Shingles and Shingles Vaccination

Synonyms: herpes zoster and varicella zoster

Shingles is caused by the human herpesvirus-3 (HHV-3). Primary infection usually occurs in childhood, producing chickenpox (varicella) although it can be subclinical. After this the virus lies dormant in the sensory nervous system in the geniculate, trigeminal or dorsal root ganglia. It may lie dormant for many years or many decades, kept in check by the immune system before flaring up in a single dermatome segment.

When this happens, the virus travels down the affected nerve over a period of 3 to 4 days, causing perineural and intraneural inflammation along the way. There is not always a clear reason for a flare-up but associations include ageing (most patients are over 50 years old), immunosuppressive illness, or psychological or physical trauma. Reactivation of the virus is thought to be associated with immunosuppression as a result of a decline in cell-mediated immunity.\(^1\)

In immunocompetent patients, the most frequent site of reactivation is the thoracic nerves followed by the ophthalmic division of the trigeminal nerve (ophthalmic shingles), which can progress to involve all structures of the eye. If the mucocutaneous division of the VII cranial nerve is involved, the lesions in the ear, facial paralysis and associated hearing and vestibulary symptoms are known as Ramsay Hunt syndrome.\(^2\) Shingles may also affect cervical, lumbar and sacral nerve roots.

Epidemiology\(^3\)

Chickenpox is a very common childhood illness. At least 90% of adults raised in the UK are immune, having been exposed in childhood.\(^4\) All these people are therefore at risk of developing shingles. Shingles is seen as a disease of older people but it can affect all ages, including children. The incidence and severity increase with age. The annual incidence of shingles for those aged 70 to 79 years is estimated to be around 790 to 880 cases per 100,000 people in England and Wales. The lifetime risk is estimated at one in four.

Chickenpox can rarely be acquired from a patient with active shingles, as the lesions shed virus (transmission is by direct contact or droplet spread) but shingles is not caught from contact with a person with chickenpox.

Risk factors

- Increasing age significantly increases the incidence, morbidity and mortality of shingles.
- Incidence and risk are increased in the immunocompromised patient. Consider underlying immunodeficiency if anyone presents with shingles affecting more than one dermatome.
- HIV, Hodgkin's lymphoma and bone marrow transplants all present a high risk.

Presentation

The disease can be divided into the pre-eruptive phase, acute eruptive phase and chronic phase - postherpetic neuralgia (PHN).

Pre-eruptive phase

- In the pre-eruptive phase there is no skin lesion to see but 80% of patients complain of burning, itching or paraesthesia in one dermatome.
- This usually lasts for a day or two but it can be over a week before the characteristic eruption appears.
- The patient may feel unwell with malaise, myalgia, headache and fever but these symptoms may abate as the eruption appears.
- In the pre-eruptive phase the skin may be tender but there are no lesions to see. There may be lymphadenopathy.
- Diagnosis is difficult before the characteristic rash appears.
**Eruptive phase**

- The eruptive phase occurs when the skin lesions appear. Most, but not all, adults have acute, neuritic pain in this phase. A few have severe pain without any eruption, called zoster sine herpete. Young adults and children are most likely to be free of pain.
- Crust formation and drying occurs over 7 to 10 days and is followed by resolution at 14 to 21 days.
- Patients are infectious (resulting infection is chickenpox) until lesions have dried.
- In the eruptive phase the rash first appears as a patch of erythematous, swollen plaques with clusters of small vesicles. This eruption is virtually diagnostic of shingles. It may not affect the whole dermatome but it will not extend outside it. Hence, **any rash that crosses the midline is not shingles**.
- More vesicles may erupt over the next 5 to 7 days. They form crusts that fall off inside three weeks.
- In elderly and immunocompromised patients, the eruptive phase is longer and more extensive. It occasionally results in haemorrhagic blisters, skin necrosis and secondary bacterial infections.

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**Chronic phase**

- Chronic phase, or PHN, is persistent or recurring pain lasting 30 days or more after the acute infection or after all lesions have crusted.

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**Variations**

**Ophthalmic shingles**[^5]

*Synonyms: herpes zoster ophthalmicus, ophthalmic herpes zoster*
Example of ophthalmic shingles

Ophthalmic shingles accounts for 10-20% of cases of zoster. Ophthalmic herpes is a danger to sight and the patient should see an ophthalmologist the same day. Antiviral therapy is mandatory for this at any age.

