CLINICAL PRACTICE

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Herpes Zoster

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 65-year-old man presents with a rash of 2 days' duration over the right forehead with vesicles and pustules, a few lesions on the right side and tip of the nose, and slight blurring of vision in the right eye. The rash was preceded by tingling in the area and is now associated with aching pain. How should this patient be evaluated and treated?

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N Engl J Med 2013;369:255-63.
DOI: 10.1056/NEJMcp1302674

An audio version of this article is available at NEJM.org

THE CLINICAL PROBLEM

Primary infection with varicella–zoster virus (VZV) results in chickenpox, characterized by viremia with a diffuse rash and seeding of multiple sensory ganglia, where the virus establishes lifelong latency. Herpes zoster is caused by reactivation of latent VZV in cranial-nerve or dorsal-root ganglia, with spread of the virus along the sensory nerve to the dermatome. There are more than 1 million cases of herpes zoster in the United States each year, with an annual rate of 3 to 4 cases per 1000 persons. Studies suggest that the incidence of herpes zoster is increasing.[1] Unvaccinated persons who live to 85 years of age have a 50% risk of herpes zoster. Up to 3% of patients with the disease require hospitalization.

The major risk factor for herpes zoster is increasing age. With increasing time after varicella infection, there is a reduction in the level of T-cell immunity to VZV,[2] which, unlike levels of virus-specific antibodies, correlates with protection against herpes zoster. The risk is higher for women than for men, for whites than for blacks, and for persons with a family history of herpes zoster than for those without such a background.[3] Chickenpox that occurs in utero or early in infancy, at a time when the cellular immune system is not fully mature, is associated with herpes zoster in childhood. Immunocompromised persons with impaired T-cell immunity, including recipients of organ or hematopoietic stem-cell transplants, those receiving immunosuppressive therapy, and those with lymphoma, leukemia, or human immunodeficiency virus (HIV) infection, are at increased risk for herpes zoster and for severe disease.

Postherpetic neuralgia, or pain persisting after the rash has resolved (often defined specifically as pain persisting for 90 days or more after the onset of the rash), is a feared complication of herpes zoster. The pain may persist for many months or even years; it may be severe and interfere with sleep and activities of daily living, resulting in anorexia, weight loss, fatigue, depression, withdrawal from social activities and employment, and loss of independent living. Depending on age and the definition used, postherpetic neuralgia develops in 10 to 50% of persons with herpes zoster. The risk increases with age (particularly after 50 years of age) and is also increased among persons with severe pain at the onset of herpes zoster or with a severe rash and a large number of lesions.

Various neurologic complications have been reported to occur with herpes zos-

KEY CLINICAL POINTS

HERPES ZOSTER

- In the absence of the herpes zoster vaccine, persons who live to 85 years of age have a 50% risk of herpes zoster.
- The persons most likely to benefit from antiviral therapy for herpes zoster are those who have or are at risk for complications of herpes zoster, including immunocompromised persons, those 50 years of age or older, and those with severe pain or severe rash.
- Antiviral agents hasten the resolution of herpes zoster lesions and decrease the severity of acute pain but have not been shown to reduce the risk of postherpetic neuralgia.
- Valacyclovir or famciclovir is preferable to acyclovir because of ease of dosing and higher levels of antiviral drug activity.
- Patients with herpes zoster and new visual symptoms should be evaluated by an ophthalmologist to determine whether eye-specific therapy is needed.
- The herpes zoster vaccine is recommended by the Advisory Committee on Immunization Practices for persons 60 years of age or older and is used in those with or without a history of herpes zoster.

ter, including Bell's palsy, the Ramsay Hunt syndrome, transverse myelitis, transient ischemic attacks, and stroke.[4] In addition, ophthalmologic complications of herpes zoster occurring in the V1 distribution of the trigeminal nerve can include keratitis, scleritis, uveitis, and acute retinal necrosis (Table 1). Immunocompromised persons can have additional complications, including disseminated skin disease, acute or progressive outer retinal necrosis, chronic herpes zoster with verrucous skin lesions, and development of acyclovir-resistant VZV. In these patients, the disease can involve multiple organs (e.g., lung, liver, brain, and gastrointestinal tract), and patients may present with hepatitis or pancreatitis several days before the rash appears.[5]

