THE JOURNAL OF FAMILY PRACTICE

Battling shingles: Fine-tune your care

Which of the 3 antiviral agents works best for accelerating rash healing and reducing pain? And what about corticosteroids—are they a good idea, or not? Read on.

Sarah L. Cartwright, MD
Department of Family and Community Medicine, Wake Forest University School of Medicine, Winston-Salem, NC

scartwri@wfubmc.edu

The author reported no potential conflict of interest relevant to this article.

PRACTICE RECOMMENDATIONS

› *Reserve laboratory testing for unclear or complicated cases of herpes zoster (HZ), as the condition can be diagnosed clinically in most cases.* (B)

› *Whenever possible, initiate oral antiviral therapy within 72 hours of the onset of the shingles rash to accelerate healing and reduce the duration and severity of pain.* (A)

› *Offer the HZ vaccine (Zostavax) to patients ages 60 and older to reduce the risk of shingles and postherpetic neuralgia.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence
(B) Inconsistent or limited-quality patient-oriented evidence
(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE▶ Jane T, a 53-year-old patient, calls her family physician's office for a same-day appointment; she has severe right upper quadrant pain that developed a few hours ago. When Jane comes in, she tells her physician that the pain feels like the gallbladder attacks she used to have—before her gallbladder was removed 2 years ago. She has nausea but no vomiting, is afebrile, and has no urinary symptoms.

A series of in-office tests—urinalysis, complete blood count, comprehensive metabolic profile, amylase, and lipase—are all normal. The physician gives Jane an intramuscular injection of ketorolac and a prescription for oral tramadol, and sends her for a right upper quadrant ultrasound, which is also normal. The next morning, the pain intensifies, and Jane goes to the emergency department, where she undergoes computed tomography of the abdomen and pelvis—also normal. After a night in the hospital for observation, she is released. She returns to the family physician 3 days later, this time with an erythematous papular rash in a dermatomal distribution over her back and right upper quadrant that her doctor immediately recognizes as shingles.

Jane is not alone. Each year, about 1 million US residents develop herpes zoster (HZ),[1] and 70% to 80% of them experience prodromal pain in the affected dermatome.[2] For some, the pain is significant enough to prompt a medical work-up to rule out other potential causes, such as myocardial infarction, nephrolithiasis, pancreatitis, cholecystitis, and appendicitis.

The time and resources spent on such a work-up may be unavoidable when a patient presents with severe pain. But alert primary care physicians can avoid unnecessary diagnostic tests by being aware of the prodromal symptoms of HZ and being on the lookout for the rash that follows.

Age alone is a key factor in the detection of HZ, of course. One in 3 people will develop shingles during their lifetime,[1]

with half of all cases occurring in people ages 60 and older.[3] In addition to early detection and treatment, physicians can do their part to battle HZ by routinely recommending the shingles vaccine (Zostavax) to patients in this age group.

Diagnosing HZ: From prodrome to rash

For many patients, an abnormal skin sensation on one side of the body, such as itching, burning, or altered sensitivity to touch, is the first symptom of HZ. These sensations, including pain that can range from mild to severe, may precede the rash by days or even weeks.[4] Systemic symptoms are far less common; less than 20% of patients develop fever, headache, malaise, or fatigue as part of the HZ prodrome.[2]

Suspect shingles in an older patient who has an abnormal skin sensation on one side of the body.

The shingles rash is usually unilateral and does not cross the midline. However, it may occur in up to 3 adjacent dermatomes. The trunk is the most common site for the rash, but it may also develop on the face, buttocks, or other parts of the body. The lesions start as erythematous papules and evolve into vesicles within 12 to 24 hours.[5]

Once the rash emerges, HZ can usually be diagnosed clinically in a primary care setting, and laboratory testing should be considered only when diagnosis is uncertain. In a cohort study of 260 patients older than 50 years with clinically diagnosed HZ, 236 (91%) cases were confirmed on serologic testing.[6] In an Icelandic study, 93% of 505 cases were diagnosed correctly by general practitioners, using expert opinion and clinical course as the gold standard.[7]

If diagnostic testing is necessary, physicians have a number of choices:

Varicella zoster polymerase chain reaction (PCR) test. PCR testing for HZ can provide rapid and reliable diagnosis and is becoming more widely available, but its use should be limited because of the cost (approximately $300).

Tzanck smear. This test is quick and inexpensive, and can reliably diagnose a herpetic lesion based on the presence of acantholytic and multinucleated giant cells in a sample collected from the base of a vesicle.[8] However, this technique cannot differentiate HZ from herpes simplex infection, and lack of experience with collection or interpretation of the Tzanck smear limits its usefulness.

