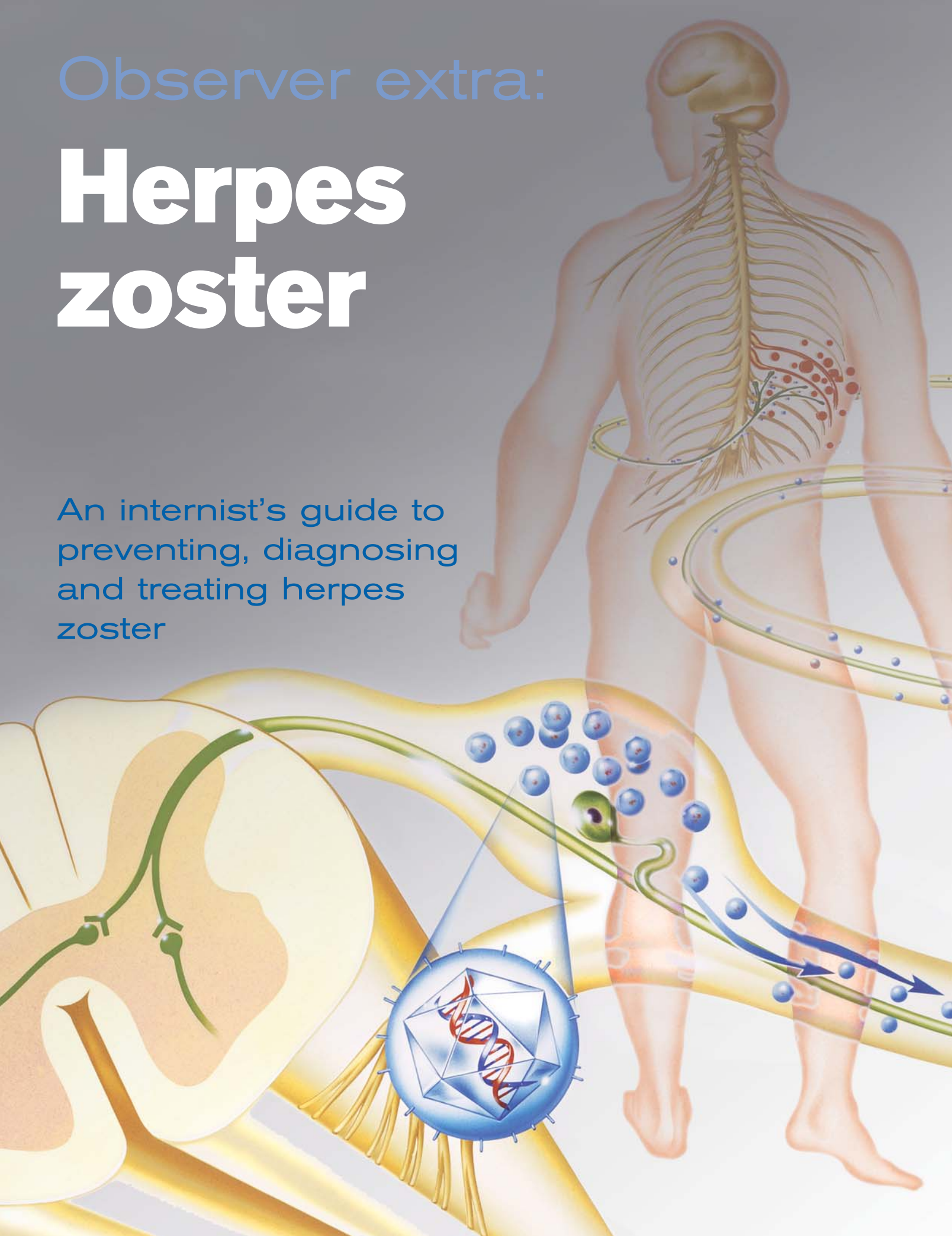


Observer extra:

# Herpes zoster

An internist's guide to preventing, diagnosing and treating herpes zoster



# Herpes zoster

Herpes zoster (shingles) is caused by reactivation of the varicella-zoster virus (VZV) from latency after infection with chickenpox. After acute infection, the virus lies dormant, typically for decades, in the sensory dorsal root ganglia. The cause for VZV reactivation is unclear. However, decline in cell-mediated immunity with age, certain diseases (such as HIV infection), or effects of immunosuppressive therapy are associated with reactivation of the virus. Herpes zoster occurs only occasionally before the age of 50, and at least half of the more than 1 million cases in the U.S. annually occur among people older than age 60.

