

Herpes zoster vaccine: *Helping your patients make educated decisions*

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Multiple vaccines are now indicated in the older adult patient, but if my patients are in any way similar to yours, convincing them to get their vaccines can be a struggle. Since 2006, we have had a new vaccine in the armamentarium—the herpes zoster vaccine.^{1,2} In regard to this vaccine, many of my patients have asked, “I get a flu shot every year, I had the pneumonia shot, and now I need *another* vaccine?”

We have all seen the ravages of postherpetic neuralgia (PHN), which we can describe to our patients as an important reason to be vaccinated against herpes zoster. However, when discussing the vaccine, it is more helpful to explain the actual risk of developing herpes zoster, as well as the protection offered by the vaccine, so that patients can make an educated decision about whether to proceed.

Who is at risk?

Herpes zoster (ie, shingles) is a disorder that arises from reactivated varicella-zoster virus (VZV). Approximately 98% of the adult population in the United States is infected with VZV, with equal gender distribution.³

The varicella-zoster virus, which is highly contagious, is present worldwide, though it is typically acquired earlier in life in temperate climates than in tropical climates. At least 90% of individuals in temperate climates (eg, United States, Japan) are infected with VZV by age 15.⁴ In tropical climates, VZV is acquired later, so more new varicella infections are seen in adults. For example, in St. Lucia, less than 10% of the population is seropositive at age 15, and only approximately 70% by age 40.⁵ Thus, just about all of your patients are at risk for herpes zoster later in life.

How does VZV occur?

The varicella-zoster virus infects epidermal

cells during its viremic phase, causing the characteristic pruritic maculopapular and vesicular rash. The virus then travels down skin sensory neurons, via retrograde axonal transport, to dorsal root ganglia. It becomes latent in these ganglia cell bodies, usually concentrated in the cranial, cervical, or thoracic areas.

Between approximately 1% and 7% of sensory ganglia neurons can contain latent virus.^{4,6} The amount of infected ganglia neurons may be linked to the severity of the viremia or to the number of skin lesions. At the present time, however, the factors that result in viral binding or entry into dorsal root ganglia cells are not known.

As the primary infection resolves, the lesions crust over and slough off.³ Cell-mediated immunity and humoral immunity resolve the infection. Cell-mediated immunity clears the virally infected cells and limits replication of the virus in the skin, and immunoglobulin (ie, IgA, IgG, IgM) antibodies help neutralize the virus. Antibodies appear within one to three days after rash onset, and the virus then becomes latent. Research suggests that cell-mediated immunity is important in maintaining the latent state of VZV, and cell-mediated immunity itself is maintained by periodic immunologic boosting.^{4,6}

With age, cell-mediated immunity wanes, which may explain the emergence of herpes zoster in elderly patients. Cell-mediated immunity may also be impaired in patients who are immunocompromised by human immunodeficiency virus (HIV), malignancies, or immunosuppressive medications—leading to reactivation of VZV.

What happens when the virus reactivates?

When VZV is reactivated from latency, it replicates in the dorsal root ganglia and travels down neurons, resulting in herpes zoster. Many patients experience a prodrome of headache, malaise, photophobia,

or—less commonly—fever. However, the primary symptom of reactivated VZV is pain and/or paresthesia, because the virus causes an intense neuritis.

The pain or paresthesia typically persists for one to five days, but 40% of patients may have these symptoms longer than four days.⁷ The pain has been described as aching, burning, itching, lancinating, or tingling. It can be associated with an altered sensation to light touch, known as allodynia, in which a minimal stimulus, such as a light breeze, can trigger severe pain.⁸ Rarely, pain is the only symptom of reactivated VZV, a condition called zoster sine herpete.

Severe pain is often the trigger for patients to visit their physicians' offices. However, because a visible rash is not initially present, the symptoms can be mistaken for other conditions, such as appendicitis, biliary or renal colic, myocardial infarction, or pleurisy. Misdiagnosis can lead to prolonged symptoms, as well as unnecessary medications or testing.