STRATEGIES AND EVIDENCE

SYMPTOMS

The rash of herpes zoster is dermatomal and does not cross the midline, a feature that is consistent with reactivation from a single dorsal-root or cranial-nerve ganglion. The thoracic, trigeminal (Fig. 1A), lumbar, and cervical dermatomes are the most frequent sites of rash, although any area of the skin can be involved. In nonimmunocompromised persons, a few scattered lesions outside the affected dermatome are not unexpected. The rash is often preceded by tingling, itching, or pain (or a combination of these) for 2 to 3 days, and these symptoms can be continuous or episodic. Depending on the location and severity, this prodromal pain may lead to misdiagnosis and costly testing. The rash begins as macules and papules, which evolve into vesicles and then pustules (Fig. 1B). New lesions appear over a period of 3 to 5 days, often with filling in of the dermatome despite antiviral treatment. The rash usually dries with crusting in 7 to 10 days. Some persons have pain in the absence of a rash, termed zoster sine herpete, which is difficult to diagnose and may lead to numerous unnecessary tests or procedures. Immunocompromised patients may have disseminated rashes with viremia and new lesions occurring for up to 2 weeks. The characteristics of pain associated with herpes zoster vary. Patients may have paresthesias (e.g., burning and tingling), dysesthesia (altered or painful sensitivity to touch), allodynia (pain associated with nonpainful stimuli), or hyperesthesia (exaggerated or prolonged response to pain). Pruritus is also commonly associated with herpes zoster.

DIAGNOSIS

Most cases of herpes zoster can be diagnosed clinically, although atypical rashes may require a direct immunofluorescence assay for VZV antigen or a polymerase-chain-reaction (PCR) assay for VZV DNA in cells from the base of lesions after they are unroofed. In a study comparing PCR with other diagnostic methods, the sensitivity and specificity of PCR for detecting VZV DNA were 95% and 100%, respectively, whereas the values

Table 1. Selected Complications of Herpes Zoster in Nonimmunocompromised Persons.*

Complication	Manifestations	Site of VZV Reactivation
Aseptic meningitis	Headache, meningismus	Cranial nerve V
Bacterial superinfection	Streptococcus, staphylococcus cellulitis	Any sensory ganglia
Bell's palsy	Unilateral facial paralysis	Cranial nerve VII
Eye involvement (herpes zoster ophthalmicus)	Keratitis, episcleritis, iritis, conjunctivitis, uveitis, acute retinal necrosis, optic neuritis, acute glaucoma	Cranial nerve II, III, or V (ophthalmic [V1] branch)
Hearing impairment	Deafness	Cranial nerve VIII
Motor neuropathy	Weakness, diaphragmatic paralysis, neurogenic bladder	Any sensory ganglia
Postherpetic neuralgia	Pain persisting after the rash has resolved	Any sensory ganglia
Ramsay Hunt syndrome	Ear pain and vesicles in the canal, numbness of anterior tongue, facial paralysis	Cranial nerve VII geniculate ganglia, with spread to cranial nerve VIII
Transverse myelitis	Paraparesis, sensory loss, sphincter impairment	Vertebral ganglia
Vasculopathy (encephalitis)	Vasculitis of cerebral arteries, confusion, seizures, TIAs, stroke	Cranial nerve V

* TIA denotes transient ischemic attack, and VZV varicella–zoster virus.

for immunofluorescence testing for VZV antigen were 82% and 76%.[6] The condition that is most commonly mistaken for herpes zoster is herpes simplex virus infection, which can recur in a dermatomal distribution; accordingly, when patients present with "recurrent zoster" or atypical lesions or are immunocompromised with disseminated skin lesions, specific testing for both VZV and herpes simplex virus is often useful. VZV has been detected in the saliva of persons with herpes zoster,[7] although such testing does not currently have a demonstrated role in clinical practice.

A PCR assay of the cerebrospinal fluid (CSF) has been used for the diagnosis of central nervous system (CNS) vasculopathy; evidence of an increase in the ratio of the anti-VZV antibody level in the CSF to that in the blood is more sensitive.[4] A PCR assay of the blood may be helpful for the diagnosis of visceral herpes zoster in immunocompromised persons who present with hepatitis or pancreatitis in the absence of a rash.[5] A PCR assay for VZV in the blood or CSF has been used for the diagnosis of zoster sine herpete.