Following VZV reactivation, virus replication leads to ganglionitis and extensive inflammation and destruction of neurons and supporting cells. The dermatomal distribution of the subsequent vesicular rash corresponds to the sensory fields of infected neurons within a ganglion.

A herpes zoster outbreak is usually limited to two to three weeks. Associated pain, however, may persist much longer. Postherpetic neuralgia is the most common complication of herpes zoster. It is a neuralgic pain that persists for more than three months after the healing of the rash and it can range in severity from trivial to debilitating. At six months after lesions have resolved, postherpetic neuralgia occurs in 13% to 35% of patients older than age 60. In 37% of people over age

60 and 48% over age 70, associated pain lasts for more than a year.

The associated pain interferes with the quality of life in a manner similar to that seen in patients with congestive heart failure, depression or Type 2 diabetes, said Bennett Lorber, FACP, in an Update on Infectious Diseases at ACP's Annual Session 2006. Clinical factors, such as older age and more extensive rash, increase the likelihood of more prolonged pain.

People with active herpes zoster can be infectious. The virus can be transmitted, primarily through direct contact with lesions from a patient with active dermatomal zoster, and can cause varicella in susceptible individuals. VZV also can be transmitted through an airborne route, particularly by patients with disseminated herpes zoster. Patients with active herpes zoster should be especially careful to avoid contact with susceptible infants or small children, susceptible pregnant women or potentially susceptible immunocompromised individuals. Standard precautions and use of gloves when touching the lesions of patients with localized zoster are recommended. Severely immunocompromised patients who develop dermatomal zoster should be placed in strict airborne and contact isolation, until it is clear that dissemination is not developing, as should all patients with disseminated zoster.

## Prevention

Herpes zoster can now be prevented, at least in some people. The FDA approved the first live VZV vaccine, called Zostavax (Oka/Merck), in May 2006. The single-dose vaccine contains 18,700 to 60,000 plaque-forming units of virus, considerably more than the approximately 1,350 plaque-forming units found in the Oka/Merck VZV vaccine for prevention of varicella in children. The VZV vaccine reduces herpes zoster incidence by half and postherpetic neuralgia by two-thirds in adults at least 60 years old, according to a study involving more than 38,000 people. Adverse effects are limited to mild injection-site reactions, itching and headache.

Use of the vaccine is not yet widespread. The Advisory Committee on Immunization Practices unanimously endorsed the usage of VZV vaccine for all adults age 60 and older. A cost-effectiveness model suggested that VZV vaccination to prevent herpes zoster in immunocompetent older adults could increase quality-adjusted survival by 0.6 days compared with no vaccine. The vaccine would be cost effective only for adults age 60 to 69 if it cost less than \$200 and if efficacy exceeded 30 years. Doctors do not yet know whether varicella vaccination in childhood, which became routine relatively recently, plays any role in preventing herpes zoster.

Vaccination with VZV vaccine is recommended for adults age 60 years and older without contraindications for a live vaccine. Contraindications include:

- ◆ Primary or acquired immunodeficiencies
- ◆ Pregnancy

Zoster vaccine should not be used for the treatment of zoster or post-herpetic neuralgia.

## Diagnosis

Suspect herpes zoster when a patient complains of localized pain and an erythematous vesicular rash that follows a dermatomal distribution. Cutaneous involvement may be patchy or confluent, with skin changes beginning with redness and inflammation followed by the development of clusters of small, clear vesicles. The rash is characteristically dermatomal. A history and clinical examination can usually confirm the diagnosis. (See table, "History and physical examination elements of herpes zoster," page 7.)

Pain is the most common symptom of zoster and can precede the rash by days to weeks. Most patients describe a deep burning sensation or report dysesthesias. The rash is limited to one dermatome in normal hosts, but can occasionally affect two or three neighboring dermatomes. Some patients have a few scattered vesicles located at a distance away from the involved dermatome and this has no particular prognostic significance. Dissemination of herpes zoster to visceral organs occurs very rarely in immunologically intact individuals, although some patients with vasculitis and myelitis have been reported.