In most cases, VZV is eventually released around the nerve endings in the skin, causing the characteristic rash. Once the rash emerges, the patient may transmit the virus to susceptible individuals. The rash classically progresses from erythematous and maculopapular to clustered vesicles on an erythematous base. Because the reactivation of VZV usually involves a single sensory nerve, the rash typically appears in a unilateral dermatome after the virus reaches the skin—though a few lesions may appear outside the primary dermatome. In immunocompromised patients, the rash can affect multiple noncontiguous dermatomes.

What areas are most affected?

The areas most commonly affected by the rash are supplied by the trigeminal nerve or by sensory ganglia from nerves T1 to L2—sites where the original varicella rash was

most concentrated. About 50% of cases involve the thoracic nerves T5 to T12, and 16% of cases involve the lumbosacral region.⁹ The rash persists for seven to 10 days, then crusts over and sloughs off in two to four weeks—though permanent scarring and pigment changes may occur.³

Although all body regions affected by herpes zoster can be intensely painful, zoster affecting the trigeminal nerve, particularly the ophthalmic division, can be especially severe. Zoster ophthalmicus, as this condition is called, accounts for 10% to 25% of herpes zoster cases, including 250,000 new cases per year in the United States.¹⁰

Zoster ophthalmicus can affect the vision in between 50% and 70% of patients with herpes zoster. Symptoms include rash in the affected dermatome, as well as swelling and inflammation of the eyelid, a condition called blepharoptosis. Additionally the eye itself may be involved leading to conjunctivitis, corneal keratitis, oculomotor palsies, scleritis, or uveitis. Zoster can also cause a necrotizing retinitis.⁴ Some patients may experience chronic symptoms, including chronic inflammation, pain and vision loss.

Involvement of the eye in patients with herpes zoster can be preceded by lesions that appear on the tip of the nose, a condition called Hutchinson's sign. These lesions represent involvement of the nasociliary branch of the trigeminal nerve, and should prompt an ophthalmologist referral.

Less commonly, VZV may spread proximally along the posterior nerve root to involve motor neurons in the anterior spinal cord, leading to local palsies. If VZV affects the geniculate ganglion of the facial nerve, it may cause Ramsay Hunt syndrome. This condition is characterized by rash on the ear, paralysis of the palate or tongue, and a peripheral facial palsy. It can also be accompanied by loss of hearing and taste, as well as pain, phonophobia, tinnitus and vertigo.¹¹

What about complications?

Rare complications of VZV infection include granulomatous angiitis, in which VZV from the trigeminal ganglion spreads to the internal carotid artery or its branch-

es, causing stroke. Other possible neurologic complications include Guillain-Barre syndrome, aseptic meningitis, meningoen- cephalitis and myelitis. Some patients may also have skin complications, such as a bacterial superinfection of the rash.¹¹

The risk of neurologic complications is increased in immunocompromised patients. Some immunocompromised individuals may have a more prolonged or severe rash than is seen in the typical course of herpes zoster. Dissemination of the rash to multiple dermatomes, which is also more likely in immunocompromised individuals, may be a marker for viremia that can seed other areas, including the brain, liver, lungs and gut.

One of the most common and debilitating complications of herpes zoster is postherpetic neuralgia (PHN). The definitions of PHN vary and have included zoster pain that persists more than 30 days after the rash resolves to pain that lasts more than six months after the rash.^{3,12} Degeneration, scarring and atrophy of the axons and cell bodies, as well as denervation of the epidermis, can be observed in patients with PHN.

Symptoms of PHN can persist for many years, with varying levels of severity. The pain can be constant or intermittent, and it can be triggered by even minimal stimulation. One of my patients experiences spasms of pain during the simple activity of getting dressed, when her clothing touches the affected area. The pain of PHN can have substantial effects on a patient's quality of life, causing disrupted sleep, mood, or work; inability to manage activities of daily living; social withdrawal; and depression.

Research findings on risk

In the landmark 1965 study on the epidemiologic factors of herpes zoster, Hope-Simpson¹³ evaluated risk in patients in a general practice setting over a period of 26 years. In this study population of 3,600 to 3,800 patients, the overall annual incidence of herpes zoster was 3.4 per 1,000 person-years. However, the risk was 5.6 per 1,000 person-years for those patients older than 50 years, and 11 per 1,000 person-years

in those older than 80 years.