Serologic testing. Serology has limited utility in the diagnosis of acute HZ, but may provide a retrospective diagnosis, if needed. In a study of 260 patients older than 50 years with clinically diagnosed acute HZ, varicella zoster IgA or IgM was positive in 61% of patients at the time of presentation, and in 91% of patients 5 to 10 days later.[6]

Viral culture. Obtaining a viral culture of varicella zoster is another option, but it is not recommended, as sensitivity is poor and incubation requires several days.

The course of illness, and risk of complications

For some patients, the acute pain and hypersensitivity at the site of the rash resolve in several days; for others, this may take several weeks or more. One recent study found a median of 32.5 days for pain duration in patients ages 50 and older.[9] The suffering can last far longer, however, if complications arise.

Postherpetic neuralgia (PHN), a chronic and often debilitating condition with pain that can last months, or even indefinitely, affects about 10% to 15% of patients with HZ.[10] Risk factors for the development of PHN include advanced age, female sex, presence of a prodrome, severe acute HZ pain, and a severe rash.[11]

Trigeminal nerve involvement. HZ affects the first branch of the trigeminal nerve in about 10% to 15% of patients.[5] In such cases, the rash may erupt on the forehead, periocular area, and nose. Patients with trigeminal nerve involvement are at significant risk for ocular complications (HZ ophthalmicus), including keratitis, iritis, and possible vision loss, and should be treated and referred to an ophthalmologist without delay.

In addition to these complications, others reported in a review of 859 patients include bacterial skin infection, motor neuropathy, and, rarely, meningitis and HZ oticus.[12] Advanced age markedly increased the likelihood of complications.

TABLE
FDA-approved oral antiviral regimens

Drug	Dosing regimen	Cost of regimen*
Acyclovir	800 mg 5 times/d for 7-10 days	$55.97
Famciclovir	500 mg tid for 7 days	$319.99
Valacyclovir	1000 mg tid for 7 days	$315.99

***Source**: http://www.drugstore.com. Accessed December 6, 2010.

Initiate treatment without delay

Multiple randomized controlled clinical trials have demonstrated the efficacy of oral antiviral treatment in reducing the duration of viral shedding, accelerating rash healing, and reducing the severity and duration of acute HZ pain.[2] In all the studies, however, antiviral therapy was started within 72 hours of the onset of the rash; the efficacy of initiating antiviral treatment after >72 hours has not been systematically studied.[2] When it's not possible to begin therapy within this time frame, however, many experts recommend initiating therapy as soon as possible thereafter.[1]

Three antiviral agents—acyclovir, famciclovir, and valacyclovir—have been approved by the US Food and Drug Administration to treat HZ. Evidence suggests that famciclovir and valacyclovir have comparable efficacy with regard to resolution of both the rash and the acute pain,[13] and result in more rapid pain resolution compared with acyclovir.[14,15] Famciclovir and valacyclovir also offer simpler dosing schedules—both are taken 3 times a day, while acyclovir requires 5 daily doses—but they are significantly more expensive (**TABLE**).

Oral antiviral therapy is strongly recommended for patients who are older than 50 and those who have moderate-to-severe pain or rash—or whose rash appears somewhere other than the trunk.[2] But given the safety of oral antiviral agents, treatment can be considered for younger patients and those with milder cases of HZ, as well. (Routine use of antiviral agents is not indicated for unexplained unilateral pain, as varicella zoster infection without the classic rash [zoster sine herpete] is a rare cause.[16])

Results regarding the efficacy of oral antiviral agents for reducing the duration of chronic pain and preventing PHN are mixed.[2] A recent Cochrane review concluded that oral acyclovir does not significantly reduce the incidence of PHN and that there is insufficient evidence to determine if other antivirals do.[17]

Add a corticosteroid? The evidence is mixed

Oral corticosteroids have been studied as an adjunct to antiviral therapy for the treatment of HZ. One clinical trial of 208 immunocompetent adults older than 50 found that the addition of a 21-day prednisone taper to acyclovir led to accelerated healing of cutaneous lesions, cessation of analgesic use, and return to normal activities and uninterrupted sleep.[18] However, this study and another randomized trial of oral corticosteroids did not show that steroids had any effect on longer-term pain relief or the development of PHN.[18,19] A recent Cochrane review concluded that there is insufficient evidence that corticosteroids are safe or effective in the prevention of PHN.[20] Given the potential adverse effects of oral corticosteroids, their use should be weighed carefully.