The complications of herpes zoster include ocular and neurologic manifestations, bacterial superinfection of the skin

## Differential diagnosis of herpes zoster

In general, once herpes zoster is fully developed, the clinical appearance is distinctive from any other disease. Herpes zoster can be confused, however, with "zosteriform" herpes simplex virus infection, especially in the sacral area.

Immunocompetent patients with a history of recurrent "shingles" ( $\geq 2$  episodes) often have recurrent herpes simplex virus infection rather than herpes zoster.

Diagnosis is more difficult in patients with dermatomal pain before developing skin lesions. Consider a broad differential diagnosis of localized pain in patients who present before the rash appears. The diagnosis may not be herpes zoster if the patient:

- ◆ has a rash without pain or dysesthesias
  - ◆ has a rash that does not conform to the typical dermatomal distribution
  - ◆ has persistent neuralgic pain without the appearance of a typical skin eruption
- When the presentation is atypical or complex, consultation may be necessary.
- ◆ Consult an infectious disease specialist or dermatologist for assistance with recognizing atypical presentations or with procedures such as viral culture or skin biopsy.
  - ◆ Consult an ophthalmologist for assistance with diagnosing herpes zoster involving the first division of the trigeminal nerve.
  - ◆ Consult an otolaryngologist for assistance with diagnosing Ramsay Hunt syndrome.

and postherpetic neuralgia. Herpes zoster may also result in meningeal inflammation and clinical encephalitis.

Occasionally, VZV reactivation affects motor neurons in the spinal cord and brain stem resulting in motor neuropathies. Consider the possibility of VZV multifocal vasculopathy in patients with altered mental status or focal neurologic findings during or after an episode of herpes zoster. Evaluate patients with hemiparesis that follows an episode of herpes zoster ophthalmicus by weeks or months for possible VZV-related central nervous system vasculitis.

Herpes zoster ophthalmicus is a serious complication linked to VZV reactivation within the trigeminal ganglion. The syndrome begins with headache and fever followed by a vesicular eruption along the trigeminal dermatome and can be responsible for conjunctivitis, episcleritis and lid droop. Most patients will go on to develop keratitis (corneal involvement). Rapid diagnosis and treatment are essential to prevent visual loss. VZV has also been implicated as a causative pathogen of acute retinal necrosis in immunocompetent patients. Patients typically complain of blurred vision and pain in the affected eye and may demonstrate features of acute iridocyclitis, vitritis, necrotizing retinitis and occlusive retinal vasculitis.

The major otologic complication of VZV reactivation is the Ramsay Hunt syndrome

## ACP Observer extra

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*Shingles rash caused by the infection of sensory nerves with the varicella-zoster virus. The outbreak of vesicles on the skin in the area supplied by the nerve last around two weeks, and are followed by severe pain in the affected area. Antiviral drugs such as acyclovir can help to prevent the pain if taken early in the attack. If the drug treatment is delayed, however, there is no treatment, although painkilling drugs may provide some relief.*



*Shingles involving the eye. The herpes zoster virus infects sensory nerves and causes vesicles on the skin supplied by those nerves. The nerve infected here is the nasociliary nerve, a branch of the trigeminal nerve. The vesicles are highly infectious as they contain fluid that contains virus particles.*

(ipsilateral facial paralysis, ear pain, and vesicles in the auditory canal and auricle). Taste perception, hearing (hyperacusis or tinnitus) and increased lacrimation may be affected, and some patients experience acute vertigo.

## Treatment

Treatment for herpes zoster consists of both non-drug and drug therapy. Many patients will only require basic interventions to reduce infection risk and minimize pain. Others may require oral or intravenous antiviral therapy to accelerate healing and reduce pain. For patients with severe herpes zoster infection, consider hospitalization for parenteral antiviral therapy and close observation. This is especially important to consider for patients with ocular or visceral involvement.

## Non-drug therapy

Both involved and uninvolved skin in the affected dermatome may be tender and exhibit increased sensitivity to the touch. Some basic interventions can reduce the risk for infection and relieve symptoms. Patients should be advised to:

- ◆ Keep the cutaneous lesions clean (soap and water) and dry to reduce the risk for bacterial superinfection.
- ◆ Apply compresses (water, saline, Burrow's solution) and protective dressing for symptomatic relief.
- ◆ Protect lesions with sterile, occlusive, nonadherent dressing.
- ◆ Wear loose-fitting clothing for improved comfort.

