MedicineToday 2014; 15(4): 20-27

PEER REVIEWED FEATURE
2 CPD POINTS

Shingles
How to prevent it, how to treat it

ANTHONY L. CUNNINGHAM AO, MD, FRACP, FRCPA, FASM
JOHN LITT MB BS, MSc, DRACOG, FRACGP, FAFPHM, PhD

Zoster vaccine is the most effective strategy to prevent shingles and to ameliorate complications such as postherpetic neuralgia. Antiviral treatment is effective in treating shingles attacks if used early.

Key points

- **Shingles, or herpes zoster, is common, with a lifetime risk of up to 50% in people who live to the age of 85 years.**
- **Complications, especially postherpetic neuralgia (PHN), increase significantly in older age groups.**
- **Immunisation with zoster vaccine is the most effective strategy to boost immunity and prevent shingles and ameliorate its complications including PHN.**
- **Antiviral treatment with famciclovir, valaciclovir or aciclovir has proven efficacy for shingles and is most effective if commenced within 72 hours of rash onset.**
- **Analgesia for acute pain should be titrated against the severity of the pain; referral of patients to a pain clinic is recommended if pain is**

Before widespread use of the childhood varicella vaccine, the varicella–zoster virus (VZV) infected more than 90% of the population by adulthood, establishing latency within the cranial and peripheral nerve dorsal root ganglia near the spinal cord. Herpes zoster (shingles) arises from the reactivation of VZV after lifelong latent infection. The lifetime risk of developing zoster is up to 50% in people living to the age of 85 years. Although the key predisposing factor for reactivation of the virus is diminished cell-mediated immunity caused by increasing age or immunosuppression, the exact triggers for reactivation of the virus are unknown.

Reactivation of VZV results in its passage along nerves to the skin, thereby causing characteristic zoster pain and a linear dermatomal rash, which commences as erythematous papules and progresses through vesicles and crusting. The reactivation of VZV was previously thought to occur only once, unlike recurrent herpes simplex, which recurs frequently. It is now known from studies on astronauts and others that the virus does recur asymptomatically, albeit less frequently than herpes simplex virus, and is held in check by immune mechanisms which prevent disease. However, these immune mechanisms, especially T-cell immunity, eventually wane allowing the clinical syndrome to emerge. Levin and colleagues recognised that it would be possible to boost this T-cell immunity with varicella vaccine (and then with a concentrated version of the vaccine) to restimulate T-cell immunity and prevent the emergence of disease.[1] Following clinical trials, this has led to the era of immunisation for shingles.

CLINICAL MANIFESTATIONS

In addition to age and declining cell-mediated immunity, other risk factors for zoster include being female and having a family history of zoster. VZV reactivation leads to a localised inflammatory response with nerve cell damage (ganglionitis). The degree of inflammation is associated with subsequent disease severity and the likelihood of complications such as postherpetic neuralgia (PHN).

In the acute phase, a prodrome of dermatomal pain often precedes the eruption by several days or occasionally longer. The character of the acute pain in the affected dermatome (neuritis)

Professor Cunningham is Executive Director of the Westmead Millennium Institute for Medical Research and the Institute's Centre for Virus Research and Professor of Research Medicine at The University of Sydney, NSW. Associate Professor Litt is Associate Professor of General Practice in the Discipline of General Practice at Flinders Prevention, Promotion and Primary Health Care, School of Medicine, Flinders University, Adelaide, SA.

has been described as burning, deep aching, tingling, itching or stabbing. Headache, photophobia and malaise may also occur.

Patients not uncommonly experience neuropathic pain. Depending on the degree of associated neuronitis and ganglionitis, this includes:

- paraesthesias (burning and tingling)
- dysaesthesia (altered or painful sensitivity to touch)
- allodynia (pain associated with nonpainful stimuli)
- hyperaesthesia (exaggerated or prolonged response to pain).

Although such symptoms may commence during the acute phase, they are more commonly associated with subacute pain (30 to 90 days after onset) or chronic pain (more than 90 days after onset), known as PHN.

The rash, often pruritic, spreads throughout the affected dermatome, evolving through papular, vesicular (three to five days) and crusting (seven to 10 days) stages, taking two to four weeks to heal (Figures 1a and b). Occasionally, a rash does not follow the pain (referred to as zoster sine herpete).

