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PRACTICE

BEST PRACTICE

Herpes zoster infection

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What you need to know

- A typical history for herpes zoster might include neuropathic pain for around three days followed by a vesicular rash in a dermatomal distribution
- Consider treatment with an antiviral for those over 50, or with evidence of trigeminal nerve involvement (ideally within 72 hours of symptoms), and refer those who are immunocompromised and/or have eye involvement
- The rash takes around two weeks to resolve and can scar
- Post-herpetic neuralgia is the most common complication and is more likely in older people, where it can take six months or more to resolve
- In some areas a new recombinant zoster vaccine has been licensed; there is variation in whether the new or previous vaccine is recommended

Herpes zoster is caused by reactivation of a primary infection with varicella zoster virus.[1] After a primary infection, the virus lies dormant in dorsal root or cranial nerve ganglia. Reactivation causes the typical dermatomal pain and vesicular rash (fig 1).

Varicella zoster (commonly known as chickenpox) and herpes zoster (commonly known as shingles) are caused by the same herpes virus. Varicella follows the initial infection and causes a generalised rash, whereas herpes zoster occurs after reactivation, years later, and symptoms are usually localised to a specific dermatome.

The overall annual incidence of herpes zoster in the UK is estimated to be 1.85-3.9 cases per 1000 population,[2] increasing with age from fewer than two cases per 1000 among people under 50 to 11 cases per 1000 among people aged 80 or older. In the US, incidence ranges from 1.2 to 3.4 cases per 1000 person years, increasing with age to 3.9 to 11.8 cases per 1000 person years among people aged 65 or older.[3 4]

Who is at risk?

Over 90% of adults in the US have serological evidence of primary varicella zoster virus infection and are therefore at risk of reactivation.[5]

Risk of herpes zoster increases with age, and with any condition or treatment causing immunosuppression.[2 6]

Herpes zoster is not seasonal. Women have a higher risk than men,[4 7] and one study suggests that black people are less likely to develop herpes zoster than other ethnicities.[8]

Principal risk factors for developing herpes zoster are listed in box 1.

Box 1: Risk factors

Strong

Age over 50[3]

HIV: herpes zoster incidence is up to 15 times higher in people infected with HIV than in those uninfected[9-11]

Other immunosuppression: eg, chronic use of corticosteroids,[12] lymphoproliferative malignancies,[13] or chemotherapy[6]

Weak

Gender: studies suggest women have a greater risk of developing herpes zoster than men[4 7]

White ethnicity: one study suggests that black people are substantially less likely than white people to develop herpes zoster[8]

It isn't clear whether greater exposure to children gives some protection.[14] Recent studies showed an increase in herpes zoster incidence in the US, both before and after the varicella (chickenpox) vaccination programme.[15 16] Incidence has also increased in Canada, the UK, and Japan, where a varicella vaccination programme is not available.[17-19]

How does herpes zoster typically present?

Herpes zoster is characterised by a prodromal period with burning pain for two to three days, then a vesicular eruption in the dermatomal distribution of the infected ganglion. In immunocompetent people, the infection usually affects a single dermatome. The most commonly affected dermatomes are T1 to L2.[20] Sensory neurones are usually affected, but 5-15% of patients have motor neurone involvement.[21]

The pain usually lasts two to three days (more rarely up to a week) before the appearance of a rash. The pain can be constant or intermittent and is typically burning, stabbing, or throbbing. Pain can be severe enough to interfere with sleep and quality

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of life.[22] Persistent post-herpetic pain is a common complication.[23]

The rash is initially erythematous with a macular base and is followed rapidly by the appearance of vesicles within one to two days. The lesions tend to be clustered along the branches of the cutaneous sensory nerve (fig 2).

The hallmark of a herpes zoster rash is that it does not cross the midline, whereas other rashes can. The dermatomal distribution is specific to herpes zoster.

Pustulation of vesicles begins within one week of the onset of rash, followed three to five days later by ulceration and crusting (fig 2). The presence of a few skin lesions outside the primary or adjacent dermatome is not unusual.

Healing occurs over two to four weeks, and often results in scarring and permanent pigmentation in the affected area.

