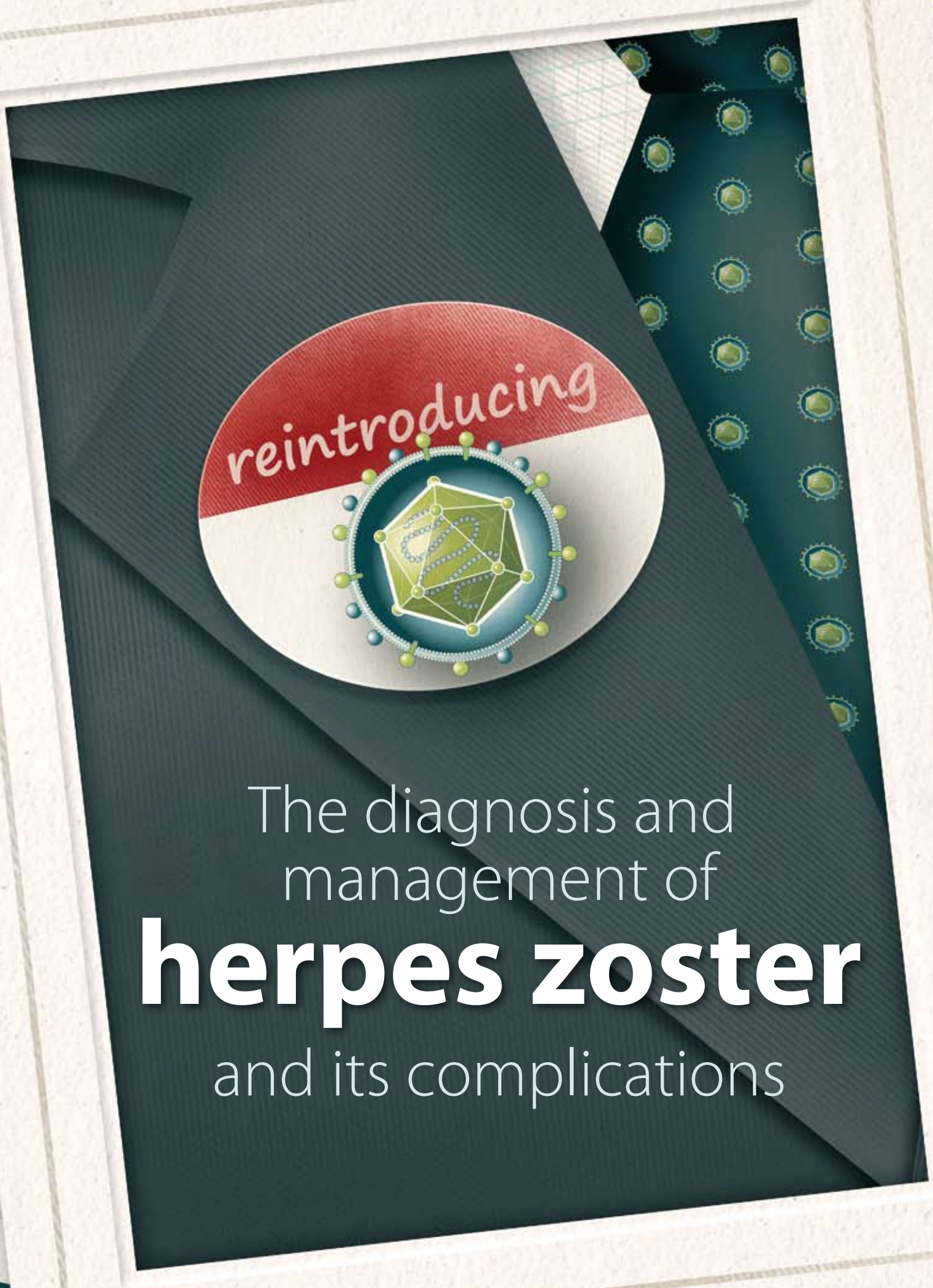

The diagnosis and management of **herpes zoster** and its complications

Herpes zoster (shingles) is a self-limiting condition caused by reactivation of the Varicella zoster *virus. Shingles most frequently develops in older people and people who are immunocompromised. Diagnosis is straightforward if the characteristic rash of shingles is present, however, patients can present with atypical features. Antiviral medicines may reduce the duration of the rash and associated pain, however, they do not reduce the risk of patients developing post-herpetic neuralgia, the most common long-term complication of shingles.*

What is herpes zoster?

Herpes zoster, also known as shingles, is a condition usually characterised by pain, followed by the development of a vesicular rash, which is unilateral and typically affects one dermatome. One-third of people are estimated to be affected by shingles during their lifetime, rising to one-half of those who live to age 80 years.[1]

Shingles is caused by reactivation of the *Varicella zoster* virus (VZV). Initial infection with VZV occurs as varicella (chicken pox); over 97% of people are infected with VZV by age 40 years.[1] The virus then resides in a dormant state in cranial nerve and dorsal-root ganglia.[2] If VZV is reactivated, it travels from the cell bodies of neurons to their nerve terminals in the skin. This causes local inflammation and pain, followed by the distinctive shingles rash.

