This representation shows the herpes virus replication within a host cell. The glycoprotein spikes in the viral envelope (green) allow the virus to fuse with the membrane of the host cell (upper right). The viral capsid (the protein coating in blue), which contains the DNA genome (red), is released into the cell's cytoplasm. The virus particle travels to the nucleus (pink) where it replicates its own DNA and produces new capsids. The daughter DNA enters the new capsids. The new capsids leave the nucleus, acquire a protein envelope in the cytoplasm, and leave the cell to infect other cells.

Illustration by Russell Kightley / Science Source ©

CE 2.3 CONTACT HOURS  Rx 1.0 CONTACT HOURS

# Herpes zoster

## A rash demanding careful evaluation

***Abstract: This article discusses the incidence, epidemiology, clinical presentation, diagnosis, and treatment of herpes zoster, complications such as postherpetic neuralgia, and prevention through vaccination. Information on vaccine cost and insurance coverage is provided as well as two case studies illustrating various clinical presentations.***

**By Denise D. Wilson, PhD, APN, FNP, ANP, GNP**

***Case 1:*** *A 78-year-old male who resides in an assisted-living complex is brought to the office by his daughter. She states that staff at the facility had contacted her to report that her father had "not been himself" for the past 2 days and was staying in his apartment rather than joining other residents for meals and activities. The patient reports that he has not felt well for a week and now has a very painful rash on the left side of his abdomen, which extends posteriorly to the mid-lumbar area. The rash does not extend beyond the midline. The nurse practitioner (NP) explains to him that he has herpes zoster (HZ), commonly known as "shingles."*

***Case 2:*** *An 81-year-old female presents to the office complaining of a "sore area" on the top of her head. She states that she first noticed the area when she brushed her hair yesterday morning. She denies any injury to the area. Her past medical history includes hypertension well-controlled with lisinopril, hyperlipidemia well-controlled with rosuvastatin, and glaucoma controlled with both dorzolamide and latanoprost drops. Past surgical procedures include a three-vessel coronary artery bypass and a trabeculectomy of her right eye. At her last ophthalmic exam 2 months ago, her intraocular pressure (IOP) readings were as follows: left eye, 12 mm Hg; right eye, 14 mm Hg. Physical exam reveals two 2 mm vesicular lesions on the right frontal scalp area. An additional 1 mm vesicle is noted on the right side of the nose. The skin on the right lateral forehead is sensitive to light palpation but is free of lesions. There is slight edema of the right upper eyelid. Otherwise, the eye appears normal. The HEENT exam is otherwise negative. The NP diagnoses the patient with HZ ophthalmicus.*

What do these two patients have in common? They both had varicella (chickenpox) as children, have decreased immune function due to aging, and have developed HZ, also known as shingles.

### The condition defined

Viruses in the herpes family are known for their ability to lie dormant in the body and then reappear at unpredictable times. This pattern of latency and reactivation occurs with HZ. The primary infection, typically occurring during childhood, is due to the presence of the varicella-zoster virus (VZV) and results in varicella (chickenpox). The virus then becomes dormant in sensory dorsal root ganglia of the nervous system.[1] Cell-mediated immunity (CMI) normally prevents VZV from

**Keywords: herpes zoster, herpes zoster ophthalmicus, postherpetic neuralgia, shingles, zoster vaccine**

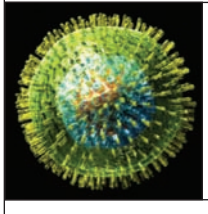
emerging from latency. When CMI declines as a result of normal aging or an immune-deficiency state, VZV can reactivate, resulting in HZ.[2]

## The risk of developing HZ

According to the CDC, almost one out of every three people in the United States will develop HZ.[3] Of the estimated 1 million cases occurring each year, approximately 50% occur in individuals ages 60 years and older.[3]

Surveillance studies in the United States have shown that over 99% of adults over 40 have serologic evidence of previous VZV infection as measured by VZV-specific immunoglobulin G antibody.[4] This is not surprising when one considers that the recommendation for a routine, one-dose varicella vaccination did not occur until 1996.[5] Considering the direct relationship between HZ incidence and age, the lifetime risk of HZ is estimated to be approximately 25% in the general population, but rises to 50% in those over age 85.[6]