Approximately 20% of patients present with systemic symptoms such as fever, headache, malaise, or fatigue.[21] Rarely, pain can occur without a rash (zoster sine herpete).[24]

Herpes zoster can almost always be diagnosed clinically. Confirmatory diagnostic tests (box 2) may be necessary to differentiate genital herpes zoster from herpes simplex (polymerase chain reaction, PCR, of samples from lesions), or to diagnose herpes zoster in patients with typical pain but no rash (blood PCR).

Box 2: Possible tests for herpes zoster

Polymerase chain reaction The most sensitive and specific test.[25] Detects DNA in fluids and tissues

Immunohistochemistry Cells are scraped from the base of a lesion and stained with fluorescein conjugated monoclonal antibodies to detect viral glycoprotein. This test is more sensitive than viral culture[26 27]

Viral culture from vesicular fluid This test is less sensitive than immunofluorescence as a result of virus lability[1]

Possible differential diagnoses are given in box 3.

Box 3: Differential diagnoses

Rash

Contact dermatitis: localised rash or irritation of the skin caused by contact with a foreign substance. The pain and the rash usually occur simultaneously

Herpes simplex: grouped vesicles in a non-dermatomal pattern, often preceded by pruritis and pain. Oral and genital lesions most common

Pain

Cholecystitis: pain in the right upper quadrant of the abdomen

Acute appendicitis: pain in the right lower abdominal quadrant

Renal calculi: severe colicky pain and inability to lie still; flank pain on examination

Herpes zoster ophthalmicus

Ulcerative keratitis: pain and redness in the affected eye, with visual changes dependent on the ulcer location

Acute angle closure glaucoma: periorbital pain, blurred vision, and headache

Trigeminal neuralgia: intense, stabbing, electric shock like pain in the areas of the face innervated by the trigeminal nerve

What are the complications?

The commonest complication of herpes zoster is post-herpetic neuralgia, the pain that persists long beyond cutaneous healing. Depending on the definition of post-herpetic neuralgia, (the number of days of persistent pain after the onset of the rash), the risk ranges from 5% to 32%[2] and increases with patients' age. The duration of pain also varies widely and can extend for years, although it usually resolves within six months. People over 70 are at increased risk of more persistent pain.

Ocular complications are common and occur when the virus infects the ophthalmic division of the trigeminal nerve. Infection may cause conjunctivitis, keratitis, corneal ulceration, iridocyclitis, glaucoma, and blindness if untreated.[28-30]

Other complications include bacterial superinfections (1.1%), peripheral nerve palsies (1.8%), sensory loss (1.8%), encephalitis, and disseminated herpes zoster (1.7%).[31] Herpes zoster is rarely fatal in patients who are immunocompetent but can be life threatening in immunocompromised people.

Is it infectious?

Patients can transmit the virus through fluids from the lesions to people who have not had chickenpox, so direct body contact should be avoided. Covering lesions that are not usually covered by clothing may also decrease transmission. Immunocompromised people may shed virus from lesions and from the respiratory tract.

When should I prescribe antivirals?

Herpes zoster is usually self limiting, but consider antivirals in all patients—especially those who have severe disease, are over 50, are immunocompromised, or have evidence of trigeminal nerve involvement.

Treatment is usually a seven day (or 10 day for patients with eye involvement) course of an oral antiviral drug such as aciclovir, famciclovir, and valaciclovir. Treatment is most effective when started within 72 hours of rash onset. Intravenous aciclovir is an option for patients who cannot tolerate oral treatments. Topical antivirals are not recommended. Treatment aims to reduce viral replication, stop the formation of new lesions, manage pain, prevent ocular complications, and reduce the risk of post-herpetic neuralgia.

Advise patients to keep the rash clean and dry to reduce the risk of bacterial superinfection. Patients should also avoid topical antibiotics or dressings with adhesive that may cause irritation and may delay healing of the rash.

Which antiviral to prescribe?

