

DECISIONS

A 69-year-old man with a painful vesicular rash

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A previously healthy 69-year-old man presents to his primary care physician with a painful vesicular eruption of 24 hours' duration. He recalls that his 65-year-old brother had a similar rash one year earlier, which had been diagnosed as shingles. He wants to know what can be done to prevent the development of the severe pain experienced by his brother and whether his 62-year-old wife would be a candidate for the "shingles vaccine."

How do we know if this patient has herpes zoster (shingles)?

Herpes zoster, caused by varicella zoster virus, most commonly presents as a unilateral dermatomal, vesicular eruption. A sensory prodrome, ranging from minor tingling to severe pain, precedes the rash by 1–5 days.^{1,2} Typically, the rash involves a single dermatome and does not cross the midline. The presence of the characteristic rash (Figure 1) is sufficient to allow for clinical diagnosis.^{1,2}

What risk factors does this patient have for herpes zoster?

After acute infection by varicella zoster virus, typically as chickenpox in childhood, the virus remains dormant in the dorsal nerve root ganglia.^{1,2} When viral suppression is interrupted by mechanisms that impair cell-mediated immunity, varicella zoster virus can propagate distally along sensory neurons to cause shingles. The most common risk factor for reactivation, and the one most likely responsible for this patient's presentation, is advancing age (immunosenescence). The incidence of herpes zoster dramatically increases with age, with an incidence of 1.3–4.2 cases per 1000 person-years in those aged less than 60 years to 6.0–10.7 cases per 1000 person-years in those aged 60 or older.³ Other risk factors include HIV infection, hematologic malignancy and the use of drugs that impair cellular immune function, such as corticosteroids.^{1,2}

How should this patient's herpes zoster be treated?

Pain, as described by this patient, is the most common morbidity associated with herpes zoster.^{1,2} In a population-based study of herpes zoster before the introduction of zoster vaccine, 18% of patients reported pain lasting more than 30 days following onset of the rash, termed postherpetic neuralgia.³ The incidence and severity of postherpetic neuralgia increases with age and occurs in up to 33% of adults with zoster over 79 years of age.³ Starting oral antiviral therapy within 72 hours of onset of the rash reduces the severity of acute pain.^{1,2} A meta-analysis of 4 randomized placebo-controlled trials comparing acyclovir to placebo in 691 patients aged 50 years or older showed a reduction in the median time to complete resolution of pain from 101 days to 41 days.⁴ A more recent meta-analysis of 4 randomized placebo-

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Figure 1: A unilateral vesicular rash in a right-sided T4 dermatomal distribution.

controlled trials involving 692 patients showed a relative risk of postherpetic neuralgia at 1 month following the onset of rash of 0.83 (95% confidence interval [CI] 0.71–0.96) in patients receiving acyclovir. This benefit, however, was no longer present at four and six months following the onset of rash.⁵ Methodologic differences in the inclusion and analysis of individual studies in the meta-analyses may account for some of the difference in outcomes. Therefore, uncertainty remains regarding the impact of antiviral therapy on pain outcomes in patients with herpes zoster. When prescribing antiviral therapy, valacyclovir and famciclovir may be superior to acyclovir in achieving complete cessation of pain.^{2,6} For cases of V1 dermatomal zoster

(zoster ophthalmicus), antiviral therapy should always be initiated, even if the patient presents beyond 72 hours after the onset of rash, to reduce late ocular complications.² Treatment regimens are presented in Table 1.^{1,7}

One small randomized placebo-controlled trial suggested the possible benefit of amitriptyline in the prevention of postherpetic neuralgia, when prescribed at presentation; however, the use of antivirals in this trial was not standardized, making the results difficult to interpret.⁸ Two large randomized placebo-controlled trials assessing anti-inflammatory therapy with corticosteroids in combination with acyclovir showed no effect on the incidence or duration of postherpetic neuralgia.^{4,9}