TREATMENT AND PREVENTION

Antiviral Therapy

Antiviral therapy is recommended for herpes zoster in certain nonimmunocompromised patients and all immunocompromised patients (Table 2). Other persons might also benefit from antiviral therapy, although they have a lower risk of complications from herpes zoster. Three guanosine analogues — acyclovir, valacyclovir, and famciclovir — have been approved by the Food and Drug Administration (FDA) for the treatment of herpes zoster (Table 3). The oral bioavailability and levels of antiviral drug activity in the blood are higher and more consistent in patients receiving thrice-daily valacyclovir or famciclovir than in those receiving acyclovir five times daily. This is important because VZV is less sensitive than herpes simplex virus to acyclovir, valacyclovir, and famciclovir.

These antiviral agents hasten the resolution of lesions, reduce the formation of new lesions, reduce viral shedding, and decrease the severity of acute pain (Table 3). For example, in the largest randomized, double-blind trial of acyclovir for herpes zoster, oral acyclovir given within 47 hours after the onset of rash shortened the mean time to the last day of new-lesion formation, the loss of vesicles, and full crusting by 0.5 days, 1.8 days, and 2.2 days, respectively, as compared with placebo.[10] In another large trial, acyclovir reduced the duration of viral shedding by 0.8 days as compared with placebo.[11] In a meta-analysis of several randomized, controlled trials, antiviral agents did not significantly reduce the incidence

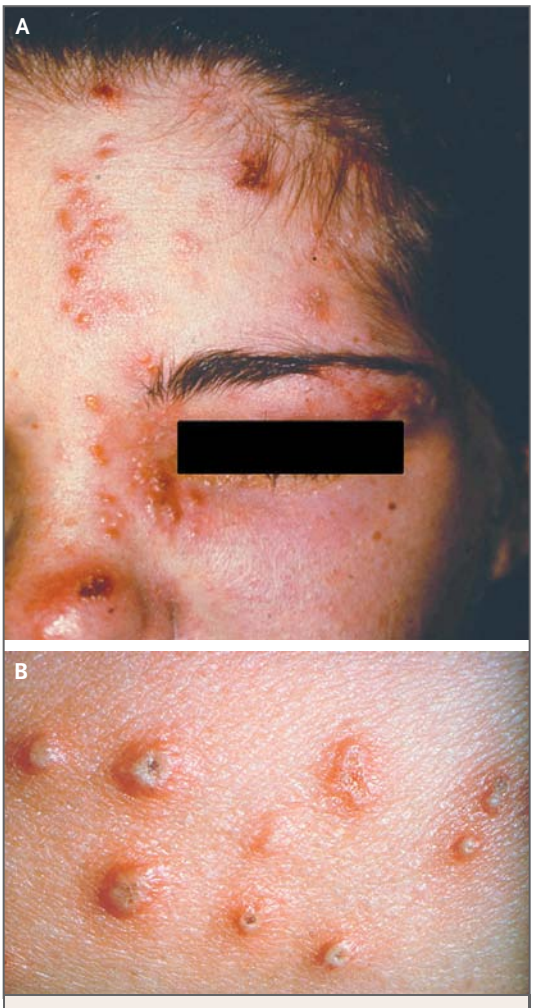

Figure 1. Clinical Features of Herpes Zoster.
Panel A shows herpes zoster in the ophthalmic (V1) branch of the trigeminal ganglia. Photograph courtesy of Michael Oxman, M.D. Panel B shows vesicles and pustules in a patient with herpes zoster. These are representative photographs and are not from the case presented.

of postherpetic neuralgia,[20] and they are not approved for the prevention of the condition by the FDA. In some studies, treatment with either valacyclovir or famciclovir has been shown to be superior to treatment with acyclovir for reducing pain associated with herpes zoster.[14,15] Valacyclovir is similar to famciclovir in terms of efficacy in reducing acute pain and accelerating healing.[21] As compared with acyclovir, valacyclovir and famciclovir require fewer daily doses but are more expensive.