Subsequent studies have found risk results similar to those reported by Hope-Simpson.¹³ A 1995 retrospective study of 250,204 primary care patients in the Harvard Community Health Plan found an overall herpes zoster incidence of 2.2 per 1,000 person-years.¹⁴ The risk of herpes zoster increased substantially with age, peaking at 14.2 per 1,000 person-years for patients older than 75 years.

One of the most recent studies on herpes zoster incidence was published in 2007 by Yawn et al¹¹ at the Mayo Clinic. This retrospective community-based study identified 1,669 cases of herpes zoster from records of more than 125,000 patients who were treated from January 1996 through December 2001 in Olmsted County, Minnesota. The researchers found that, when adjusted to the US population, the risk for herpes zoster overall was 3.6 per 1,000 person-years. The risk increased sharply with age, beginning at 4.7 per 1,000 person-years for patients aged 50 to 59 years and culminating in 12 per 1,000 person-years for patients aged 80 years or more. Hospitalizations were relatively infrequent, involving 3% of the patients.¹¹ Most hospital admissions were for patients with intact immunity, and the number of hospitalizations increased with age. Yawn et al¹¹ reported that recurrences of herpes zoster occurred infrequently, only 1.4% in three years. Other studies have reported low recurrence rates as well—1.7% to 5.2%.⁴

Risk factors

The Immunocompromised

Reduced cell-mediated immunity increases the risk for herpes zoster and its complications. Those with hematologic malignancies or solid tumors, those undergoing immunosuppressive therapy (eg, patients with transplants or autoimmune disease), those with genetic disorders of immunity and those with HIV are all at significantly increased risk.

Gender

Studies have varied regarding their findings of an individual's sex as a risk factor for herpes zoster and complications. Several stud-

ies have documented a heightened risk among women—ranging from 11% to 38% additional risk compared with men. In the Mayo Clinic study,¹¹ however, men were slightly more affected by herpes zoster than women (3.9 vs 3.2 per 1,000 person-years, respectively) when rates were adjusted to the US population. Still other studies have found no risk difference by sex.

Race

Racial differences in herpes zoster risk have been suggested by some studies. Schmadler^{15, 16} reported lower zoster incidence in black patients than in white patients (65% vs 75%, respectively) in two studies, after adjusting for confounding factors. Similarly, a study in the United Kingdom found a 54% lower zoster incidence in black patients than in white patients.¹⁷

Psychological stress

Psychological stress within the previous six months has been implicated as a risk factor for herpes zoster by a case-control study.¹⁸ Trauma or surgery within the previous one month has been associated with VZV reactivation in the affected dermatome.¹⁹ Micronutrients in the diet have been shown to have a protective effect against herpes zoster.²⁰

Complications

Once the patient has zoster, what is the risk for complications? Complications from herpes zoster identified by Yawn et al¹¹ involved 21% of the immunocompetent patients. Complications were higher in Immunocompetent patients than in other groups. The main complications were pain and PHN.

The risk for PHN has generally been difficult to ascertain because of the inconsistent definitions of the disorder used in various studies, as well as varying demographics of study populations. For example, studies of patients with herpes zoster who were using antiviral drugs have found persistent pain in one-third of placebo-treated individuals after three months and in one-fourth of placebo-treated individuals after six months.^{21,22} However, those studies might have overestimated the inci-

dence of PHN, because they may have consisted of populations with more severe pain overall compared with the general population.

In the Shingles Prevention Study,²³ the rate of PHN at 30 days was 30.3%, declining to 5.1% at 180 days. However, this rigorously studied group might not reflect a community-based sample.

In the community-based Mayo Clinic study by Yawn et al,¹¹ PHN occurred at a rate of 18% of patients at 30 days, declining to 10% of patients at 90 days. This recent (ie, 2007) study¹¹ provides a contemporary picture of the burden of herpes zoster. However, because this study was a retrospective chart review, it may have underestimated the incidence of herpes zoster and its complications. The Mayo investigators may have missed patients who did not seek medical attention or who were misdiagnosed. Since most of the participants were white, the finding might not be representative of all practice populations. At higher risk for the development of PHN are patients older than 50 years,^{24,25} patients with severe pain before or after the rash, patients with a large burden of disease and patients with involvement of the trigeminal or ophthalmic areas.