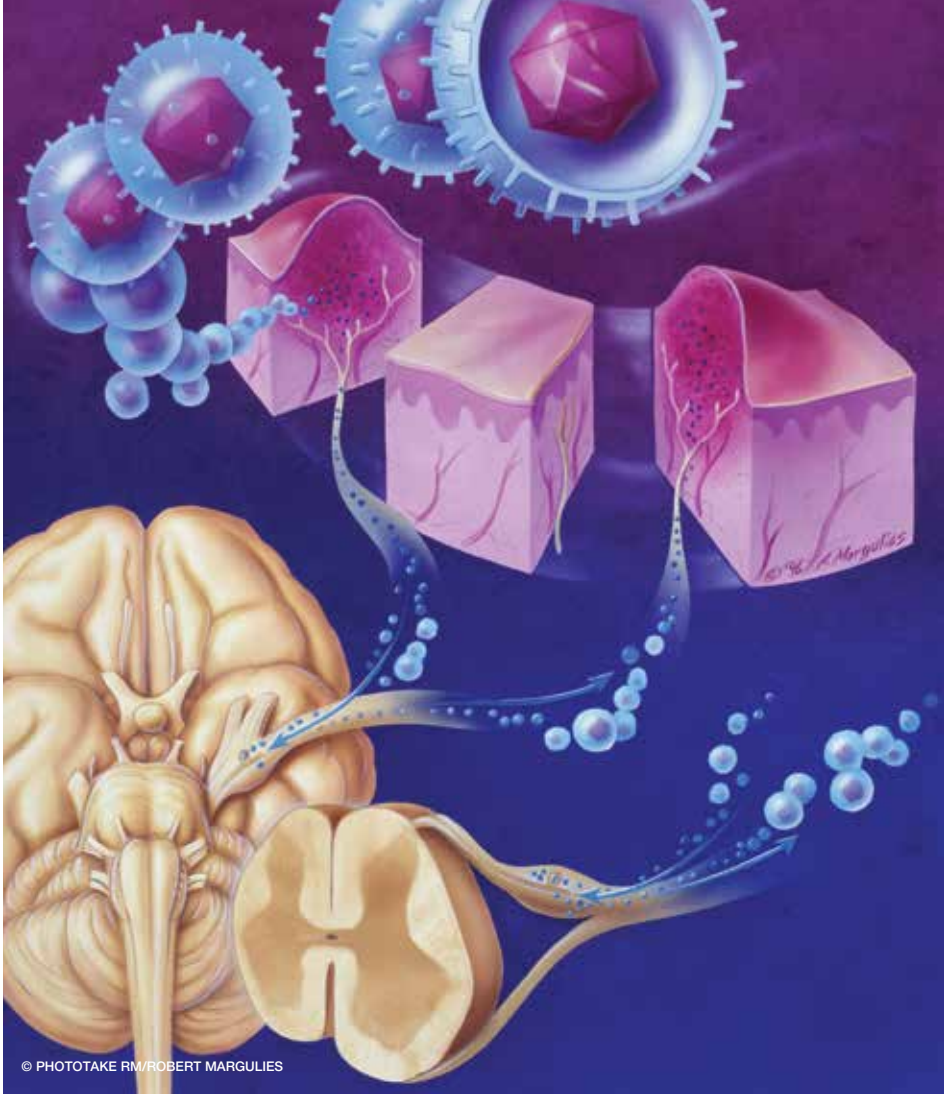
Herpes zoster is infectious from the time the skin lesions appear until they crust. Infection leads to classic varicella in susceptible contacts. Herpes zoster is usually less infectious than varicella because of the lack of person-to-person respiratory spread.

Complications associated with zoster can be:

- cutaneous (scarring, postinflammatory pigmentation changes and bacterial superinfection)
- ophthalmic (keratitis/uveitis, corneal erosion and uncommonly retinal necrosis or optic neuritis) (Figure 2)
- neurological (mainly PHN but also occasionally motor neuropathies, cerebral arteritis and encephalitis)
- disseminated (skin or other organs).[2]

Herpes zoster in pregnancy

Herpes zoster in pregnancy has not been shown to result in intrauterine infection and congenital varicella syndrome in the fetus, although these might occur when zoster is disseminated. Furthermore, maternal zoster occurring near term does not appear to pose a risk to the newborn.[3]