In controlled trials, treatment has been initiated within 72 hours after the onset of the rash, and it is recommended that treatment start as early as possible within this interval. However, many experts recommend that if new skin lesions are still appearing or complications of herpes zoster are present, treatment should be initiated even if the rash began more than 3 days earlier. Treatment is usually given for 7 days in the absence of complications of herpes zoster. Intravenous acyclovir is recommended for immunocompromised persons who require hospitalization and for persons with severe neurologic complications. Foscarnet is used for immunocompromised patients with acyclovir-resistant VZV.

Table 2. Indications for Antiviral Treatment in Patients with Herpes Zoster.*

Age ≥50 yr
Moderate or severe pain
Severe rash
Involvement of the face or eye
Other complications of herpes zoster
Immunocompromised state

* Although antiviral agents may benefit other patients with herpes zoster, they are primarily recommended by experts for patients with these indications who either have complications or are at increased risk for complications from herpes zoster.[8,9]

Glucocorticoids

The use of glucocorticoids with antiviral therapy for uncomplicated herpes zoster remains controversial. Randomized, controlled trials have shown benefits of a tapering course of predisone[22] or prednisolone,[12] including a reduction in acute pain,[12,22] improved performance of activities of daily living,[22] accelerated early healing,[12] and in one study[22] but not another,[12] a reduction in the time to complete healing. The addition of glucocorticoids to antiviral therapy has not been shown to reduce the incidence of postherpetic neuralgia. Owing to their immunosuppressive properties, glucocorticoids should not be administered for herpes zoster without concomitant antiviral therapy. Glucocorticoids should be avoided in patients with hypertension, diabetes mellitus, peptic ulcer disease, or osteoporosis; particular caution is warranted in the case of elderly patients, who are at increased risk for serious adverse events. Prednisone is used for the treatment of certain CNS com-

Table 3. Antiviral Therapy for Herpes Zoster.

Medication	Dose	Effects Observed in Controlled Trials	Side Effects
Nonimmunocompromised persons			
Acyclovir (e.g., Zovirax)	800 mg orally five times daily for 7–10 days	Reduced time to last new-lesion formation, loss of vesicles, full crusting, cessation of viral shedding, reduced severity of acute pain[10-12]	Malaise
Famciclovir (e.g., Famvir)	500 mg orally three times daily for 7 days	Reduced time to last new-lesion formation, loss of vesicles, full crusting, cessation of viral shedding, cessation of pain[13,14]	Headache, nausea
Valacyclovir (e.g., Valtrex)	1 g orally three times daily for 7 days	Reduced time to last new-lesion formation, loss of vesicles, full crusting, cessation of pain[15,16]	Headache, nausea
Brivudin (e.g., Zostex, Helpin)*	125 mg orally once daily for 7 days	Reduced time to last new-lesion formation, full crusting, cessation of pain[17]	Headache, nausea; contraindicated in persons receiving fluorouracil or other fluoropyrimidines
Immunocompromised persons requiring hospitalization or persons with severe neurologic complications			
Acyclovir (e.g., Zovirax)	10 mg/kg intravenously every 8 hr for 7–10 days	Reduced time to last new-lesion formation, full crusting, cessation of viral shedding, cessation of pain, reduced cutaneous dissemination, reduced visceral herpes zoster[18,19]	Renal insufficiency
Foscarnet (e.g., Foscavir) for acyclovir-resistant VZV†	40 mg/kg intravenously every 8 hr until lesions are healed	Not reported	Renal insufficiency, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, nausea, diarrhea, vomiting, anemia, granulocytopenia, headache

* Brivudin is not available in the United States and has not been approved by the Food and Drug Administration (FDA).
† Foscarnet is not approved for this use by the FDA.

plications of herpes zoster, such as vasculopathy or Bell's palsy in nonimmunocompromised patients.

Acute Pain Associated with Herpes Zoster

Several medications have been used for the treatment of acute pain associated with herpes zoster (Table 4). Nonsteroidal antiinflammatory drugs or acetaminophen can be administered in patients with mild pain. Opioids, such as oxycodone, are used for more severe pain associated with herpes zoster. Opioids were more effective than gabapentin for herpes zoster–related pain in a randomized, placebo-controlled trial.[23] In one controlled trial[24] but not another,[23] gabapentin reduced pain associated with herpes zoster. Lidocaine patches reduced pain associated with herpes zoster in a placebo-controlled trial; they should be applied to intact skin only, not to the area of the rash.[25] Although tricyclic antidepressants have not been shown to be effective in randomized, controlled clinical trials for acute pain associated with herpes zoster, they have been used when opioids were insufficient for pain.