If the ophthalmic branch of the trigeminal nerve is involved this may affect the eye in up to 70% of cases (the likelihood of this occurring is not related to age or the severity of the rash) but this is a justly feared complication of this condition. If the tip of the nose has a rash, the nasociliary branch of the trigeminal nerve is involved. This branch supplies the globe and so it is very likely that the eye will be affected (at least 75% of cases). This is called Hutchinson’s sign, as he described it in 1868. The eye can be seriously affected with little evidence of a shingles rash.

- Acute lesions of the orbit or globe develop within three weeks of the onset of the rash. They may resolve swiftly or linger and recur over years.
- Patients may have a red eye, decreased visual acuity, epiphora, photophobia and forehead tenderness.
- Other problems affect various parts of the eye:[8]
  - **Lids** - bilateral eyelid oedema can develop, as well as blepharitis and ptosis.
  - **Conjunctiva** - giving rise to a follicular conjunctivitis.
  - **Episclera and sclera** - resulting in inflammation (episcleritis and scleritis).
  - **Cornea** - keratitis; multiple features may occur - eg, multiple small epithelial dendrites (seen after instilling fluorescein), stromal and neurotrophic keratitis, raised mucous plaques and so on. This is one of the sites where significant visual loss can occur.
  - **Anterior part of the eye** - uveitis, paralysis ± atrophy of the iris and secondary glaucoma (about 10% of cases).
  - **Posterior part of the eye** - retinitis, choroiditis and optic neuritis.

- Nerve damage can include oculomotor palsies and neuralgia.
- Tissue scarring can include lid deformities, neuralgia and lipid keratopathy.

**Ramsay Hunt syndrome**

See separate *Herpes Zoster Oticus (Ramsay Hunt Syndrome)* article.
Differential diagnosis

- Before the rash appears the pain may be thought to originate from under that dermatome and so it must be considered as a possible cause of chest or abdominal pain.
- Cluster headaches or migraine - consider in the prodromal phase.
- Ramsay Hunt syndrome may present as Bell's palsy before the rash appears.
- The rash, especially if without pain, may be mistaken for atopic eczema, eczema herpeticum, contact dermatitis, herpes simplex or impetigo. Diagnosis of eczema/dermatitis may lead to this viral infection being treated with steroid cream.
- Consider the differentials of the acute red eye where there is no rash (eg, conjunctivitis, corneal abrasion, keratitis).
- If you strongly suspect ophthalmic shingles, look for a rash or evidence of a previous rash, such as pigmentary changes along the hairline, or consider zoster sine herpete.

Investigation

The diagnosis is usually clinical, based on typical lesions in a single dermatome. Various techniques to detect the virus or antibody detection may be possible after consultation with a microbiologist. Scraping for smears and cultures are usually negative, as the viruses are difficult to recover from the scrapes. A direct immunofluorescence assay can be used; it is more sensitive than viral culture and can differentiate herpes simplex viral infections from varicella-zoster virus (VZV) infections.

Where the presentation is atypical (eg, severe disease or a rash extending beyond one dermatome), the patient needs to be investigated for immunodeficiency.

Management

General
The rash should be kept clean and dry to avoid secondary bacterial infection. Adhesive dressings should be avoided. If the rash can be covered, or if the lesions have all crusted, there is no need to avoid school or work. If the rash is weeping and not in a covered part of skin, however, the person should stay off school or work.

Topical therapy
Topical antiviral treatment is not recommended. Topical antibiotic treatment may be indicated for secondary bacterial infection.

Oral antiviral therapy
Oral aciclovir has been shown to shorten the duration of signs and symptoms and may reduce the incidence and severity of complications from ophthalmic shingles. However, Cochrane reviews have found no evidence that aciclovir reduces the incidence of PHN, and insufficient evidence for other antivirals.

The antivirals that are used are (adult dose):[10]
- Aciclovir 800 mg five times a day for seven days (continuing until two days after crusting of lesions in those who are immunocompromised).
- Valaciclovir 1000 mg three times a day for seven days; or
- Famciclovir 500 mg three times a day for seven days (or ten days in immunocompromised individuals) or 750 mg once or twice a day for seven days.