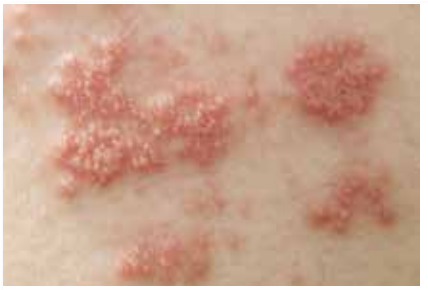


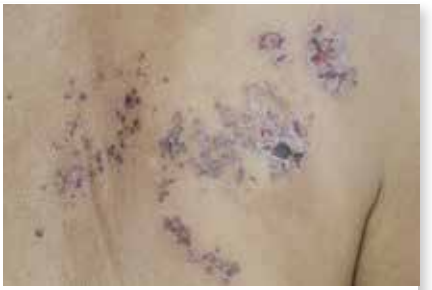
Herpes zoster in the immunocompromised host

Herpes zoster can cause severe disease and/or systemic spread to skin or viscera (eye, brain, liver) in severely immunocompromised patients, particularly those with haematological malignancy and especially if they are receiving chemotherapy or undergoing haemopoietic stem cell transplantation. In HIV-positive patients with a CD4 lymphocyte percentage less than 15% of total T lymphocytes, herpes zoster can be severe, involve multiple dermatomes and be disseminated or recurrent. However, since the introduction of combination antiretroviral therapy the incidence has dropped sixfold and severity has been attenuated. Herpes zoster is also more severe in patients with autoimmune disease receiving antitumour necrosis factor (TNF) and other biological therapy.

PATHOLOGY

After reactivation in the neurons of the dorsal root ganglion, VZV spreads laterally to infect surrounding satellite cells, other support cells and neurons, causing localised inflammation





Figures 1a and 1b. a (left). Vesicular stage of the shingles (herpes zoster) rash. b (right). Healing stage of the shingles rash showing crusting with no lesions still present.

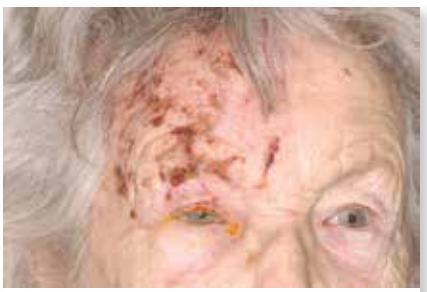


Figure 2. Herpes zoster affecting the trigeminal nerve, 10 days after onset. Shingles in this location can have ophthalmic complications, such as keratitis, uveitis and corneal erosions.

and haemorrhagic necrosis with varying degrees of nerve cell damage. Simultaneously, VZV is transported down the axon to the skin of the corresponding dermatome, causing similar necrosis and oedema in the epidermis, leading to characteristic vesicles. In both settings, virus-infected cells induce infiltration of CD4 and CD8 lymphocytes, which have a major role in controlling and eradicating infection.

DIAGNOSIS

The clinical syndrome of pain and rash in a dermatomal distribution is usually so characteristic of shingles that no diagnostic test is required (Figure 3).[4] However, presentations can be atypical, with pain occurring in advance of the rash or only a very few vesicles being present, as in Ramsay–Hunt syndrome in the external auditory meatus. Shingles may also occur in regions of the body where it can be confused with others diseases, such as in the sacral region where it can be confused with recurrent herpes simplex. In these cases, diagnostic tests are required.

The most sensitive and specific tests for herpes zoster are VZV nucleic acid detection by polymerase chain reaction (PCR) – often combined with herpes simplex virus PCR to distinguish the differential diagnoses of vesicular rash – and immunofluorescence. Virus isolation is slow and insensitive. Serological testing is occasionally used for retrospective diagnosis as IgM reappears in about 70% of patients with zoster. Immunocompromised patients with recurrent zoster or disseminated skin lesions may also require diagnostic testing.

VACCINES AGAINST HERPES ZOSTER

Current vaccines against herpes zoster are described in Box 1. Following pioneering experiments with varicella vaccines in small trials, a double-blind placebo-controlled trial was conducted of a concentrated (14 fold) form of the live attenuated varicella (Oka strain) vaccine (Zostavax). This involved over 38,000 people over the age of 60 years across 22 sites in the USA (the Shingles Prevention Study; SPS).[5] Participants were followed up for a median of 3.1 years. This landmark trial showed the vaccine to be both safe and efficacious, preventing herpes zoster completely in just over 50% of participants, preventing PHN in 66% of participants and reducing the burden of illness (a measure of severity and duration of pain) in more than 60% of participants. Although the efficacy in preventing shingles was reduced in people aged over 70 years and waned further with increasing age, the impact on the incidence of PHN was similar in the older group.