Eye Disease Associated with Herpes Zoster

Patients with herpes zoster in the V1 distribution of the trigeminal nerve (including lesions on the forehead and the upper eyelid) and either lesions on the tip or side of the nose or new visual symptoms should be evaluated by an ophthalmologist. Other treatment may be needed in addition to antiviral therapy, including mydriatic eyedrops to dilate the pupil and reduce the risk of scarring (synechiae); topical glucocorticoids for keratitis, episcleritis, or iritis; medications to reduce intraocular pressure for the treatment of glaucoma; and intravitreal antiviral therapy for immunocompromised patients with retinal necrosis.

Table 4. Medications Commonly Used for Treatment of Acute Pain Associated with Herpes Zoster.*

Medication	Dose	Dose Adjustment	Maximum Dose	Side Effects
Opioid and nonopioid analgesics				
Oxycodone	5 mg every 4 hr as needed	Increase by 5 mg four times daily every 2 days as tolerated	None specified, but should not exceed 120 mg daily except in consultation with a pain specialist	Drowsiness, dizziness, constipation, nausea, vomiting
Tramadol	50 mg once or twice daily	Increase by 50–100 mg daily in divided doses every 2 days as tolerated	400 mg daily; 300 mg daily if patient is >75 years of age	Drowsiness, dizziness, constipation, nausea, vomiting
Glucocorticoids†				
Prednisone	60 mg daily for 7 days, then decrease to 30 mg daily for 7 days, then decrease to 15 mg daily for 7 days	None	60 mg daily	Gastrointestinal distress, nausea, vomiting, mood changes, edema, glucose intolerance, increased blood pressure
Anticonvulsants				
Gabapentin	300 mg at bedtime or 100–300 mg three times daily	Increase by 100–300 mg three times daily every 2 days as tolerated	3600 mg daily	Drowsiness, dizziness, ataxia, peripheral edema
Pregabalin	75 mg at bedtime or 75 mg twice daily	Increase by 75 mg twice daily every 3 days as tolerated	600 mg daily	Drowsiness, dizziness, ataxia, peripheral edema
Tricyclic antidepressants				
Nortriptyline	25 mg at bedtime	Increase by 25 mg daily every 2–3 days as tolerated	150 mg daily	Drowsiness, dry mouth, blurred vision, weight gain, urinary retention
Topical therapy				
Lidocaine patch (5%)	One patch, applied to intact skin only, for up to 12 hr per day	None	One patch for up to 12 hr per day	Local irritation; if systemic, absorption can cause drowsiness, dizziness

* This table provides examples and is not meant to be comprehensive. Modified from Dworkin et al.[8] by permission of Oxford University Press.
† The use of glucocorticoids is controversial because they are often associated with adverse events in older patients.

Postherpetic Neuralgia

Pain associated with postherpetic neuralgia is often challenging to treat. A detailed discussion of the management of postherpetic neuralgia is beyond the scope of this article. In brief, medications shown in randomized trials to reduce pain associated with postherpetic neuralgia include topical lidocaine,[26] anticonvulsant agents (e.g., gabapentin[27] and pregabalin[28]), opioids,[29] tricyclic antidepressants (e.g., nortriptyline[30]), and capsaicin.[31] Combination therapy, such as gabapentin and nortriptyline[32] or an opiate and gabapentin,[33] have been more effective for postherpetic neuralgia than single-agent therapy but also confer a greater risk of side effects. Even with treatment, many patients do not have adequate relief of pain, and for such patients, referral to a pain specialist can be helpful.

