

An updated approach to treating and preventing herpes zoster

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ABSTRACT

Varicella zoster virus (VZV) causes chickenpox and herpes zoster. Herpes zoster is a common infection in older adults and can lead to potentially debilitating postherpetic neuralgia. This article reviews the diagnosis and management of herpes zoster, including strategies to reduce disease frequency and severity with the herpes zoster vaccine.

Keywords: varicella zoster virus, herpes, shingles, postherpetic neuralgia, herpes zoster ophthalmicus, antiviral

Varicella zoster virus (VZV) is responsible for an estimated 1 million cases of herpes zoster infection per year, with about 50% of these cases affecting patients age 50 years or older. Ten percent to 20% of the US population will develop VZV, and about 50% of persons age 85 years can be expected to develop VZV, as the incidence increases with age.¹ The chickenpox (VZV) vaccine was licensed for use in the United States in 1995 and has become widely used. Thanks to this vaccine, the number of people in the United States who get chickenpox each year has declined dramatically, as have hospitalizations and deaths.²

VZV infection can cause many physical manifestations and significant morbidity. One of the most common complications of VZV in adults is postherpetic neuralgia (PHN). The discomfort and pain from PHN can cause severe limitations for patients, and can disrupt sleep patterns, work ability, and activities of daily living, often leading to social withdrawal and depression.¹ Clinicians need to be well educated about VZV and understand the benefits and risks of preventive strategies.

PATHOPHYSIOLOGY

VZV is also referred to as herpes zoster virus, human herpesvirus 3, chickenpox virus, and shingles. The genome

of the viral particle includes a linear double-stranded DNA molecule encapsulated by a nucleocapsid, surrounded by tegument and an outer lipid envelope. This envelope is covered by glycoprotein spikes that are the mechanism by which the virus attaches to human cell walls, likely in the respiratory tract.

Glycoproteins on the virus let it attach and fuse with the cell membrane. Once fusion occurs, the capsid is released into the cytoplasm of the cell. Viral DNA is released from the capsid and enters the nucleus, then the capsid is discarded. Enzymes from the host cell catalyze the early transcription, and viral mRNA directs the production of viral enzymes which in turn, facilitate the replication of viral DNA in the nucleus. Then, mRNA encodes production of viral proteins and capsid elements, and DNA is packaged in the capsid. Glycoproteins affix to nuclear membrane and capsid buds off.

The genome of VZV is similar to that of the herpes simplex virus. VZV infection produces a cytopathic effect when examined in tissue culture and is characterized by the formation of large multinucleated cells without the release of significant quantities of stable infectious virus particles. Because VZV infection is highly cell mediated, researchers find it difficult to make sufficient quantities of cell-free virus for molecular analysis.

A symptomatic episode of shingles is caused by reactivation of latent varicella virus found in sensory ganglia. An inflammatory reaction in the posterior nerve roots and



FIGURE 1. Dermatomal distribution of zoster

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ganglia causes a vesicular eruption on the skin that is supplied by the affected nerves. Host immunologic mechanisms suppress viral replication but manifestation occurs when these mechanisms are compromised. This is believed to be a cell-mediated response. A typical clinical presentation begins with clusters of small papules appearing on the skin, followed by vesicle formation and enlargement, then rupture of vesicles. Eventually, the lesions crust over and heal. The entire course takes 4 to 5 weeks. Between 10% and 20% of patients develop PHN; the higher incidence rates occurring with advanced age are thought to be due to nerve damage.^{1,3}

RISK FACTORS, SIGNS, AND SYMPTOMS

To be diagnosed with herpes zoster infection, a patient must have had a previous varicella infection. Other key risk factors to ask about in the patient history are: age greater than 50 years, an immunocompromised state (such as caused by HIV, malignancy, immunosuppressive drugs, or solid organ or bone marrow transplantation), psychological stressors, and physical trauma.

Signs and symptoms include pruritus, pain, dysesthesias, and paresthesias before a vesicular rash eruption. Ninety percent of patients experience acute neuritic pain and hypersensitivity in the affected area; about 20% of patients experience symptoms of hopelessness and depression, and 12% develop flu-like symptoms.¹

The physical examination should be tailored to the area of complaint and manifestation. Perform a careful skin examination including sensory testing in the affected area. The most common presentation includes a vesicular rash of a thoracic dermatome (**Figure 1**). Patients may also have erythematous macules and papules following a prodrome of pain and hyperesthesia that will eventually progress to the more typically identified vesicular rash. Pain and sensory loss is common; motor weakness can occur when the virus extends to the motor root, which is often missed on examination. Include a cranial nerve examination when the appropriate associated symptoms occur relative to specific nerves.