Famciclovir, valaciclovir, and aciclovir have been shown to be superior to placebo in reducing the amount of time to complete cessation of pain.[32-35]

Studies report no differences between famciclovir and valaciclovir on cutaneous and pain end points.[36]

The treatment of herpes zoster during pregnancy is the same as for any other patient with the condition. Among antivirals, aciclovir has been the most extensively studied among pregnant women and is most commonly used

Who requires referral?

People who are immunocompromised

Herpes zoster is common and often more complicated in immunocompromised people, so refer such patients to secondary care. The main objective of treatment is to reduce the incidence of cutaneous and visceral dissemination that can lead to life threatening complications. Immunocompromised patients require prompt antiviral therapy within one week of rash onset or at any time before full crusting of lesions. Treat localised disease with oral valacyiclovir, famciclovir, or aciclovir, with close outpatient follow-up. Reserve intravenous aciclovir for patients

with disseminated infection, ophthalmic involvement, severe immunosuppression, or the inability to take oral medications.

People with eye involvement (herpes zoster ophthalmicus)

Patients with eye manifestations require prompt referral to an ophthalmologist. Begin antiviral treatment as soon as possible, and before referral.[21] Give aciclovir, famciclovir, or valaciclovir for seven to 10 days, started preferably within 72 hours of rash onset. Supply lubricating eye ointment to patients with an impaired blinking reflex to prevent damage to the corneal epithelium. Other treatments include analgesia, antibiotic ophthalmic ointment to protect the ocular surface, and topical corticosteroids.

How should I approach analgesia?

Acute herpetic pain

For mild pain, analgesics such as paracetamol and ibuprofen are appropriate. For severe pain, opioid analgesics are an option. Topically administered lidocaine and nerve blocks are also effective.[28 37 38] Lotions containing calamine may also be used on open lesions to reduce pain and pruritus.

Warn patients about the possibility of post-herpetic pain and offer advice on how to psychologically manage chronic pain (eg, with relaxation techniques and counselling). Referral to a pain management consultant is indicated if the pain interferes with daily living.

Post-herpetic pain

Treat mild to moderate pain with non-steroidal anti-inflammatory drugs or paracetamol, alone or in combination with a weak opioid analgesic such as codeine or tramadol.[39-43] Topical capsaicin can also provide pain relief.[44-47] Patients with moderate to severe pain can be treated in the short term with a stronger opioid analgesic such as oxycodone or morphine. Where these treatments are ineffective, offer a tricyclic antidepressant such as amitriptyline[48] or an anti-convulsant such as gabapentin or pregabalin.[49-51] A meta-analysis showed no difference in pain relief between gabapentin and tricyclic antidepressants.[52] For those intolerant of opioids, one or a combination of anticonvulsants, tricyclic antidepressants, or corticosteroids are appropriate.

What are the latest vaccine recommendations?

Two vaccines are licensed for the prevention of herpes zoster and post-herpetic neuralgia in older adults: Zostavax, a live attenuated vaccine, and Shingrix, a recombinant subunit vaccine. Shingrix was approved in the US in 2017 and in Europe in January 2018.

Zostavax is still recommended in the UK for adults aged 70-79; however, the US Advisory Committee on Immunization Practices (ACIP) updated its guidance in January 2018 and now recommends Shingrix for adults aged 50 or older.[53] Shingrix is recommended regardless of previous episodes of herpes zoster, or receipt of Zostavax. The latest guidelines are outlined in box 4.

Box 4: Latest guidelines from the UK and US

- Public Health England (PHE) 2017
- Shingles: guidance and vaccination programme
- https://www.gov.uk/government/collections/shingles-vaccination-programme
- UK guidance on the characteristics, management, and surveillance of shingles, including vaccination
- US Centers for Disease Control and Prevention (CDC) 2018
- Recommended immunisation schedule for adults aged 19 or older: United States, 2018
- http://www.cdc.gov/vaccines/schedules/hcp/adult.html
- US Recommendations on the use of licensed vaccines in adults, including herpes zoster vaccine
- US Centers for Disease Control and Prevention 2018
- Update on recommendations for use of herpes zoster vaccine
- http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/shingles.html
- Updated recommendations from the CDC on the use of herpes zoster vaccine
- National Institute for health and care excellence 2017
- Neuropathic pain in adults: pharmacological management in non-specialist settings
- https://www.nice.org.uk/guidance/cg173

The updated US guidance still lists Zostavax as a recommended option for adults aged 60 or older, but explicitly states that Shingrix is preferred.[54]

What's the difference between Zostavax and Shingrix?