Table 1: Medications used in the treatment of herpes zoster and postherpetic neuralgia			
Drug	Dose and duration	Adverse events*	Daily cost, \$†
Acute herpes zoster‡			
Acyclovir	800 mg five times daily for 7 d ¹	<ul style="list-style-type: none"> Common: nausea, vomiting, diarrhea Severe: acute kidney injury, cytopenia, Stevens–Johnson syndrome 	6.34
Valacyclovir	1000 mg three times daily for 7 d ¹	<ul style="list-style-type: none"> Common: headache, diarrhea, nausea Severe: acute kidney injury, thrombotic thrombocytopenia purpura, cytopenia, hepatitis 	5.09
Famciclovir	500 mg three times daily for 7 d ¹	<ul style="list-style-type: none"> Common: headache, nausea, confusion Severe: Stevens–Johnson syndrome, hepatitis, thrombocytopenia 	5.07
Postherpetic neuralgia			
Amitriptyline	12.5–200 mg/d ⁷	<ul style="list-style-type: none"> Common: anticholinergic effects (dry mouth, urinary retention, confusion) Severe: cardiac arrhythmia, cytopenia 	0.12–0.96
Nortriptyline	30–120 mg/d ^{7§}	<ul style="list-style-type: none"> Common: anticholinergic effects (dry mouth, urinary retention, confusion) Severe: cardiac arrhythmia, cytopenia 	0.15–0.60
Gabapentin	1800–3600 mg/d ^{7¶}	<ul style="list-style-type: none"> Common: somnolence, fatigue, ataxia Severe: leukopenia, Stevens–Johnson syndrome 	1.55–3.09
Pregabalin	300 mg/d ^{7**}	<ul style="list-style-type: none"> Common: dizziness, somnolence, peripheral edema Severe: acute kidney injury, congestive heart failure 	2.23
Divalproate	1000 mg/d ⁷	<ul style="list-style-type: none"> Common: nausea, vomiting, gastrointestinal upset Severe: drug-induced lupus, cytopenia, pancreatitis, hepatitis 	2.18
Capsaicin	0.075% cream ^{7††}	<ul style="list-style-type: none"> Common: local burning, coughing 	Market price
<p>*The adverse events listed are not comprehensive but are a representative sample based on selections from monographs at www.e-therapeutics.ca †Average daily cost in Canadian dollars (excluding dispensing fees) based on data from the Ontario Drug Formulary at www.health.gov.on.ca/english/providers/program/drugs/odbf_mn.html ‡Antivirals (acyclovir, valacyclovir or famciclovir) should be started within 72 h of onset of rash. §Titrated to maximum tolerable dose. ¶Titrated over a 4-week dose escalation period. **Titrated over a 1-week dose escalation period. ††Typically administered four times daily or by a 60-minute high-concentration patch.</p>			

If postherpetic neuralgia develops, how can it be treated?

Postherpetic neuralgia often requires complex analgesic management. Common medications used for its treatment, taken alone or in combination, are presented in Table 1.^{1,7} There are limited evidence-based data to suggest a benefit of one analgesic regimen over another;⁷ typically, tricyclic antidepressants or anticonvulsants are used as first-line agents. For the individual patient, both cost and adverse outcomes should guide the choice of agent. Topical capsaicin can also be used alone or in combination with oral agents.⁷ In refractory cases, referral to a specialized pain management centre should be considered.²

Should the patient's wife receive the herpes zoster vaccine?

A randomized placebo-controlled trial involving 38 546 adults aged 60 years and older showed that zoster vaccine reduced the incidence of herpes zoster by 51.3% (11.1 cases per 1000 person-years in the placebo arm, and 5.4 cases per 1000 person-years in the vaccine arm; $p < 0.001$) and decreased the incidence of postherpetic neuralgia by 67% (1.38 cases per 1000 person-years in the placebo arm, and 0.46 cases per 1000 person-years in the vaccine arm; $p < 0.001$).¹⁰ The Canadian National Advisory Committee on Immunization currently recommends administration of zoster vaccine to adults over 60 years of age, which includes this patient's wife. These recommendations may change, because a recent randomized placebo-controlled trial involving 22 439 adults aged 50–59 years showed that zoster vaccine reduced the incidence of herpes zoster by 69.8% (6.57 cases per 1000 person-years in the placebo arm, and 1.99 cases per 1000 person-years in the vaccine arm; 95% CI 54.1%–80.6%).¹¹ Contraindication to vaccination includes immunodeficiency states. Zoster vaccine is not indicated for patients with active zoster or for the treatment of postherpetic neuralgia.

The case revisited

After herpes zoster was diagnosed by his primary care physician, the patient was prescribed a one-week course of valacyclovir. Ongoing pain required treatment with gabapentin, which was eventually stopped. His wife received the herpes zoster vaccine.

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