There is no role for topical creams or ointments, including topical corticosteroids, acyclovir or penciclovir.

## Drug therapy

### Antiviral drug therapy

Antiviral drug therapy accelerates the healing of skin lesions and reduces the duration of pain, presumably by limiting the extent of damage done to the involved sensory nerves by the replicating of VZV and by shortening the duration of new lesion formation.

Three oral antiviral drugs are approved in the U.S. for treatment of herpes zoster in immunocompetent patients: acyclovir, valacyclovir and famciclovir. Valacyclovir and famciclovir are now preferred in practice because they have a simplified dosing schedule and improved pharmacokinetic characteristics compared with acyclovir. Valacyclovir and famciclovir are therapeutically equivalent for treatment of herpes zoster in the normal host, and valacyclovir has been found to be more cost effective.

◆ **Valacyclovir** produces serum acyclovir levels three- to five-fold higher than those achievable with oral acyclovir. In a placebo-controlled trial, valacyclovir and acyclovir were equivalent in terms of accelerating the events of cutaneous healing in patients with herpes zoster, and valacyclovir was superior for shortening the duration of zoster-associated pain and duration of postherpetic neuralgia in immunocompetent adults 50 years and older. A seven-day course of valacyclovir (1 g po tid) is advised.

◆ **Famciclovir** is significantly superior to placebo in reducing the duration of viral shedding, limiting the duration of new lesion formation, accelerating cutaneous healing and, especially in patients older than 50, reducing the duration of postherpetic neuralgia. A seven-day course of famciclovir (500 mg po tid) is advised, although other regimens have been shown to be effective with respect to cutaneous healing and resolution of acute pain.

◆ **If neither drug** is available, then prescribe acyclovir (800 mg po 5/d) for 7-10 days. Acyclovir effectively reduces the duration of viral shedding, shortens the duration of new lesion formation, and accelerates the events of cutaneous healing.

Clinical trials with antiviral drugs for herpes zoster have focused on patients presenting within 72 hours of lesion onset; the value of antiviral therapy for patients presenting beyond this time period is not known. Initiation of antiviral therapy later than 72 hours after lesion onset should be considered, especially in older patients with severe pain and a large area of skin involvement, with continued new vesicle formation, or when there are cutaneous, motor, neurologic, or ocular complications.

The cranial nerve most frequently affected by herpes zoster is the ophthalmic division of the trigeminal nerve. Patients with herpes zoster ophthalmicus should be treated with antiviral therapy even if lesions have been present for more than 72 hours. In the absence of any antiviral therapy, approximately 50% of patients with this condition will develop ocular complications. Trials have confirmed that oral acyclovir therapy reduces the frequency of late ocular inflammatory complications from 50%-60% to 20%-30%. Systemic antiviral therapy has largely replaced topical antiviral preparations for treating ocular complications of herpes zoster ophthalmicus. Emergently consult an ophthalmologist for appropriate eye evaluation if there are symptoms suggesting ocular involvement, and do not use topical ophthalmic antiviral, steroid or anesthetic preparations without supervision by an ophthalmologist.

Patients with central nervous system involvement should also receive intravenous acyclovir. Although

the role of antiviral drugs in managing such neurologic complications has not been well evaluated, intravenous acyclovir is recommended for situations in which viral replication likely plays an important role in pathogenesis such as zoster myelitis or vasculopathy. For manifestations such as delayed contralateral hemiparesis, in which the role of active viral replication is less clear, the value of antiviral therapy is uncertain, but the potential benefits of acyclovir probably outweigh any potential risks.

### Narcotic analgesics

While the neuralgic pain of herpes zoster can be severe and may be disproportional to the rash; patients with relatively limited skin involvement can still have severe pain. This pain should not be underestimated and should be managed aggressively. Early efforts to attenuate acute pain may prevent chronic pain initiation and thereby reduce the risk of postherpetic neuralgia.

Short-acting narcotic analgesics such as oxycodone may be prescribed on a schedule for patients who experience acute neuralgic pain during active herpes zoster. For patients with chronic pain, consider prescribing long-acting analgesics, such as controlled-

Patients with relatively limited skin involvement can still have severe pain.