Prevention: The herpes zoster vaccine

The study that established the efficacy of the herpes zoster vaccine was the Shingles Prevention Study (SPS).²³ Oxman et al²³ studied 38,546 community-dwelling patients at 22 US sites for a median of three years. All patients were aged 60 years or older and immunocompetent. They had no previous episodes of herpes zoster. Patients were randomized to receive vaccine or placebo in a double-blinded manner.

Oxman et al²³ found that the vaccine reduced the incidence of herpes zoster by 51.3% compared with placebo. Although not all zoster episodes were prevented by vaccination, the vaccine reduced the incidence of PHN by 66.5% compared with placebo, and vaccinated patients in whom PHN did develop were noted to have less severe pain than those given placebo. The vaccine was most effective at preventing

herpes zoster in patients aged between 60 and 70 years, and it was also effective at attenuating the disease in older patients.

The dramatic results of the SPS²³ led to the licensing of the herpes zoster vaccine for immunocompetent adults aged 60 years and older in 2006. The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommended using the vaccine for this population the same year.⁶

Although certain population studies, such as that by Yawn et al,¹¹ suggest that the risk for herpes zoster increases for individuals older than age 50 years, the use of the vaccine is indicated only for patients aged 60 years and older because that was the population in the SPS.²³

The duration of immunity provided by the herpes zoster vaccine is unclear. Because the vaccine's efficacy was maintained over the duration of the SPS,²³ immunity is known to remain intact for at least four years. It has not yet been determined when or if booster vaccines will be needed in association with the herpes zoster vaccine, but this is currently under investigation.

Based on data from the SPS,²³ over a period of three years, about 60 patients will need to be given the vaccine to prevent one episode of herpes zoster, and 360 patients will need to be treated to prevent one episode of PHN. However, even vaccinated patients in whom herpes zoster does develop will have less severe symptoms than had they not received vaccination.

The efficacy of the herpes zoster vaccine in patients who have had previous episodes of zoster is unknown. The vaccine has not yet been studied in this population. It's possible that previous episodes of herpes zoster may boost cell-mediated immunity against VZV, though the vaccine may provide additional protection. To improve simplicity of vaccine use, the ACIP¹³ recommends that all patients aged 60 years or older be given the vaccine regardless of whether they reported past episodes of herpes zoster.

It is also not necessary to confirm past history of varicella before vaccination, because almost all patients have been exposed to VZV via chickenpox. However, if a patient does have a negative result in a VZV

titer, the varicella vaccine, rather than the herpes zoster vaccine, should be offered.

Safety

Overall, the herpes zoster vaccine has been shown to be safe. No cases of zoster-type rash were reported after vaccination in the SPS.²³ However, a smaller study of the vaccine did report two cases of rash, and the virus cultured from the rash was the same strain as that in the vaccine.¹

Minor adverse events associated with the vaccine were reported in the SPS²³ and the Adverse Event Monitoring Substudy (AEMS)²³—a subgroup of the SPS with 3,345 patients. These adverse events included headache (1.4%) and injection-site reactions such as erythema (33.7%), pain (33.4%), swelling (24.9%), pruritus (6.6%), warmth (1.5%), and hematoma (1.4%).

Serious adverse events, such as cardiovascular events, occurred at similar rates in patients given vaccine and placebo in the SPS.⁹ The rate of cardiovascular events in both groups was 0.4%. In the AEMS, however, adverse events were significantly more frequent in vaccinated patients at 1.9% vs 1.3% in placebo-treated patients. There were no significant differences in the distribution of the type of adverse events. The AEMS identified two (1.9%) vaccinated patients and three (1.3%) placebo-receiving patients in whom asthma exacerbation and polymyalgia rheumatica developed. Rarely, vaccinated patients may transmit vaccine virus to susceptible contacts.