One review found a significant reduction in risk of pain with valaciclovir and famciclovir for management of herpes zoster virus (HZV) including ophthalmicus. Valaciclovir or famciclovir were both shown to provide significant reduction in the risk of HZV-associated pain.[11]

An oral antiviral drug should be started within 72 hours of rash onset for:
- Anyone over the age of 50 years.
- People of any age with non-truncal involvement (eg, affecting the neck, limbs or perineum).
- Cases where there is moderate or severe pain or rash.
- Those with ophthalmic involvement.
- People who are immunocompromised.
If it is not possible to initiate treatment within 72 hours, consider starting an antiviral drug up to one week after rash onset, especially if the person is at higher risk of severe shingles or complications (eg, continued vesicle formation, older age or severe pain).

- For pregnant women, seek specialist advice regarding prescribing antiviral treatment in pregnancy.
- Children who are not immunocompromised do not usually require antiviral treatment. Immunocompromised children at high risk of disseminated or severe infection should be treated with a parenteral antiviral drug.
- Longer and more intense (intravenous) treatments may be required in the elderly and the immunocompromised.
- Early and effective treatment reduces complications.[12]

**Steroids**[13]

The use of oral corticosteroids in the treatment of patients with zoster infection is controversial. As an adjuvant option in the treatment of patients with acute zoster infection, oral corticosteroids have been shown in some studies to ameliorate the inflammatory features and so reduce pain and cosmetically improve the rash.

However, studies have shown conflicting results and many consider that any limited benefit is outweighed by the adverse effects of corticosteroids, especially in the elderly. Where used, they must be co-prescribed with antiviral therapy due to their immunosuppressive properties. Steroids should be avoided in people with:

- Hypertension
- Diabetes mellitus
- Peptic ulcer
- Osteoporosis

Caution is required where prescribing for elderly patients, who are at increased risk for serious adverse events.

**Management of ocular problems**

Where there is intraocular involvement, various agents are used depending on which tissue is involved. An ophthalmologist should be involved to carry out a detailed assessment and tailor a management plan accordingly.

- Patients may benefit from long-term application of ocular lubricants; cool compresses are advised for the conjunctivitis in the acute phase. Epithelial defects are sometimes treated with additional chloramphenicol ointment.
- Patients may also require cycloplegics to help pain relief and intraocular pressure-lowering drugs.
- Where there is retinitis, choroiditis or optic neuritis, admission for intravenous antivirals may be required.
- **Topical steroids may only be started under ophthalmic supervision** (these are beneficial in certain specific cases and harmful in others).
- Intravitreal antiviral therapy may be needed for immunocompromised patients with retinal necrosis.
- Where neurotrophic ulcers develop, botulinum toxin administration to produce a protective ptosis may be considered (the effects wear off after about three months). Other options available to manage these ulcers include bandage contact lenses, tissue glue and tarsorrhaphy (the lids are sutured together; depending on the type of procedure, this may or may not be irreversible).
- Treatment may go on for many months or even years.
- Corneal scarring may require penetrating keratoplasty (corneal transplant).

**Analgesia**

It may be necessary to give quite strong analgesia if there is pain. First-line treatments include paracetamol (with or without codeine) and non steroidal anti-inflammatory drugs (NSAIDs). Tricyclic antidepressants, gabapentin, pregabalin, steroids and opioids are options used to reduce acute pain where the first-line treatments fail. Topical analgesia with lidocaine patches has also been shown to be of benefit in the acute stage as well as for PHN. They must be applied to intact skin, not to the area of the rash.

If the pain is severe beyond the moment that the vesicles have crusted over then **PHN** has probably developed.
Referral

- Ophthalmic involvement: get immediate specialist advice or refer immediately (to be seen within 24 hours).
- Immunocompromised patients: get immediate specialist advice regarding treatment or refer immediately. Any patient with known immunodeficiency (including those with organ transplants and patients on systemic immunosuppression or chemotherapy) should be seen urgently by physicians in an infectious disease unit.
- More severe disease, recurrence or multiple dermatomal involvement should raise suspicions of underlying immunosuppression; actively look for causes. Consider HIV in patients under 65 years of age.
- Refer urgently where complications are present:
  - Signs of meningitis, encephalitis, or myelitis.
  - Cranial nerve palsies
  - Patients with extensive associated cellulitis may need to be admitted for intravenous antibiotics.