Shingles itself is self-limiting, however, post-herpetic neuralgia is a frequent complication, where pain persists for months or years after the rash has resolved.

Who is at risk of shingles?

Only people who have previously had chicken pox are at risk of shingles. The risk of shingles and its complications increases with age, due to a decline in cell-mediated immunity to VZV.[3] Shingles most often affects people aged over 60 years, but infants who contract chicken pox in their first year have an increased risk of developing shingles before age 60 years.[2] Approximately 60% of people who develop shingles are female.[4] Compromised immunity is a significant risk factor for developing shingles, e.g. patients undergoing immunosuppressive treatment or people with HIV infection. There does not appear to be an increased prevalence of shingles in women who are pregnant, and shingles does not appear to pose the same risk to the foetus as chicken pox.[5]

Clinical features and diagnosis of shingles

Symptoms and signs

The course of shingles can be divided into three stages:[6]

1. Prodrome (early symptoms stage) – one to four days prior to rash appearing
2. Infectious rash (acute stage) – seven to ten days duration
3. Resolution (healing stage) – two to four weeks duration

Prodrome

Acute neuralgia is usually the first symptom of shingles and occurs in approximately 70 – 80% of patients.[7] It is experienced as a localised tingling, itching or burning sensation with intermittent stabbing pain. The type and intensity of pain can vary over time, but the pain usually persists through all three stages of shingles.

Systemic symptoms, including malaise, fever and headache, may also be present in some patients; reportedly in less than 20% of cases.[7] Lymph nodes in the affected area may also be enlarged.[8]

Infectious rash

The shingles rash usually affects a single dermatome in a unilateral band-like pattern and sometimes extends past the midline (Figure 1). More rarely the rash can occur in multiple adjacent dermatomes.[4] The rash most often appears on the trunk, but can also occur on other sites, such as the neck, forehead and genitals. Pain almost always accompanies the rash, but in rare cases the rash may be painless; this is more likely in children.[8] Immunocompromised people may have an atypical presentation of shingles, e.g. a widespread non-dermatomal rash.

The first stage of the shingles rash is a brief erythematous and macular phase, which is often missed. Papules appear over the

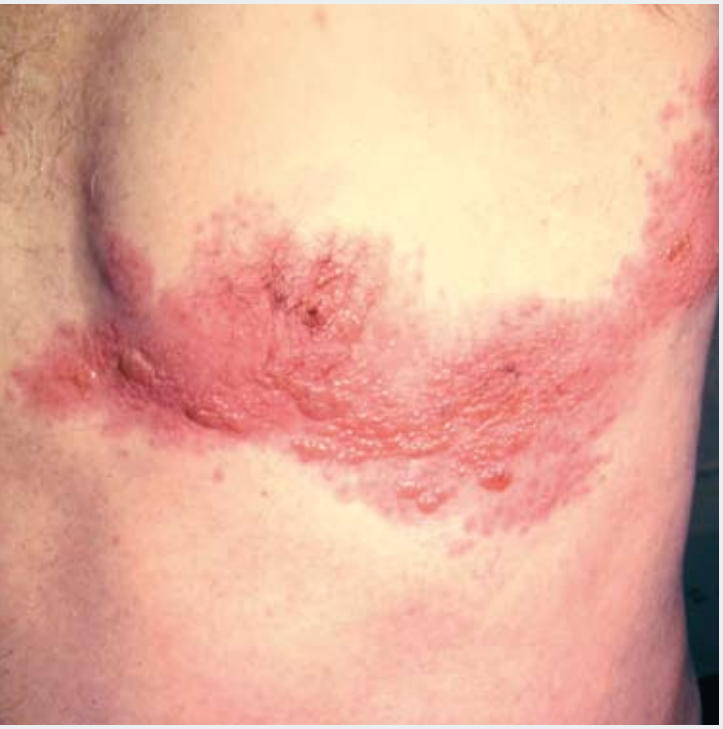

Figure 1: Unilateral shingles rash affecting a thoracic dermatome with slight extension past the midline (Supplied by Dermnet NZ)