## Lab test options

When the clinical diagnosis of herpes zoster is not obvious, laboratory confirmation is important, especially when antiviral therapy is planned.

Possible tests include:

**Viral culture:** Recovery of VZV is highly dependent on the stage of the lesions, the quality of the specimen collected and the time elapsed between specimen collection and inoculation of tissue culture. For maximum yield, fluid from fresh vesicles should be aspirated into a tuberculin syringe containing viral transport media and delivered immediately to the virology laboratory. If there is delivery delay, the specimen should be refrigerated or stored on wet ice, not frozen. Growth of VZV in tissue culture may take 3-14 days. The test is 30% to 70% sensitive and 100% specific.

**Antigen detection:** Direct fluorescent antigen assay is more sensitive than

viral culture. Using a modified Tzanck technique, cells are scraped from the base of the lesion with a scalpel blade or the bevel edge of a large-gauge needle, smeared on a glass slide, then stained using fluorescein-conjugated monoclonal antibodies to detect viral glycoproteins. Unlike a traditional Tzanck smear, direct fluorescent antigen assay (DFA) can distinguish between herpes simplex virus and VZV.

**Serology:** Patients with herpes zoster will, by definition, be VZV seropositive at the onset of illness. Although some patients will show an enhanced VZV antibody titer after an episode of herpes zoster, serology is not a very sensitive or specific diagnostic method. Most laboratories use enzyme-linked immunosorbent assay (ELISA) or latex agglutination methods; more sensitive assays such as the fluorescent antibody to

membrane antigen test and glycoprotein ELISA are not widely available. The latex agglutination test is generally more sensitive than ELISA for detecting VZV antibody after natural infection or vaccination. Commercial ELISA tests range in sensitivity from 86%-97% and range in specificity from 82%-99% in detecting antibody after natural varicella infection but are less reliable for detecting antibody after vaccination.

**PCR:** Useful for detecting VZV DNA in fluids (e.g., cerebral spinal fluid). Not widely available. Sensitivity and specificity are unknown. Polymerase chain reaction on cerebral spinal fluid is the test of choice along with antibody testing for VZV in patients with suspected VZV myelitis, vasculopathy or zoster sine herpete (herpes zoster with abnormal skin sensations and pain in a dermatomal distribution but without a rash).

release oxycodone. Consider, as well, the addition of the anticonvulsant agent, gabapentin, or the tricyclic antidepressant, amitriptyline, early in the course of herpes zoster to reduce the prevalence and severity of pain. In refractory cases, an epidural injection of 80 mg methylprednisolone acetate and 10 mg bupivacaine can be added to oral analgesics for pain relief.

### Oral corticosteroids

Oral corticosteroids provide symptomatic relief but do not reduce the risk of postherpetic neuralgia. The optimal dosing regimen has not been determined but clinicians should consider adding a 10- to 14-day tapering course of oral prednisone, starting at 60 mg daily, to antiviral therapy in patients with herpes zoster who are older than age 50 and have moderate to severe pain at presentation and are not responding to an opioid analgesic. Corticosteroids should not be used in patients with contraindications, such as diabetes mellitus, osteoporosis, and gastritis, because they can cause potentially serious adverse effects.

The benefits of prednisone seem to be maintained when combined with an antiviral. Two large controlled studies have clarified the role of acyclovir plus corticosteroids therapy for herpes zoster. Both studies showed that the corticosteroids reduced the patients' need for analgesics and quickened their return to usual activities and uninterrupted sleep. Significant pain reduction occurred in patients with moderate to severe pain but not in those with no pain or mild pain at presentation. Neither study showed any reduction in the incidence of postherpetic neuralgia.

## Patient education and follow-up

Now that a vaccine for herpes zoster is available, immunocompetent patients who are 60 years old and older should be advised about immunization.

For patients who develop herpes zoster, it is important to provide education about what to expect.

The infection is often frustrating because of its unpredictability and its potential to cause pain lasting from a few days to years.

- ◆ Prepare patients psychologically to manage this chronic pain, if necessary, and encourage them to check back if pain control measures are ineffective or inadequate. Carefully explain the dosing regimen for analgesic medications, emphasizing the need for around-the-clock pain control for optimum relief.