When more than one dermatome is involved, the condition is called *zoster multiplex*. This condition is more common in immunocompromised patients. Previously undiagnosed immunosuppression should also be considered if zoster multiplex is identified on physical examination.

Herpes zoster ophthalmicus (**Figure 2**) occurs when the virus invades the ophthalmic division of the trigeminal nerve. Patients with this condition should be referred to an ophthalmologist because of possible conjunctivitis and corneal ulceration. Blindness, although rare, may also occur. Typical presentation of herpes zoster ophthalmicus includes blepharitis, conjunctivitis, scleritis, or episcleritis. VZV infection affecting the trigeminal nerve often causes a vesicular presentation, but this is not required for diagnosis.



FIGURE 2. Herpes zoster ophthalmicus

About one-third of all patients with herpes zoster ophthalmicus have nasociliary nerve involvement, as indicated by a lesion on the tip of the nose (Hutchinson sign); the nasociliary nerve innervates the tip of the nose.⁴ Severe complications include intracranial thrombotic cerebrovasculopathy, severe headache, and hemiplegia.

In a Taiwanese population-based study of a retrospective cohort design, the frequency and risk of stroke after herpes zoster attack were examined. Patients previously treated for herpes zoster were matched with randomly selected subjects, and 1-year stroke-free survival rates were estimated. Results identified that patients with herpes zoster had significantly lower stroke-free survival rates by comparison, and the adjusted hazard ratios of stroke following herpes zoster was 1.31 and herpes zoster ophthalmicus was 4.28 during a 1-year follow-up period.⁵ Studies have not yet been completed to determine if anything, such as early antiviral treatment, will decrease the risk of vasculopathy or associated stroke. Careful monitoring and management of preexisting risk factors for stroke, such as hypertension, diabetes, and hyperlipidemia, may help to reduce the risk of stroke.

Ramsay-Hunt syndrome occurs when varicella affects the geniculate ganglion of the facial nerve. This presentation typically involves a peripheral facial palsy and pain in the ear and face with vesicles in the external ear canal, and should be examined otoscopically (**Figure 3**). Auditory

and vestibular disturbances can occur with this manifestation, so test the patient's hearing and balance.

COMPLICATIONS

PHN is the most common complication of VZV infection, and is more common in patients who have acute pain during the initial VZV outbreak. PHN typically occurs between 1 and 6 months following the onset of zoster manifestation. The presentation is heterogenous and pain can be intermittent or constant in duration, and throbbing, stabbing, aching, or burning in quality. The patient may have intense itching, allodynia, or hyperalgesia. Other symptoms of PHN include chronic fatigue, weight loss, anorexia, insomnia, and difficulty with activities of daily living.

Herpes myelitis is a rare complication that is more common in immunocompromised patients. The neurologic manifestations typically are bilateral in nature. Zoster encephalitis can occur with this manifestation, although it is quite rare.

DIAGNOSIS

The diagnosis of VZV infection is based solely on clinical findings such as the characteristic prodrome and rash and possible associated pain. Laboratory confirmation is occasionally used for atypical presentations. Viral cultures may be done but are often difficult to obtain. The process of direct immunofluorescence assay is more easily obtained but the best and most widely used method is polymerase chain reaction. This test is also best for differentiating between herpes simplex virus and VZV when the patient's clinical findings could represent either disease.

A study in Holland by Opstelten and colleagues sought to determine how well the clinical diagnosis of VZV infection is made in family medicine.⁶ The study's objective was to determine the positive predictive value of physician judgment in diagnosing herpes zoster and to determine the applicability of blood spot analysis using ELISA (enzyme-linked immunosorbent assay) for diagnosis. Criteria included patients older than 50 years with VZV with a rash that was less than 7 days old. VZV antibodies were measured at baseline, then 5 and 10 days later. Dried blood spot analysis, possible in 260 patients, was used to determine serologic confirmation of herpes zoster. In 236 patients, herpes zoster was serologically confirmed (positive predictive value of clinical judgment was 90.8%). The results of the study demonstrated that good clinical judgment is exercised when diagnosing zoster in patients older than 50 years.