The SPS and subsequent related studies posed many additional questions, including the duration of efficacy, whether the vaccine could be used in mildly immunocompromised patients and whether it would be more useful if used in younger people.

Duration of efficacy and cost effectiveness

The duration of efficacy was addressed in short-term and long-term follow-up studies from the SPS. However, the long-term follow-up study relied on historical

1. VACCINES FOR HERPES ZOSTER

Currently available: Zostavax

- Live attenuated varicella zoster vaccine
- Efficacious against herpes zoster and postherpetic neuralgia
- Efficacy wanes with age
- Duration of immunity is possibly five to eight years; a booster dose may be necessary
- Licensed by the TGA in Australia for immunocompetent patients aged over 50 years
- Application for the National Immunisation Program in older people is pending
- Contraindicated in people who are severely immunocompromised
- Trials of a heat-killed form of Zostavax are under way
- Status uncertain for patients taking biological therapy for autoimmune diseases (trials underway)

In trials

- A zoster vaccine comprising a recombinant varicella protein with adjuvants

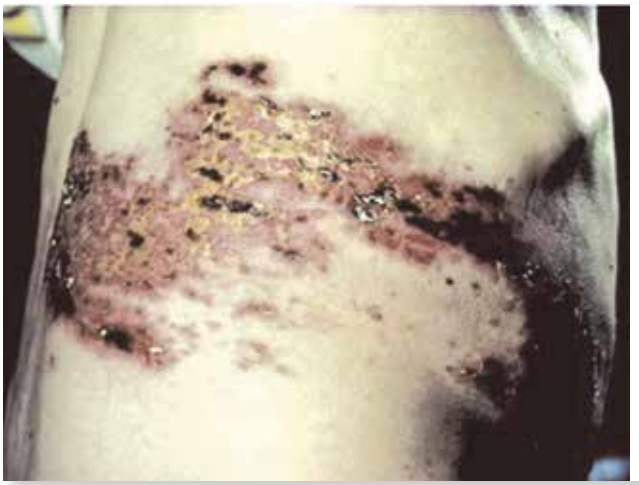


Figure 3. Severe herpes zoster affecting the hip and buttock showing a typical dermatomal distribution of the rash. The dark area on the right represents crusting of lesions.

Reproduced with permission from Cunningham AL, et al. Med J Aust 2008; 188: 171-176.

controls and is therefore less robust. Nevertheless, the follow-up studies suggest efficacy may wane, probably over five to eight years, which led to suggestions that a booster may be necessary at 10 years. Although a 10-year booster was recently shown to be safe, this is yet to be approved by licensing authorities in any country.

A recent systematic review of cost effectiveness demonstrated that Zostavax was cost effective but also noted that the age at vaccination, vaccine costs, incidence of zoster, duration of vaccine efficacy and of PHN all had a significant impact on cost effectiveness.[6]

Timing of vaccine delivery

New trials in younger patients showed efficacy in the 50- to 59-year-old age group, but most countries continue to recommend immunisation at the age of 60 years or over or, in the case of the UK, 70 years or over. Studies of simultaneous immunisation with Zostavax and influenza vaccine at age 60 years found no change in efficacy of either vaccine. However, there is doubt whether Zostavax retains full efficacy when administered simultaneously with pneumococcal vaccine and this is not recommended.

Immunocompromised patients

Live attenuated vaccines, especially concentrated vaccines such as Zostavax, are contraindicated in severely immunocompromised patients. These include in particular those with haematological malignancy undergoing haemopoietic stem cell transplantation, those with advanced HIV infection (CD4 lymphocyte percentage less than 15%) and patients receiving more than 20 mg prednisone per day for two weeks. However, in the mildly immunocompromised group of patients receiving antitumour necrosis factor or other biological agents and in HIV-infected patients without severe immune compromise, the picture is less clear. A recent small trial suggested that Zostavax may be safe in patients being treated with biological agents or low doses of immunosuppressive agents for autoimmune diseases, but more extensive studies are needed.[7,8]

Zoster vaccine today

Analysis of US postlicensure studies of patients receiving Zostavax using records of Medicare or large healthcare organisations (such as Kaiser Permanente) have confirmed the efficacy of the vaccine at similar levels to the original trial across the age spectrum, including patients aged 80 years and older.