Give analgesics for shingles pain

Many clinical trials have looked at the efficacy of different analgesics in the treatment of PHN, but data regarding analgesics for the treatment of acute HZ pain are limited. One RCT of 87 patients older than 50 divided participants into 3 groups: One group took controlled-release oxycodone, another received a placebo, and the third group took gabapentin.[21] (The study did not include patients with

Initiate treatment with an oral antiviral agent within 72 hours of the onset of the rash, or as soon after as possible.

mild pain, for whom nonnarcotic analgesics would likely be more appropriate.)

The researchers found that the oxycodone significantly reduced acute HZ pain during the first 2 weeks of treatment as compared with placebo or gabapentin. There was no statistically significant reduction in pain for the gabapentin group, compared with those on placebo. The oxycodone group did have the highest dropout rate (27.6% vs 6.9% for the placebo group), however, primarily because of constipation. This study showed that narcotic analgesics are effective and relatively well tolerated for the treatment of acute HZ pain.[21]

Because severe pain with acute HZ is a well-established risk factor for the development of PHN, there is interest in determining whether effective pain control in the acute setting decreases the risk of chronic pain. One placebo-controlled trial of 72 patients older than 60 years found that 25 mg amitriptyline daily, started within 48 hours of rash onset and continued for 90 days, reduced pain prevalence by more than half at 6 months from diagnosis.[22] This study did not control for the use of antiviral agents, however, so further investigation is needed.

Reserve opioids for patients with moderate-to-severe pain; those with milder pain would likely benefit from nonnarcotic analgesics.

CASE▶ Jane T began a course of antiviral therapy with valacyclovir shortly after her rash appeared, and continued to take oral tramadol for the pain. Her rash and pain level improved over the next several days, and within 2 weeks she was fully recovered.

Prevention: Vaccination holds the key

HZ is contagious and can cause primary varicella in people who are susceptible. Indeed, one study found that 15.5% of susceptible household contacts developed varicella after exposure to HZ.[1] Advise patients with HZ to avoid contact with those at high risk for severe varicella—including pregnant women, premature infants, and immunocompromised individuals of all ages—until their lesions are crusted. They can further avoid transmission by keeping the lesions covered.[23]

Increased use of the HZ vaccine, however, is the key to prevention of shingles. The Centers for Disease Control and Prevention (CDC) recommends Zostavax, a live attenuated varicella zoster vaccine given as a single subcutaneous injection, for people ages 60 and older. Compared with the varicella vaccines designed for children, Zostavax has a significantly higher potency in order to elicit a significant and durable response in older adults.[24]

The vaccine is generally safe, with a mild injection site reaction being the most common adverse event. No evidence exists of transmission of virus from vaccine recipients to contacts.[1] Like other live virus vaccines, Zostavax is contraindicated in pregnant women and immunocompromised patients. It can be given to patients regardless of their history of chicken pox or previous episodes of HZ, as studies have shown that the recurrence rate for HZ is similar to the rate for initial episodes.

How well does it work? In a Shingles Prevention Study Group trial of 38,546 people 60 years of age or older, the vaccine reduced the incidence of HZ by 51% and the incidence of PHN by 67% over a 3-year follow-up period.[25] The vaccine was most effective for the prevention of HZ in the 60- to 69-year age group, but there was no significant difference in its efficacy in preventing PHN or reducing the burden of illness (a measure based on the incidence, severity, and duration of pain and discomfort) in 60- to 69-year-olds vs those ages 70 and older.[25] An analysis by the CDC suggests that approximately 17 people would need to be vaccinated with Zostavax to prevent one case of HZ, and approximately 31 people would need to be vaccinated to prevent one case of PHN.[24]

Ongoing studies are examining the safety and efficacy of Zostavax for patients ages 50 to 59.[26] Although results thus far look promising, there is no recommendation for routine vaccination for this age group, and insurance companies do not routinely cover the cost of vaccinating them.

While primary care physicians generally favor the concept of HZ vaccination,[27] a CDC survey conducted in 2007—a year after the vaccine received FDA approval—found that only 1.9% of eligible patients received the vaccine.[28] Physicians cite concerns about re-

imbursement as a barrier to its use.[28]

Zostavax is not covered by Medicare Part B, in contrast to other adult vaccines, such as influenza and pneumococcal.[29] However, the HZ vaccine is covered by many private insurers, as well as by Medicare Part D. Advise patients to check with their insurance carrier for specific details regarding their coverage, as some plans require the patient to purchase the vaccine from a pharmacy prior to administration in a physician's office. JFP

CORRESPONDENCE
Sarah L. Cartwright, MD, Wake Forest University School of Medicine, Department of Family and Community Medicine, Medical Center Boulevard, Winston-Salem, NC 27157; scartwri@wfubmc.edu

While primary care physicians generally favor the concept of HZ vaccination, only 1.9% of eligible patients receive the vaccine. Physicians cite concerns about reimbursement as a barrier to its use.