Contraindications

Because the herpes zoster vaccine contains live attenuated virus, it cannot be given to patients with impaired immunity from any cause (eg, HIV, primary immunodeficiency, malignancies affecting the bone marrow or lymphatic system, immunosuppressive medications). In addition, the vaccine cannot be given to patients with fever higher than 38.5°C (101.3°F).² The effects of the herpes zoster vaccine has not been studied in pregnant animals or humans—though pregnancy would not be expected to be an issue in the indicated age group.

Vaccine components must be taken into

account when considering vaccination of patients. The herpes zoster vaccine should not be given to any patient with a history of anaphylaxis or anaphylactoid reaction to gelatin, neomycin, or other vaccine components. The vaccine also contains monosodium L-glutamate, potassium chloride, potassium phosphate monobasic, sodium chloride, sodium phosphate dibasic, sucrose, residual components of human diploid cell cultures (eg, DNA, protein) and trace amounts of bovine calf serum.² The vaccine contains no thimerosal or other preservatives.

Administration and storage

The herpes zoster vaccine is given as a single subcutaneous injection of 0.65 mL in the deltoid area.² It is stored frozen and is reconstituted using sterile diluent supplied with the vaccine. Because the vaccine remains potent for only 30 minutes at room temperature, once reconstituted, it must be used within that time frame.

For the herpes zoster vaccine to maintain its potency over extended periods, it must be stored frozen at a temperature of at least -15°C (5°F).² Freezer temperatures should be checked and recorded at least twice daily. Your office freezer should be evaluated for adequacy and reliability in maintaining the necessary temperature. The standard dormitory-style freezer is incapable of reliably maintaining this temperature. The diluent may be stored at either room or refrigerator temperatures.

Cost and reimbursement

Most physicians will agree that the herpes zoster vaccine is worthwhile for their patients, but the logistics of providing the vaccine to patients can be cumbersome as a result of reimbursement issues.

For patients aged between 60 and 64 years, or older patients with commercial insurance, the herpes zoster vaccine is typically covered as a medical benefit. Thus, as with other vaccines (eg, influenza) administered in the office, the physician can usually be reimbursed for both purchasing and administering the herpes zoster vaccine under the patient's medical benefits plan. However, not all plans cover the vaccine, so

your office needs to determine the eligibility and copay. Alternatively, the patient may agree to payment if the cost is denied by his or her plan.

For patients aged 65 years or older who have Medicare Part D coverage, the herpes zoster vaccine and its administration are covered as a prescription benefit. This means that physician offices cannot bill for the vaccine in the usual manner. However, an online interface called eDispense™ (Dispensing Solutions Inc, Santa Ana, California. Enroll.edispense.com)²⁶ allows physician offices to determine eligibility and copays and to submit claims for reimbursement through Medicare Part D plans.

Alternatively, the provider can give the Medicare Part D patients a prescription to pick up the herpes zoster vaccine at a pharmacy and bring it to the office for administration. However, a physician's office still cannot bill for the administration of the vaccine unless it is using eDispense™.²⁶ In addition, unless the patient is given the vaccine within 30 minutes of picking it up at the pharmacy, the vaccine potency will be reduced.

A final method bypasses the physician office and utilizes the pharmacy. Several pharmacies are now certified to administer the herpes zoster vaccine. Patients present a prescription from the physician for the vaccine to a certified pharmacy, and the pharmacist administers it and submits the claim under Medicare Part D.

Final notes

The herpes zoster vaccine is a welcome addition to the adult vaccine regimen. Virtually all of our patients are at risk for herpes zoster, and this risk increases as they age. Although the lifetime risk for herpes zoster is 10% to 30% for the overall population, approximately 50% of patients who reach age 85 years will develop herpes zoster.

For older adults who do not have immunocompromising conditions and do not use immunosuppressive medications, the herpes zoster vaccine will cut chances of the development of this painful condition in half. Perhaps even more importantly, the herpes zoster vaccine will reduce a

patient's risk of PHN by two-thirds. As our population ages, the potential impact of this vaccine is great.

The logistics of administering the herpes zoster vaccine is manageable, and should be planned by your office according to your ability to store the vaccine, number of eligible patients and administrative support for handling reimbursement. **y ww**

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