Nevertheless, there are many issues still to be resolved, the most important of which is the need for a booster. The vaccine is also clearly far from perfect but cost effective and important in our ageing population.[5] Worldwide supply has been an issue in the past but now appears to be corrected. The uptake in the USA has been slow, at only 20% in 2013.

An inactivated form of Zostavax is currently in phase III trials for severely immunocompromised patients. Another type of zoster vaccine, using a recombinant varicella protein and adjuvants, is also currently in large phase III trials but it is not yet clear whether it will be as efficacious as Zostavax. If it is, it would have the advantage of being a subunit vaccine, which would be safe in the severely immunocompromised group (and potentially compete with inactivated Zostavax in this population).[9]

2. THERAPY FOR HERPES ZOSTER

Antivirals

- Oral valaciclovir (1 g three times daily for seven days) or oral famciclovir (500 mg three times daily for seven days) are preferred to oral aciclovir (800 mg five times daily for seven days).
- Immunocompromised patients may need to begin therapy with intravenous aciclovir and may need a longer duration of therapy

Corticosteroids

- Efficacious for acute pain
- Do not prevent postherpetic neuralgia

Analgesics for acute pain

- Titrate against pain intensity by increasing potency and combining analgesics in a stepwise manner:
  - paracetamol
  - NSAIDs
  - opioids (oxycodone, tramadol)

Postherpetic neuralgia treatments

- Anticonvulsants (gabapentin, pregabalin)
- Antidepressants (e.g. amitriptyline, nortriptyline)

MANAGEMENT OF HERPES ZOSTER

Treatments for herpes zoster are summarised in Box 2.

Antiviral therapy

Three antiviral drugs aciclovir, valaciclovir and famciclovir have proven efficacy in the treatment of acute herpes zoster, by accelerating the resolution of lesions, reducing the formation of new lesions, reducing viral shedding and decreasing the severity of acute pain. These drugs also reduce the overall duration of zoster pain. A meta-analysis of randomised controlled trials did not show that they reduce the incidence of PHN. However, this may be because the definition of PHN has altered over the years (now defined as pain that persists more than 90 days after symptom onset). Famciclovir and valaciclovir are usually preferred to aciclovir because they produce higher blood levels for longer durations and therefore require less frequent dosing, although they are more expensive.

Antiviral drugs are most effective when commenced within 72 hours of onset of rash so patients should be encouraged to present early. There may also be some benefit in commencing them beyond this limit. This should be considered, especially if new lesions are still forming.

Antiviral therapy should always be considered, particularly if the patient is aged over 50 years, has moderate or severe pain or severe rash and has involvement of the eye or the face or other complications of herpes zoster. Duration of therapy is usually seven days. Antiviral therapy is always indicated in immunocompromised patients and may be initially administered intravenously as aciclovir. Duration may need to be longer than seven days. All of these antiviral agents have low toxicity, although caution is needed in patients with renal impairment.[2]

In Australia, antiviral therapy is underprescribed, further reducing its overall efficacy against herpes zoster and especially PHN. PBS surveys from 1995 to 1999 showed that about 73% of all patients with zoster in the community were treated with antiviral drugs.[4,10] The remaining 27% were probably patients who presented late, after the recommended time of administration (within 72 hours of onset).[4,10]

Corticosteroids

Controlled trials of prednisone in doses of 40 mg daily for seven days, tapering over the next two weeks, has shown benefit, particularly for reducing acute pain and improving quality of life. In contrast, there is no evidence that corticosteroids reduce the incidence of PHN and total duration of pain.[11] Corticosteroids should not be used without concomitant administration of antiviral drugs as they are immunosuppressive. Clear contraindications to their use are in patients with hypertension, diabetes mellitus or osteoporosis, especially in elderly patients. National surveys have shown low uptake of corticosteroids for herpes zoster in Australia.[9]

Analgesics for acute pain

The choice of analgesics depends on the severity of the acute pain. For mild pain, paracetamol or NSAIDs can be used. For severe pain, narcotics such as oxycodone may also be needed. As pain may escalate rapidly in the early stages of herpes zoster, patients should have regular follow up (every 10 to 14 days) to assess whether the requirement for analgesics has changed. Referral of patients to a pain clinic is recommended if pain becomes severe and especially if it is prolonged or evolving into PHN.

Postherpetic neuralgia treatment

Postherpetic neuralgia is the most common and most disabling complication of herpes zoster so the progress of acute pain needs to be monitored, and treatment matched to escalating pain. As mentioned above, referral of patients to a pain specialist is strongly recommended to select appropriate analgesic drugs according to the severity of ongoing pain.