- ◆ Educate patients about their potential infection risk to others. Patients can transmit chickenpox to a person who is VZV seronegative.

Patients with active herpes zoster should be especially careful to avoid contact with susceptible infants or small children, susceptible pregnant women or potentially susceptible immunocompromised individuals. Although the virus is transmitted primarily through direct contact with lesions from a patient with dermatomal zoster, it can also be transmitted through an airborne route, particularly from patients with disseminated herpes zoster.

- ◆ Advise health care workers to use standard precautions and use gloves when touching lesions of patients with localized zoster. Severely immunocompromised patients who develop dermatomal zoster should be placed in strict airborne and contact isolation until it is clear that dissemination is not developing. All patients with disseminated zoster should be placed in such isolation.

Follow-up laboratory and imaging studies are unnecessary unless otherwise clinically indicated. Be aware that herpes zoster is a common sentinel disease for AIDS, and consider HIV serologic testing, especially in young adults.

## Recognizing mimics

### HSV infection

**Characteristics:** Clusters of painful vesicles on the skin. HSV can occasionally occur in an elongated distribution that may mimic herpes zoster, anywhere on the skin

**Notes:** Less than 5% of immunocompetent patients with herpes zoster develop a second episode. HIV-infected persons may have multiple episodes of herpes zoster. Patients who report multiple recurrences of herpes zoster should have definitive virologic PCR testing (e.g., DFA or viral culture) to distinguish between HSV and VZV. In one study, 13% of patients clinically diagnosed with herpes zoster were proven by culture to have HSV infection.

### Allergic reactions

**Characteristics:** Contact dermatitis (e.g., reactions to rubber or nickel) or cutaneous reactions to topical medications (e.g., neomycin) can cause localized areas of erythema and vesiculation that may mimic herpes zoster.

**Notes:** Contact dermatitis does not usually conform to a dermatomal distribution.

### Chemical irritation

**Characteristics:** Contact with toxic plants (e.g., poison ivy, poison oak) can cause painful skin erythema and vesiculation in a band-like pattern.

**Notes:** Dermatitis from topical toxins does not usually conform to a dermatomal pattern.

### Zoster sine herpete

**Characteristics:** Some patients have neuralgic pain typical of herpes zoster but never develop cutaneous lesions; this has been shown to be zoster sine herpete. VZV meningitis, polyneuritis cranialis, myelitis, and vasculopathy may also occur without rash.

**Notes:** Because there is no diagnostic test for zoster sine herpete, the incidence is not known. In such cases, PCR testing on CSF is recommended.