Zostavax is a lyophilised or freeze dried preparation of live, attenuated varicella zoster virus. The vaccine is given as a single subcutaneous dose and can reduce the risk of herpes zoster by 51% for a mean duration of 3.13 years (range 1 day to 4.9 years) after vaccination, post-herpetic neuralgia by 67%, and the overall burden of illness by 61%.[31]

This live vaccine is contraindicated in severely immunosuppressed people, pregnant women, and children.

Zostavax becomes less effective with increasing age, and efficacy wanes completely approximately 10 years after vaccination.[55]

Shingrix is a recombinant subunit vaccine containing the AS01B adjuvant system and glycoprotein E antigen from the varicella zoster virus. Shingrix requires two intramuscular doses 2 to 6 months apart, and has a substantially higher efficacy than Zostavax, reducing risk herpes zoster infection by 97%[56 57] (mean duration of follow-up was 3.2 years).

Early studies suggest a single dose does not produce a robust immune response,[58] so attendance for both doses is important.

Unlike Zostavax, the efficacy of Shingrix is high even for patients over 70. Protection declines slightly four years after vaccination[59] but longer term efficacy is unknown.

Shingrix is not a live vaccine so should theoretically be safe in immunocompromised patients, but the ACIP has not yet made recommendations for vaccinating this group. The committee awaits more data from the manufacturer.

Shingrix causes more reactions at the injection site than Zostavax.[57] Grade 3 systemic vaccine reactions, defined as symptoms that prevent normal everyday activities, are more frequent after the second dose than after the first.[56] Shingrix is safe and effective in patients previously vaccinated with Zostavax.[60] It can be safely given at the same time as the influenza vaccine.[61]

Zostavax is administered as a single dose subcutaneously, and Shingrix as two doses intramuscularly. Reports of administration errors have prompted the CDC to issue a reminder to doctors.[62 63]

Education into practice

What information do you share with patients about what to expect with herpes zoster infection? Does this article offer you ideas on additional information to share?

Does your organisation routinely offer older adults vaccination in line with local or national policies?

What might you do differently for a patient with herpes zoster who is immunocompromised?

How patients were involved in this article

Best Practice did not routinely ask for patient involvement at the time that the article was commissioned, and so no patients were involved

This article is based on in a module in *Best Practice* (https://bestpractice.bmj.com/topics/en-gb/23)

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Figures

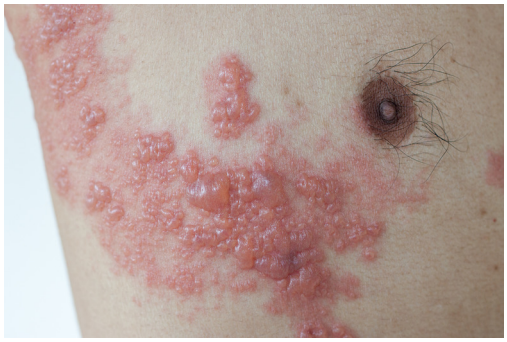

Fig 1 Vesicular rash caused by herpes zoster

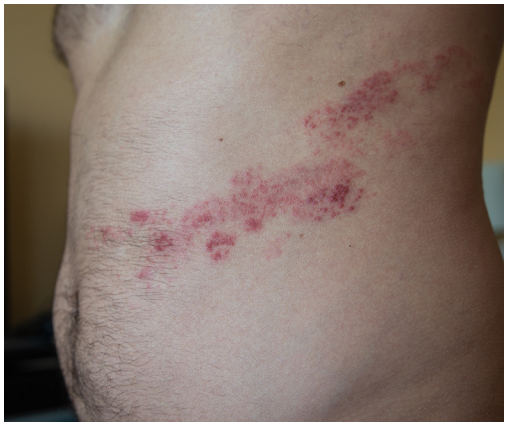

Fig 2 Herpes zoster rash showing dermatomal distribution