Combinations of pregabalin or gabapentin with an opioid, an antidepressant or an NSAID have been shown to be better than monotherapy. In some cases, capsaicin or a 5% lignocaine patch on non-affected skin may be effective if pain is particularly localised. Antidepressants that have been shown to be useful in PHN include serotonergic agents such as amitriptyline and nortriptyline. Improved therapy for both acute pain and PHN is required, as is better identification of patients who are at risk of severe pain.

Treatment of eye disease

Patients who have a herpes zoster rash distributed in the first division of the trigeminal nerve, usually on the forehead and into the hairline, need to be seen by an ophthalmologist because of the risk of keratitis and corneal scarring. Lesions on the tip of the nose are said to indicate a high likelihood of ocular disease, but such disease can occur without this sign. Ophthalmologists may use therapy such as mydriatic eye drops to reduce the risk of corneal and uveal scarring, topical corticosteroids to reduce keratitis and uveitis and medications that reduce intraocular pressure to treat glaucoma.

CONCLUSION

The introduction of a live attenuated vaccine for herpes zoster represents a major step forward in the management of this condition and its most important complication, PHN, both of which increase in incidence and severity with advancing age. Zoster vaccine is particularly important in view of the ageing of the Australian population. The vaccine is unusual in boosting declining T-cell immunity to a previous virus infection. It is not completely effective and wanes in efficacy over time, but the need for and efficacy of a booster are not yet established.

Treatment of herpes zoster has changed little over the past decade except for the introduction of more effective therapies for PHN. Further research on the pathogenesis of acute pain and PHN associated with herpes zoster followed by rational treatment is urgently required. MT

REFERENCES

1. Levin MJ, Murray M, Rotbart HA, Zerbe GO, White CJ, Hayward AR. Immune response of elderly individuals to a live attenuated varicella vaccine. J Infect Dis 1992; 166: 253-259.
2. Cohen JI. Herpes zoster. N Engl J Med 2013; 369: 1766-1767.
3. Pupco A, Bozzo P, Koren G. Herpes zoster during pregnancy. Can Fam Physician 2011; 57: 1133.
4. Cunningham AL, Breuer J, Dwyer DE, et al. The prevention and management of herpes zoster. Med J Aust 2008; 188: 171-176.
5. Oxman MN, Levin MJ, Johnson GR, et al; Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005; 352: 2271-2284.
6. Szucs TD, Pfeil AM. A systematic review of the cost effectiveness of herpes zoster vaccination. Pharmacoeconomics 2013; 31: 125-136.
7. Australian immunisation handbook 10th edition 2013. Canberra: Australian Government Department of Health and Ageing; 2013. Available online at: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home (accessed February 2014).
8. Keating GM. Shingles (herpes zoster) vaccine (zostavax(®)): a review of its use in the prevention of herpes zoster and postherpetic neuralgia in adults aged ≥50 years. Drugs 2013; 73: 1227-1244.
9. Levin MJ. Immune senescence and vaccines to prevent herpes zoster in older persons. Curr Opin Immunol 2012; 24: 494-500.
10. Stein AN, Britt H, Harrison C, Conway EL, Cunningham A, Macintyre CR. Herpes zoster burden of illness and health care resource utilisation in the Australian population aged 50 years and older. Vaccine 2009; 27: 520-529.
11. Han Y, Zhang J, Chen N, He L, Zhou M, Zhu C. Corticosteroids for preventing postherpetic neuralgia. Cochrane Database Syst Rev 2013; 3: CD005582.

COMPETING INTERESTS: Professor Cunningham is a Principal Investigator and Chair of the Publication Committee for the GlaxoSmithKline Zoster Vaccine Trial and has advised GlaxoSmithKline, SmithKline Beecham and Novartis in the past on antiviral drugs for herpes zoster. Both Professor Cunningham and Associate Professor Litt have served on the Global Adult Vaccines Advisory Board of Merck and the Zostavax Advisory Board of BioCSL.

Ask an expert

Puzzled by a presentation? Is the diagnosis a dilemma? What would a specialist in the relevant field do? Send us your baffling or hard-to-treat general practice cases for consideration for specialist comment in our 'Clinical case review' series. The case synopsis should be no longer than 150 words and include one or two specific questions that you would like answered.
Email the case to: editorial@medicinetoday.com.au, or
write to: Medicine Today, PO Box 5698, Chatswood West NSW 1515.