In addition to age, the status of the individual's immune system is an essential variable in VZV reactivation. The VZV is most likely to reactivate during times of stress, trauma, and other precipitating factors.[7] Stress can be psychological, such as stress due to problem relationships, job situations, or financial difficulties, or physical, as with the numerous conditions leading to a compromised immune system. In a study of over 59,000 HZ cases and over 616,000 controls, the most prevalent chronic conditions among both groups were hyperlipidemia, hypertension, and diabetes mellitus.[8] Another consideration is the increased risk of HZ infections in patients on certain medications, including immunosuppressants such as prednisone, tumor necrosis factor-alpha inhibitors, such as adalimumab, etanercept, and infliximab, and immunomodulating agents used for chronic inflammatory diseases, such as psoriasis, rheumatoid arthritis, and inflammatory bowel disease.[9,10]



***As the VZV reactivates within the sensory ganglia, neuronal inflammation occurs, accompanied by severe neuralgia.***

HZ (shingles) is not contagious. However, the virus that causes shingles, VZV, can be spread from a person with active shingles to a person who has never had chickenpox. This transmission means the exposed person could develop chickenpox, not shingles.[3] The varicella virus is typically spread through direct contact with fluid leaking from the rash's vesicles. Covering the rash during this phase of the condition can minimize risk of this form of transmission. In addition, VZV can be transmitted through inhalation of aerosolized virus from the rash.[5] Varicella zoster DNA may persist in saliva and blood after the HZ infection has resolved; exposure to these fluids may constitute additional potential routes of transmission.[11]

## Clinical presentation of HZ

One day to 3 weeks prior to the skin eruption, patients may initially complain of prodromal symptoms seen in many viral infections, including malaise, fever, chills, myalgia, headache, or stomach upset. As the VZV reactivates within the sensory ganglia, neuronal inflammation occurs, accompanied by severe neuralgia.[12] This is described as a burning or tingling type of pain in the skin (acute neuritis). However, some patients initially experience pruritus or numbness of the area rather than pain.

Patients often complain of hypersensitivity of the skin prior to the appearance of any rash. As the virus is released by the nerve endings in the skin, it replicates, producing a skin eruption, which may begin as macules and papules on an erythematous base and progress to a cluster of vesicles within 3 to 5 days (see *Cluster of HZ lesions*).

The rash is typically limited to one side of the body in one or more dermatomes.[1] Immunocompromised patients may experience the rash in more than one dermatome and in a bilateral pattern. Although any dermatome can be affected, HZ occurs most often in the dermatomes innervated by the first (ophthalmic) division of the trigeminal nerve and by the spinal sensory ganglia from T1 to L2.[12] (See *Thoracic dermatomal eruption*.)

After formation of vesicles, the lesions usually rupture and release VZV; they then crust over and may turn a dark color. Typically, the lesions resolve in 10 to 15 days, although some may take up to a month to heal.

Cranial nerves can also be affected by HZ. The ophthalmic division of the trigeminal nerve (fifth cranial nerve) is affected in *HZ ophthalmicus*. Blisters located on the tip of the nose are a common indicator of HZ ophthalmicus, a finding known as *Hutchinson sign*.[13] Such a presentation is a predictor for possible serious complications, such as ocular inflammation and corneal denervation. The patient described earlier in Case 2 displayed Hutchinson sign and was referred to an ophthalmologist for emergent examination. Although the patient in Case 2 had relatively few vesicles visible on the skin, the ophthalmologist found viral involvement within the eye as evidenced by

the presence of HZ virus dendrites, and the patient had an increased IOP of 36.

*Ramsay Hunt syndrome*, also known as *HZ oticus*, is an infection of the facial (seventh cranial) nerve. This syndrome is identified by the occurrence of severe ear pain, facial muscle weakness, and rash, often on the pinna or tragus of the external ear or on the tympanic membrane. Prompt diagnosis and treatment is needed to avoid hearing loss and permanent facial muscle weakness.[13]

## Diagnosis of HZ

HZ can usually be diagnosed solely on the history and physical assessment. However, the classic vesicular rash may have an atypical appearance in immunocompromised individuals. Lab testing can be performed if the clinical diagnosis of HZ is uncertain. Viral culture is an option, but recovery of VZV from HZ lesions is difficult, and growth of VZV in the culture may take 3 to 14 days. The direct fluorescent antibody (DFA) assay of cells scraped from ulcerative lesions is a more sensitive test than viral culture. The DFA is based on antigen detection and has a more rapid turnaround time.[13]