References

1. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008;57(RR-5):1-30.
2. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis*. 2007;44(suppl 1):S1-S26.
3. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352:2271-2284.
4. Gilden DH, Dueland AN, Cohrs R, et al. Preherpetic neuralgia. *Neurology*. 1991;41:1215-1218.
5. Weinberg JM. Herpes zoster: epidemiology, natural history, and common complications. *J Am Acad Dermatol*. 2007;57(6 suppl):S130-S135.
6. Opstelten W, van Loon AM, Schuller M, et al. Clinical diagnosis of herpes zoster in family practice. *Ann Fam Med*. 2007;5:305-309.
7. Helgason S, Sigurdsson J, Gudmundsson S. The clinical course of herpes zoster: a prospective study in primary care. *European J Gen Pract*. 1996;2:12-16.
8. Durdu M, Baba M, Seckin D. The value of Tzanck smear test in diagnosis of erosive, vesicular, bullous, and pustular skin lesions. *J Am Acad Dermatol*. 2008;59:958-964.
9. Brisson DM, Levin MJ, Schmader KE, et al. A prospective study of the herpes zoster severity of illness. *Clin J Pain*. 2010;26:656-666.
10. Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA*. 1998;280:1837-1842.
11. Jung BF, Johnson RW, Griffin DR, et al. Risk factors for postherpetic neuralgia in patients with herpes zoster. *Neurology*. 2004;62:1545-1551.
12. Galil K, Choo PW, Donahue JG, et al. The sequelae of herpes zoster. *Arch Intern Med*. 1997;157:1209-1213.
13. Tyring SK, Beutner KR, Tucker BA, et al. Antiviral therapy for herpes zoster: randomized, controlled clinical trial of valacyclovir and famciclovir therapy in immunocompetent patients 50 years and older. *Arch Fam Med*. 2000;9:863-869.
14. Beutner KR, Friedman DJ, Forszpaniak C, et al. Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. *Antimicrob Agents Chemother*. 1995;39:1546-1553.
15. Degreef H. Famciclovir, a new oral antiherpes drug: results of the first controlled clinical study demonstrating its efficacy and safety in the treatment of uncomplicated herpes zoster in immunocompetent patients. *Int J Antimicrob Agents*. 1994;4:241-246.
16. McKendrick MW, Care CC, Kudesia G, et al. Is VZV reactivation a common cause of unexplained unilateral pain? Results of a prospective study of 57 patients. *J Infect*. 1999;39:209-212.
17. Li Q, Chen N, Yang J, et al. Antiviral treatment for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2009;(2):CD006866.
18. Whitley RJ, Weiss H, Gnann JW Jr, et al. Acyclovir with and without prednisone for the treatment of herpes zoster. A randomized, placebo-controlled trial. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *Ann Intern Med*. 1996;125:376-383.
19. Wood MJ, Johnson RW, McKendrick MW, et al. A randomized trial of acyclovir for 7 days or 21 days with and without prednisolone for treatment of acute herpes zoster. *N Engl J Med*. 1994;330:896-900.
20. He L, Zhang D, Zhou M, et al. Corticosteroids for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2008;(1):CD005582.
21. Dworkin RH, Barbano RL, Tyring SK, et al. A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster. *Pain*. 2009;142:209-217.
22. Bowsher D. The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manage*. 1997;13:327-331.
23. Bolyard EA, Tablan OC, Williams WW, et al. Guideline for infection control in healthcare personnel, 1998. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol*. 1998;19:407-463.
24. Kimberlin DW, Whitley RJ. Varicella-zoster vaccine for the prevention of herpes zoster. *N Engl J Med*. 2007; 356:1338-1343.
25. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352:2271-2284.
26. Sutradhar SC, Wang WW, Schlienger K, et al. Comparison of the levels of immunogenicity and safety of Zostavax in adults 50 to 59 years old and in adults 60 years old or older. *Clin Vaccine Immunol*. 2009;16:646-652.
27. Hurley LP, Harpaz R, Daley MF, et al. National survey of primary care physicians regarding herpes zoster and the herpes zoster vaccine. *J Infect Dis*. 2008;197(suppl 2):S216-S223.
28. Lu PJ, Euler GL, Jumaan AO, et al. Herpes zoster vaccination among adults aged 60 years or older in the United States, 2007: uptake of the first new vaccine to target seniors. *Vaccine*. 2009;27:882-887.
29. Orenstein WA, Mootrey GT, Pazol K, et al. Financing immunization of adults in the United States. *Clin Pharmacol Ther*. 2007;82:764-768.