TREATMENT

Treatment goals for VZV are threefold: accelerate cutaneous healing, resolve acute or chronic pain, and prevent complications. Antiviral medications are the mainstay of treatment. Comparative efficacy studies of antiviral therapies have found that:



FIGURE 3. Ramsay-Hunt syndrome

- acyclovir 800 mg five times daily for 7 days was better than placebo for resolution of acute pain.⁷
- valaciclovir 1,000 mg three times a day for 7 days was slightly better than acyclovir for resolution of acute pain.⁸
- famciclovir 500 mg or 750 mg three times daily for 7 days increased the rate of lesion healing better than placebo and was equal to valaciclovir.⁹
- famciclovir 250 mg three times daily for 7 days was equal to acyclovir in resolution of pain and rate of lesion healing.¹⁰
- famciclovir 750 mg once daily for 7 days, famciclovir 500 mg twice daily for 7 days, famciclovir 250 mg three times daily for 7 days, and acyclovir 800 mg five times daily for 7 days were all equal for resolution of pain (PHN) and rate of lesion healing.¹¹

Current VZV expert panel recommendations emphasize antiviral therapy for all immunocompetent patients over age 50 years. A 7-day course of therapy should be started within 72 hours of rash onset with any one of the following regimens:

- acyclovir 800 mg five times daily
- valaciclovir 1,000 mg three times daily
- famciclovir 500 mg three times daily.¹²

Neuritic pain and hypersensitivity occur in 60% to 90% of patients with VZV. For most patients, pain resolves after several days, but acute pain is correlated with an increased risk of PHN. No one group of medications works for all patients with PHN. Some of the medications used are:^{12,13}

- gabapentin 300 mg at bedtime or 100 mg three times daily. The dosage may be increased by 100 mg to 300 mg three times daily every 2 days as tolerated.
- tramadol 50 mg once or twice daily. The dosage may be increased to 100 mg daily in divided doses every 2 days as tolerated.
- pregabalin 75 mg at bedtime or 75 mg twice daily every 3 days as tolerated

- tricyclic antidepressants, although they have a more significant adverse reaction profile than selective serotonin reuptake inhibitors (SSRIs), so SSRIs are used more often.
- oxycodone, started at 5 mg every 4 hours as needed and increased by 5 mg every 2 days as tolerated
- oral corticosteroids such as prednisone, 60 mg daily for 7 days, then tapered to 30 mg for 7 days, then 15 mg for 7 days then discontinued. Corticosteroids should only be initiated with antiviral therapy.

When using any of these medications in older adults, consider starting at a lower dose to decrease the possibility of unwanted adverse reactions.

PREVENTION

Prevention is largely addressed with the use of the herpes zoster vaccine, which has been found to reduce the incidence of VZV infection. A shingles prevention study of more than 38,000 adults (median age, 69 years) sought to determine if the herpes zoster vaccine could reduce the incidence and severity of VZV in patients age 60 years or older.¹⁴ The study was randomized to a 5.5 year, multicenter, double-blind placebo-controlled population. All participants were immunocompetent, with no history of previous shingles and with a history of previous varicella infection, or residents of the United States for at least 30 years. The primary endpoint was the burden of illness (score) calculated as a severity-by-duration measure of total pain and discomfort caused by VZV in both arms of the study. The secondary endpoint was the incidence of PHN greater than or equal to 3/10 on a pain scale present 90 days after the rash. The results demonstrated that when compared with placebo, the vaccination reduced the incidence of zoster by 51.3% and the burden of the illness by 61.1%. The incidence of PHN was reduced by 66.5% in the vaccinated group as compared to placebo.¹⁵ The vaccination was well tolerated and safety was comparable to placebo.

The CDC's Advisory Committee on Immunization Practices recommends the herpes zoster vaccine in persons age 60 years or older.³ However, the vaccine is approved by the FDA for people age 50 years and older, and studies are ongoing to determine its efficacy in patients ages 50 to 59 years.

Contraindications to the vaccine include immunosuppression, previous varicella vaccination, allergy to any of the vaccine's components, and pregnancy. The vaccine should be postponed for patients with fevers greater than 101.3° F (38.5° C). The durability of the vaccine is at least 4 years, with additional study needed to determine the need and timing of a booster. A 10-year study is ongoing related to the booster. The vaccine is considered safe and tolerable, with injection site reactions being the most common adverse reaction.¹⁴

CONCLUSION

VZV infection is a common presentation in primary care, and its incidence increases significantly with age. The virus is highly contagious and anyone who has not had varicella is susceptible. Antiviral treatment should be initiated as soon as possible to hasten lesion healing and decrease acute pain, as well as to help prevent PHN. Pregnant women who have not been exposed to varicella should avoid exposure to the virus, because spontaneous abortion, fetal demise, and congenital anomalies, although rare, may occur. The herpes zoster vaccine is recommended for all persons age 60 years and older without contraindications. **JAAPA**

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