Prevention of Herpes Zoster

A live attenuated herpes zoster vaccine is recommended by the Advisory Committee on Immunization Practices for persons 60 years of age or older to prevent herpes zoster and its complications, including postherpetic neuralgia.[9,34] On the basis of the results of a recent clinical trial, the vaccine is now approved by the FDA to prevent herpes zoster in persons 50 years of age or older.[35] The efficacy of the vaccine in preventing herpes zoster is 70% for persons 50 to 59 years of age, 64% for persons 60 to 69 years of age, and 38% for persons 70 years of age or older.[34-36] However, vaccine efficacy in preventing postherpetic neuralgia is 66% for persons 60 to 69 years of age and is undiminished at 67% for persons 70 years of age or older.[34,36] Although the effectiveness of the vaccine to prevent herpes zoster is reduced in persons 70 years of age or older, the increased risk of severe disease and the persisting efficacy of the vaccine in preventing postherpetic neuralgia in these older persons strongly favor vaccinating them. A follow-up study showed that the reduction in the risk of herpes zoster remained significant for at least 5 years after vaccination, though the effectiveness declined over time.[37] In vaccinated (as compared with unvaccinated) persons in whom herpes zoster developed, pain was significantly shorter in duration and less severe.[34]

The vaccine can be given to persons with a history of herpes zoster. In a recent study, rates of adverse events associated with vaccination were similar among persons who had had herpes zoster (at a mean of 3.6 years before vaccination) and among those with no history of the disease.[38]

The optimal timing of vaccination after an episode of herpes zoster is uncertain. Because the risk of recurrent herpes zoster after a recent episode of the disease is relatively low[39] and because the cellular immune response to VZV during the first 3 years after vaccination is similar to that after an episode of herpes zoster,[40] one might delay vaccination for 3 years in immunocompetent persons with a recent history of herpes zoster, provided that the diagnosis of herpes zoster has been well documented by a health care provider. The vaccine is contraindicated in persons with hematologic cancers whose disease is not in remission or who have received cytotoxic chemotherapy within 3 months, in persons with T-cell immunodeficiency (e.g., HIV infection with a CD4 cell count of ≤200 per cubic millimeter or <15% of total lymphocytes), and in those receiving high-dose immunosuppressive therapy (e.g., ≥20 mg of prednisone daily for ≥2 weeks or anti–tumor necrosis factor therapy).

Infection Control

Although herpes zoster is less contagious than varicella, patients with herpes zoster can transmit VZV to susceptible persons, in whom varicella may develop. For nonimmunocompromised persons with dermatomal herpes zoster, contact precautions should be used, and lesions should be covered if possible.[41] Despite these measures, viral transmission has occasionally been reported in such patients.[42] For persons with disseminated lesions and for immunocompromised persons with herpes zoster, airborne and contact precautions are required until all lesions have crusted.

AREAS OF UNCERTAINTY

Improved therapies are needed for pain associated with herpes zoster and postherpetic neuralgia and to prevent the development of postherpetic neuralgia. In addition, studies are needed to determine which patients are at highest risk for postherpetic neuralgia so that more aggressive therapy can be given. There is uncertainty regarding the safety and effectiveness of the vaccine in persons with immunocompromising conditions that are currently considered contraindications to vaccination, the duration of immunity induced by the vaccine, and the need for booster doses.

GUIDELINES

Recommendations have been developed for the management of herpes zoster by a group of experts[8] and for the prevention of herpes zoster by the Advisory Committee on Immunization Practices.[9] The present review is generally concordant with these recommendations.

CONCLUSIONS AND RECOMMENDATIONS

Whereas herpes zoster is often mild in healthy young persons, older persons are at increased risk for pain and complications, including postherpetic neuralgia, ocular disease, motor neuropathy, and CNS disease. In the vast majority of cases, the diagnosis can be made clinically. Antiviral therapy is most beneficial for persons who have complications of herpes zoster or who are at increased risk for complications, such as older persons and immunocompromised persons, and should be initiated as soon as possible, generally within 72 hours after the onset of the rash. Valacyclovir or famciclovir is preferred over acyclovir owing to the reduced frequency of dosing and higher levels of antiviral drug activity. The patient described in the vignette should receive oral antiviral therapy, medication for pain (e.g., an opioid, with the addition of gabapentin if needed), and prompt referral to an ophthalmologist. He should also be advised to avoid contact with persons who have not had varicella or have not received the varicella vaccine until his lesions have completely crusted. I would recommend herpes zoster vaccination to reduce the risk of recurrence, but in an immunocompetent patient such as this one, I would defer vaccination for approximately 3 years, since the current episode of herpes zoster should boost his cellular immune response to VZV for that period of time.

The views expressed here are those of the author and not necessarily those of the U.S. government.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

I thank Drs. Adriana Marques and Michael Oxman for their comments on an earlier version of the manuscript.

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