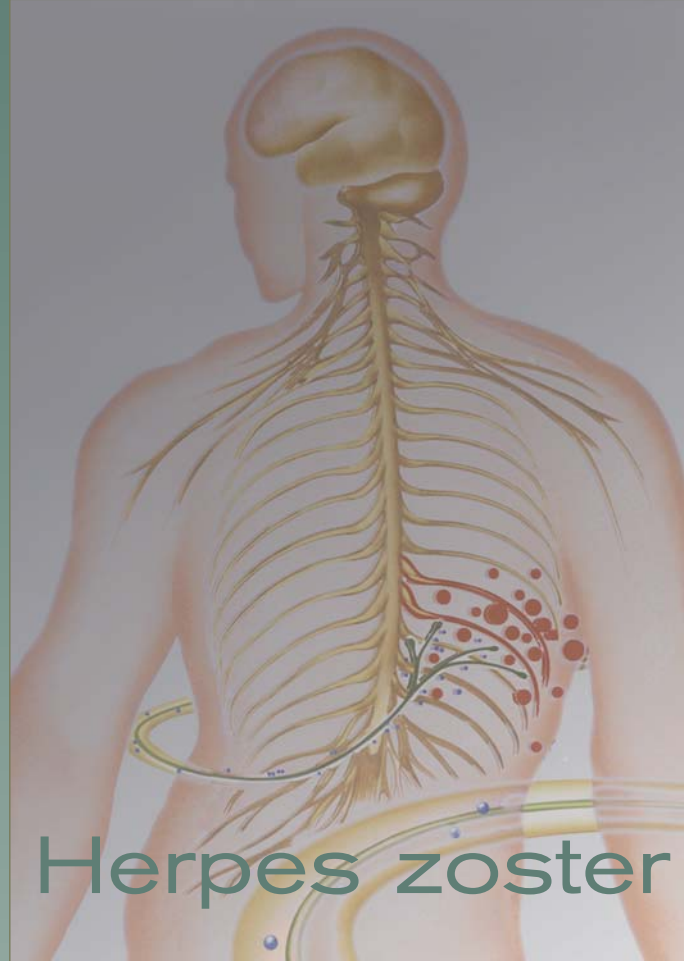
Source: PIER module on herpes zoster

## History and physical examination elements for herpes zoster

| Category             | Element                    | Notes  |
|----------------------|----------------------------|--|
| <b>History</b>       | Previous varicella         | Herpes zoster cannot develop without previous primary VZV infection. The proportion of American adults who are seropositive for VZV approaches 100%. However, some seropositive adults will not be able to provide a history of previous varicella   |
| <b>History</b>       | Constitutional symptoms    | Patients may report headache, photophobia, and malaise, but significant fever is rare  |
| <b>History</b>       | Pain                       | Patients may report localized sensations ranging from mild itching or tingling to severe pain that precedes the development of the skin lesions by 1-5 days (or occasionally weeks)  |
| <b>Physical exam</b> | Vital signs: temperature   | Patients with herpes zoster may have low-grade fever, but significant temperature elevations are atypical  |
| <b>Physical exam</b> | Cutaneous exam: rash       | Skin changes begin with an erythematous maculopapular rash followed by the appearance of clear vesicles. New vesicle formation typically continues for 3-5 days, followed by lesion pustulation and scabbing. Skin lesions heal within 2-4 weeks, often leaving skin scarring and permanent pigmentation changes. The cutaneous eruption, appearing in the skin segment innervated by a single sensory ganglion, is unilateral and does not cross the midline. Overlap of lesions into adjacent dermatomes occurs in 20% of patients. The most commonly involved dermatomes are thoracic, followed by cranial (especially trigeminal), lumbar, and cervical; sacral dermatomes are least frequently involved. Simultaneous involvement of noncontiguous dermatomes virtually never occurs in the immunocompetent host. Finding a few isolated disseminated skin lesions outside of the primary dermatome is not unusual and has no special prognostic significance in the immunocompetent host |
| <b>Physical exam</b> | Cutaneous exam: cellulitis | Bacterial superinfection of cutaneous lesions may occasionally occur   |
| <b>Physical exam</b> | HEENT exam                 | Syndromes associated with herpes zoster of the cranial nerves include herpes zoster ophthalmicus (first division of the trigeminal nerve) and Ramsay Hunt syndrome (geniculate ganglion of CN VII, with ear vesicles, diminished taste on the anterior two thirds of the tongue, and ipsilateral facial paralysis). Vesicles on the outside of the nose (Hutchinson's sign) are usually seen in patients with VZV keratitis  |
| <b>Physical exam</b> | Neurologic exam            | Allodynia (pain provoked by light touch) may be present in the involved dermatome. Various neurologic complications can occur during acute herpes zoster, including vasculopathy, myelitis, cranial and peripheral nerve palsies, and polyradiculitis  |

CN = cranial nerve; HEENT = head, ears, eyes, nose, and throat; VZV = varicella-zoster virus.

Source: *PIER module on herpes zoster*



## Additional resources

### **National Institute of Allergy and Infectious Diseases**

Shingles Index

([www3.niaid.nih.gov/healthscience/healthtopics/shingles/default.htm](http://www3.niaid.nih.gov/healthscience/healthtopics/shingles/default.htm))

### **National Institute of Neurological Disorders and Stroke**

Shingles Information Page

([www.ninds.nih.gov/disorders/shingles/shingles.htm](http://www.ninds.nih.gov/disorders/shingles/shingles.htm))

### **Center for Disease Control National Immunization Program Information: General Questions about Shingles**

(Herpes Zoster)

(<http://www.cdc.gov/nip/diseases/shingles/faqs-disease-shingles.htm>)

### **U.S. Food and Drug Administration information page: Shingles: An Unwelcome Encore**

(This article originally appeared in the May-June 2001 FDA Consumer and contains revisions made in June 2005)

([http://www.fda.gov/fdac/features/2001/301\\_pox.htm](http://www.fda.gov/fdac/features/2001/301_pox.htm))