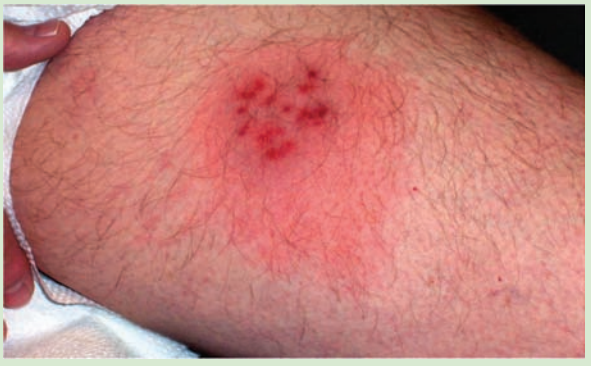
## Treatment options

Antiviral medication is the foundation of HZ treatment. The three options currently available are: famciclovir administered orally every 8 hours for 7 days; valacyclovir administered three times a day (with 8 hours between doses) for 7 days; or acyclovir administered five times a day (with 4 hours between doses) for 7 to 10 days. Famciclovir, valacyclovir, and acyclovir all require dosage adjustments for patients with renal impairment. See the manufacturer's drug label for complete prescribing information.

I.V. acyclovir is used with HZ complicated by central nervous system involvement, especially myelitis.[13]

The initiation of antiviral therapy within 72 hours of lesion onset is key to treatment success. Starting the medication quickly limits the damage to the sensory nerves from the replicating virus. This shortens the duration of new lesion formation, accelerates cutaneous healing, reduces the duration of viral shedding, and reduces the duration of pain.[13] For patients presenting for treatment after 72 hours, antiviral therapy may still be of benefit in individuals at high risk of postherpetic neuralgia (PHN), those who are over the age of 50, those with continued new vesicle formation, and anyone with cutaneous, motor, neurologic, or ocular complications.[13] HZ ophthalmicus must be treated quickly and aggressively to avoid damage to the eye or surrounding structures, including blepharitis, conjunctivitis, keratitis, uveitis, scleritis, episcleritis, and acute retinal necrosis. Such treatment includes oral antiviral therapy along with systemic or topical corticosteroids.

**Cluster of HZ lesions**



The photo is from the author's personal collection, and was previously published in Wilson DD. Herpes zoster: prevention, diagnosis, and treatment. *Nurse Pract.* 2007;32(9):19-24.

Topical antibiotics are indicated for secondary bacterial infection.[14]

Use of corticosteroids for HZ outbreaks varies among healthcare providers. Randomized controlled trials have found that adding corticosteroids to acyclovir decreases the pain of acute HZ and speeds lesion healing and return to daily activities.[15] The use of corticosteroids with antivirals should be considered in patients over 50 who have moderate-to-severe pain and who have no contraindications to their use. Relative contraindications include the presence of diabetes mellitus, osteoporosis, or gastritis. Typical dosing is a 10 to 14 day tapering course of oral prednisone starting at 60 mg daily.[13]

Assessing the patient's level of pain is essential. The healthcare provider cannot assume that the extent of the HZ lesions correlates with the severity of pain experienced by the patient. Providing pharmacologic interventions to decrease the patient's pain may reduce the risk for PHN while also improving the patient's functional status and quality of life.[13] Medications used for mild-to-moderate pain include acetaminophen, NSAIDs, and tramadol, whereas moderate-to-severe pain requires treatment with opioids, such as oxycodone and morphine.[15] Pain medication taken on a scheduled basis is more likely to provide pain control than when the pain medication is taken on an "as needed" basis.