- Seek specialist advice if a pregnant woman has shingles.
- Patients with more severe or persistent neuralgia should be referred early to a pain clinic before the condition becomes chronic.

Complications

General complications

- Skin complications may occur: scarring, pigmentation, secondary bacterial infection.
- Ramsay Hunt syndrome: describes a syndrome of lesions in the ear, facial paralysis and associated hearing and vestibular symptoms.
- Bell’s palsy.
- Rarely, meningitis, encephalitis, myelitis or hemiparesis may occur.
- Disseminated zoster occurs mainly in immunocompromised patients and may lead to visceral dissemination, resulting in pneumonia, encephalitis or hepatitis with a 5-10% mortality rate, even with antiviral drug treatment.
- There is a negative impact on quality of life.
- Morbidity associated with PHN increases with age.

Complications of ophthalmic shingles

- **Ocular complications** include pain, anterior uveitis and varieties of keratitis. Possible long-term complications include chronic uveitis, keratitis and neuropathic ulceration.
- **Lid complications** include ptosis, trichiasis, scarring of the skin and madarosis (loss of lashes).
- **Rare ocular complications** include optic neuritis, retinitis and ocular cranial nerve palsies. There is a complete or near resolution of ophthalmoplegia in about 65% of cases. Sight is threatened by neuropathic keratitis, perforation, secondary glaucoma, posterior scleritis, optic neuritis and acute retinal necrosis. Neurological complications are rare (one series reported this in 5.5% of patients) with meningoencephalitis being noted in a few patients.
- **Long-term complications** may be related to poor sensation of the cornea and poor motor function of the eyelid. This may put the eye at risk during episodes of impaired consciousness. There is risk of neuropathic ulceration and exposure keratopathy. There is also a risk of complications common to the disease elsewhere, such as PHN. The risk of long-term problems is such that it is recommended that a history of ophthalmic shingles should remain in the problems section of the medical record. There is a 6-14% chance of recurrence.
- **Permanent sequelae** of ophthalmic zoster infection may include chronic ocular inflammation, loss of vision, and debilitating pain. Gradual clouding of the cornea may occur.

Postherpetic neuralgia (PHN)

See separate Postherpetic Neuralgia article.

Prognosis

- The prognosis for younger and otherwise healthy patients is excellent.
- Pregnant women and immunosuppressed patients have the highest risk of serious sequelae.
Elderly people have a significantly increased risk of complications, including PHN, bacterial infections and scarring.

Immune compromise carries poorer prognosis.

Mortality is rare. Disseminated disease in the severely immunocompromised has a case fatality rate reported to be 5-15%, with most deaths being due to pneumonia.\(^{[6]}\)

**Prevention\(^{[1, \ 3]}\)**

Studies have shown that giving older people (adults aged over 60 years) varicella-zoster vaccine boosts their waning immunity and significantly reduces the morbidity due to HZV and PHN.\(^{[17]}\) Herpes zoster vaccine is effective in preventing herpes zoster disease. The vaccine is well tolerated and produces few systemic adverse events; it is known to last at least three years.\(^{[18]}\) It may last longer than this and the optimum time for re-vaccination has not yet been established.

In the UK, there is a shingles vaccination programme for people aged 70 years and above. The programme began in September 2013. There are catch-up programmes for those between the ages of 71-79. Eligibility currently depends on age as of September 1st each year and is outlined annually on the Public Health England (PHE) website. It is not recommended for people aged 80 years or more.

The introduction of a childhood varicella-zoster vaccine (as in the USA) would reduce the risk of HZV and, therefore, off PHN, when this cohort of children becomes elderly. However, there is concern that reducing the number of children with VZV by introducing a vaccine could lead to a short-term increase in HZV in those who are latently infected.

**Further reading & references**

- Who is eligible for the shingles vaccine beyond 2016; Public Health England
- Shingles: questions and answers for healthcare professionals; Public Health England
- Shingles (herpes zoster): the Green Book, Chapter 28a; Public Health England
- Varicella: the Green Book, Chapter 34; Public Health England (April 2013)
- Shaikh S, Ta CN; Herpes zoster ophthalmicus, American Family Physician, November 2002; comprehensive text and pictures
- Shingles, NICE CKS, May 2013 (UK access only)
- British National Formulary; NICE Evidence Services (UK access only)

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