the same as those for classic herpes zoster. The syndrome most likely represents herpes zoster with a limited area of involvement in the primary dermatome, followed quickly by generalized cutaneous dissemination.

A more serious manifestation of herpes zoster in the immunocompromised host is “abdominal zoster.” These patients present with severe abdominal pain that may precede the appearance of the cutaneous rash by hours to days [105, 106]. The diagnosis of herpes zoster is usually not considered until the typical skin vesicles begin to appear, usually in a thoracic dermatome. The patients have a high mortality rate despite initiation of appropriate antiviral therapy. Autopsy studies have revealed a high frequency of abdominal visceral involvement with VZV.

Herpes Zoster in AIDS

Compared with immunocompetent populations, herpes zoster is much more common in HIV-infected persons, occurring at a rate of 30–50 cases per 1000 persons-years [107–109]. In general,
however, the clinical features of herpes zoster in HIV-seropositive persons are similar to those in the otherwise healthy host. One unique feature of herpes zoster in AIDS patients is the much higher frequency of shingles recurrences. Some 20%–30% of HIV-infected patients will develop one or more subsequent episodes of herpes zoster, which may involve the same or different dermatomes [107, 109]. The probability of a recurrence of zoster within 1 year of the index episode is estimated to be 12% [110]. HIV-infected patients may also experience zoster simultaneously in more than one dermatome, a phenomenon virtually never seen in immunocompetent patients. Although a variety of delayed-onset neurologic complications have been described [111], visceral dissemination of VZV as reported in other immunocompromised populations is very uncommon in persons with AIDS. HIV-infected patients with herpes zoster usually respond well to oral antiviral therapy [112].

VZV can cause a variety of atypical cutaneous lesions in HIV-infected patients with low CD4 lymphocyte counts. The most commonly reported atypical lesions are multiple hyperkeratotic papules (3–20 mm in diameter) that follow no dermatomal pattern [113, 114]. These lesions may be chronic, persisting for months or years, and are sometimes associated with acyclovir-resistant strains of VZV [115]. A second dermatologic variant is ecthymatous VZV lesions, which present with multiple large (10–30 mm) punched-out ulcerations with a central black eschar and a peripheral rim of vesicles [116, 117]. VZV isolates from any of these atypical lesions should routinely be submitted for antiviral susceptibility testing.

Acute Retinal Necrosis (ARN)

VZV-associated ARN has been described in both immunocompetent and immunocompromised persons. Since the advent of the AIDS epidemic, a more aggressive variant of this disease (sometimes termed rapidly progressive herpetic retinal necrosis [RPHRN]) has been identified [118, 119]. Visual changes are usually noted weeks to months after the antecedent herpes zoster. ARN can follow either HZO or herpes zoster in a remote dermatome. Furthermore, retinal involvement is bilateral in over half of cases, suggesting that VZV reaches the CNS via hematogenous spread, possibly with extension along nerve pathways within the anterior visual system [118]. VZV retinitis presents with multifocal necrotizing lesions, often initially involving the peripheral retina. The granular, nonhemorrhagic lesions rapidly extend and coalesce, accompanied by relatively little intraocular inflammation [120–122].

In AIDS patients, VZV retinitis rapidly progresses to full thickness retinal necrosis, usually with retinal detachment, resulting in blindness in 75%–85% of involved eyes [118]. Since the involved eye is rarely salvageable in HIV-infected patients with RPHRN, the goal is to try to prevent disease progression in the uninvolved eye. Intravenous acyclovir alone is ineffective [122]. Some experts recommend intravenous therapy with ganciclovir or foscarnet (or a combination of the two) together with intravitreal injections of ganciclovir [123, 124]. Anecdotal success with cidofovir has also been reported. Results of antiviral therapy for VZV retinitis in HIV-infected patients, regardless of regimen, have been disappointing.

ARN in immunocompetent patients is a less virulent disease and more responsive to antiviral therapy. In this setting, acyclovir is clearly beneficial for preserving useful vision [125, 126]. A suggested antiviral regimen for ARN in the otherwise healthy host is intravenous acyclovir 10–15 mg/kg every 8 h for 10–14 days, followed by oral valacyclovir 1 g 3 times daily for 4–6 weeks, although this treatment approach has never been studied in a controlled fashion.

Conclusion

Most clinicians readily recognize typical clinical signs and symptoms of varicella and herpes zoster. However, in certain circumstances and in special populations, VZV infection can present with unusual manifestations and can cause potentially life-threatening complications. Clinicians must be aware of these presentations and be prepared to perform appropriate diagnostic studies. For example, a patient presenting with delayed contralateral hemiparesis may not be appropriately treated unless the acute clinical presentation is linked to the history of recent trigeminal zoster. Fortunately, most unusual manifestations of VZV are rare. The complications of varicella will become even less common as use of the varicella vaccine becomes more widespread.

The low incidence of VZV-related disorders means that attempts to conduct traditional controlled therapeutic trials with adequate numbers of patients are fraught with difficulty. Even with multicenter clinical trials networks, performing prospective studies on diseases like varicella encephalitis or congenital varicella are probably impossible. Since the morbidity associated with many of these complications is substantial and the risks associated with antiviral therapy are low, many physicians appropriately initiate antiviral therapy on the basis of limited anecdotal data. Although rigorous prospective controlled clinical trials are likely not feasible, it is still critical to collect information regarding the utility of antiviral therapy for these complications of varicella and herpes zoster. Well-documented case series (e.g., valacyclovir therapy for varicella in pregnancy or for varicella cerebellar ataxia) can still provide extremely valuable data and should be actively pursued.

References