## Complications of HZ

Several complications of HZ have been reported in the literature. These include *contralateral hemiparesis* as a late complication of HZ ophthalmicus; *multifocal vasculopathy* from dissemination of VZV to the central nervous system presenting as a transient ischemic attack (TIA), stroke, or delirium; *VZV encephalitis* following facial HZ; and retinal

necrosis presenting as visual changes acutely and up to months after an episode of acute HZ.[13,14,16]

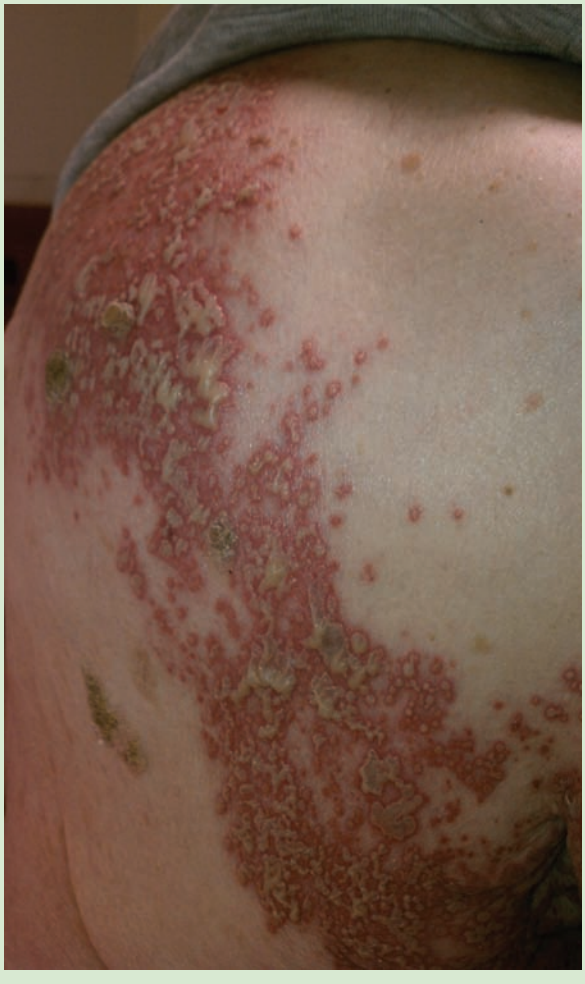
The most common complication of HZ is PHN. Pain associated with HZ can persist for 30 days to 6 months and beyond. Advanced age increases the risk of developing PHN and the length of time it persists. It is rarely seen in patients under the age of 50, but it occurs in 20% of those 60 to 65 years of age and in 30% of patients older than age 80.[15]

Living with chronic pain impacts the quality of life in older adults in several ways. The pain can affect the person's ability to perform daily living activities, such as dressing, bathing, eating, and ambulating. Physical consequences of PHN include chronic fatigue, anorexia, weight loss, physical inactivity, and difficulty sleeping. These patients may also experience depression, anxiety, and difficulty concentrating, which negatively impact the individual's ability and desire to participate in social activities.[17]

There are also increased healthcare costs associated with PHN. In a study of patients with HZ, the average excess cost per patient was $1,300 in the year after the HZ diagnosis with 30 or fewer days of analgesic use compared to $2,200 to $2,300 per patient with PHN or possible PHN.[18] The substantially greater healthcare costs associated with PHN than those associated with HZ pain that resolved within 30 days support the early treatment of HZ.

Pharmacologic management of PHN centers on treatment of nerve-related pain. Tricyclic antidepressants such as amitriptyline, desipramine, and nortriptyline have been used for chronic pain disorders and have been found to be effective in the management of PHN. The use of these medications is considered an FDA off-label indication for PHN. These are typically used at low doses at bedtime to minimize the possible sedative effect. These medications may also cause anticholinergic-like effects of dry mouth, blurred vision, constipation, and urinary retention. Tricyclic antidepressants are contraindicated during the acute recovery phase of myocardial infarction, and may cause cardiovascular adverse reactions including tachycardia, hypertension, and cardiac dysrhythmias. Opioid medications such as oxycodone, morphine, and tramadol are also effective in providing pain relief. Medications approved for use in other types of nerve pain, such as peripheral neuropathy, have also been found to be effective in the treatment of PHN. Two anticonvulsant drugs that are FDA-approved for PHN are gabapentin and pregabalin. Cautious use of these medications in older adults is needed due to the adverse reactions of dizziness and somnolence. Monitoring of the patient's creatinine clearance is imperative due to the need for decreased frequency and/or dose of the medication in the presence of decreased renal function. Two topical medications approved by the FDA for use in PHN, capsaicin 0.075% cream and lidocaine 5% patch, may also provide partial relief of pain.[15]

**Thoracic dermatomal eruption**



This photo is courtesy of the author's personal collection.

## Prevention of HZ

Primary prevention of HZ development focuses on two populations: the young and those 50 years of age and older. As discussed, in order for HZ to develop, the person must be seropositive for VZV. Primary prevention of varicella is through administration of varicella virus vaccine live. According to the CDC recommendations, the first dose of this vaccine is administered at age 12 through 15 months, with the second dose given at age 4 through 6 years. The second dose may be administered before age 4, provided at least 3 months have elapsed since the first dose.[19]

The zoster vaccine live (Zostavax), which contains live attenuated VZV, protects against the development of HZ by boosting VZV immunity. The safety and efficacy of the vaccine were evaluated in the Shingles Prevention Study, which involved over 38,000 patients 60 years of age or older. It found that administration of the vaccine resulted in a 51.3% reduction in the incidence of HZ and a 66.5% reduction in the incidence of PHN.[20] The vaccine, first marketed in 2006, was originally indicated for prevention of HZ in individuals 60 years of age and older. Further study found the zoster vaccine significantly reduced the incidence of HZ and was well tolerated in subjects ages 50 to 59 years.[21] Despite the demonstrated efficacy, fewer than 10% of eligible persons receive the HZ vaccine.[22] Although the vaccine is licensed by the FDA for administration to persons aged 50 years and older, the Advisory Committee on Immunization Practices (ACIP) recommends that vaccination begin at age 60.[23] It should be noted that concomitant administration of zoster vaccine live and the pneumococcal vaccine polyvalent (Pneumovax 23) results in decreased zoster vaccine efficacy. As a result, a 4-week interval is recommended between administration of these vaccinations.[20]

Patients may receive the zoster vaccine without serologic testing, regardless of any history of varicella virus infection or HZ. Because it contains live virus, the vaccine should be administered 2 to 4 weeks prior to initiating any immunosuppressive therapy. For patients receiving high-dose corticosteroid therapy, the vaccination should be deferred for 1 month after discontinuation of the corticosteroid.[15] The vaccination should also be deferred in patients with acute illness and those with active, untreated tuberculosis. For older adults who have not received the vaccine but now have HZ, it is recommended that the vaccine be administered as soon as the HZ rash and pain resolve. The vaccine is contraindicated in pregnancy, in those who are immunosuppressed or immunodeficient such as those with AIDS or blood cancers, and for those with anaphylaxis to gelatin or neomycin.[15]

It is expected that following administration of the zoster vaccine that there is an increase in CMI to VZV. The Depression Substudy of the Shingles Prevention Study evaluated the association between major depression and immune responses to the zoster vaccine and found that depressed patients have diminished VZV CMI responses to the zoster vaccine, leading to a reduction in the efficacy of the zoster vaccine. Treatment with antidepressant medication normalized these responses.[24]

Cost of the zoster vaccine ranges from $187 to $233.[25] The vaccine is not covered under Medicare Part B but may be reimbursed under Medicare Part D prescription drug plans or other prescription drug plans. The Centers for Medicare and Medicaid Services (CMS) views the vaccine and its administration as "intrinsically linked," meaning that only a single claim is allowed for both the vaccine and the cost of its administration. If the patient receives the vaccination at an in-network pharmacy, the pharmacy processes a single claim to the Part D plan and only collects any applicable cost-sharing fees from the patient. However, if the vaccination is administered out-of-network in a provider's office, the provider bills the patient for the entire charge, and the patient then needs to submit a paper claim to the Part D prescription plan for reimbursement.[26]

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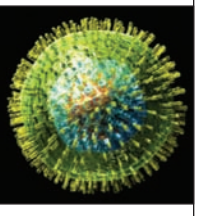

## Patient education

It is important to provide information to patients regarding symptoms of HZ, the need for prompt treatment, and the availability of the zoster vaccine are very important. See the *Guide to care for patients: HZ (Shingles)* in this issue. Patients need to understand that they can transmit VZV from draining HZ lesions to individuals who have not had VZV previously. It should be stressed that early treatment can minimize the risk of developing PHN. Thus, informing patients of the signs and symptoms of HZ is essential. Information should also be provided to assist patients in preventing development of bacterial skin infection and in treating HZ-associated pain. The zoster vaccine should be encouraged to decrease the risk of developing HZ and PHN. NP

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