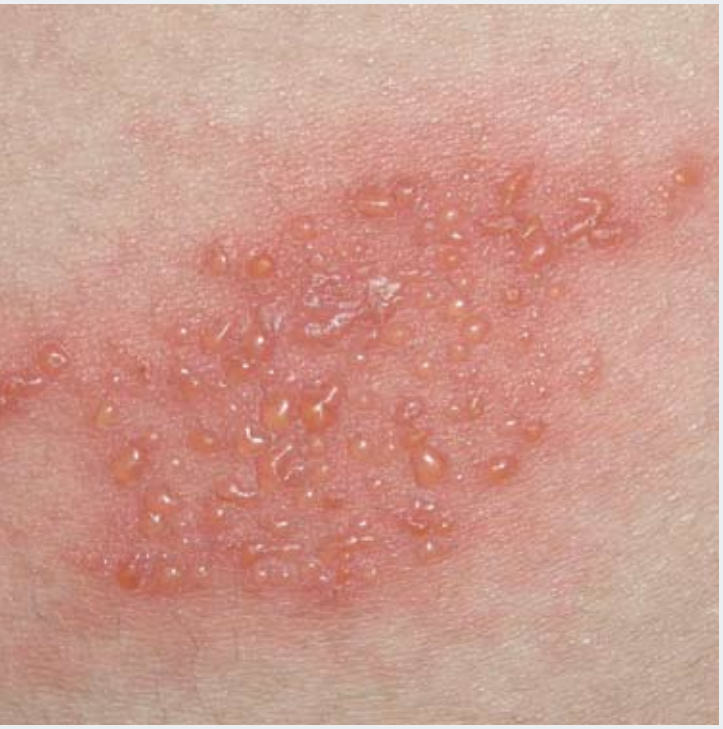

Figure 2: Characteristic vesicles due to shingles with background erythema (Supplied by Dermnet NZ)

next three to four days, and develop into vesicles within one to two days (Figure 2).[7] The vesicles then begin to pustulate within one week, followed by ulceration (which may appear black) and crusting three to five days later.[7]

Rubbing from clothing and scratching can irritate the rash, resulting in infectious lesions if vesicles burst. If this occurs, the virus can be transmitted via contact with fluid from the lesions to people who have not been previously exposed to VZV, resulting in chicken pox.[8] Transmission of VZV most often occurs to very young children and only occasionally to adults.[1]

Resolution

After the vesicles crust over, usually within ten days of onset of rash, the patient is no longer infectious. Crusted lesions may persist for a further two to four weeks.[4] Healing may take longer in older patients and patients who are immunocompromised. If the lesions have burst there may be scarring or changes in skin colour that can persist for some time after the rash has resolved.[7]

Diagnosing shingles

Dermatomal rash and pain? Shingles can be diagnosed based on the presence of the distinctive, painful dermatomal rash. Shingles is likely to be difficult to diagnose in the prodrome stage, prior to appearance of rash. The differential diagnosis at this stage will vary widely and depend on the site and nature of the pain. Severe thoracic pain, for example, can be mistaken for cardiac or pleuritic chest pain.

Dermatomal pain, but no rash? Zoster sine herpete is a rare form of shingles that occurs without the rash; diagnosis is more challenging and is based on the presence of dermatomal pain and often laboratory investigation (see below).[4] Once diagnosed, zoster sine herpete is managed in the same way as shingles.

Dermatomal rash, but no pain? A patient with a rash but no pain is less likely to have shingles, although this can occur rarely, most often in young children.[8] Other dermatological conditions that may be considered include: herpes simplex, impetigo, atopic eczema or contact dermatitis.

Laboratory testing is rarely indicated

Laboratory testing to investigate suspected shingles is not routinely required. However, there are three tests for shingles available, which may be requested if there is diagnostic uncertainty, e.g. to differentiate between herpes simplex and

herpes zoster or if shingles without a rash is suspected:

- Testing of cells from the base of a vesicle for the presence of VZV by immunofluorescent microscopy
- Real-time polymerase chain reaction (PCR), which can rapidly detect VZV DNA in skin lesion samples
- Serological testing, which can assess immunity to VZV

Both immunofluorescent staining and real-time PCR testing are useful for distinguishing *Herpes simplex* virus (HSV) from VZV.[9] Antibody testing can be used to confirm zoster sine herpete in patients without a rash but pain that is dermatomally distributed. The presence of VZV specific IgM antibodies in blood serum or cerebrospinal fluid indicates an acute infection.[10]

HIV testing may be considered in patients aged under 40 years with shingles, if there are other risk factors for HIV present.

If investigation of shingles is required talk to your local laboratory about which test is most appropriate to request.

Treatment and management of shingles

The goals of treatment for patients with shingles are to:

- Minimise the duration and severity of the rash
- Manage the associated pain

Patients should be advised not to scratch lesions to reduce the risk of transmission and avoid scarring, and to keep the lesions clean and dry. Patients should also be encouraged to avoid physical contact with other people, particularly immunocompromised people and infants aged under one year. Simple absorbent dressings can be used to cover the rash; adhesive dressings should not be used as they can delay healing and cause irritation.[6]

When vesicles pustulate, patients are at risk of secondary bacterial infection, usually with *Staphylococcus aureus* or *Streptococcus pyogenes*.[4] Topical antibiotics should not be used on the rash.[7] An oral antibiotic, e.g. flucloxacillin or cephalexin, is appropriate if secondary infection occurs.

Calamine lotion is sometimes used for symptomatic relief to reduce itch and dry lesions, although the overall usefulness of calamine lotion for shingles is limited. Antiseptics should not generally be used for the prevention of infection due to a lack of evidence that they are effective and uncertainly as to whether use of antiseptics promotes resistant strains of bacteria.

The role of antiviral medicines

There is much debate as to whether antiviral medicines are useful in the management of patients with shingles. They may have a modest effect on reducing the severity of shingles in the acute stage, but there is conflicting evidence as to whether they reduce the incidence of post-herpetic neuralgia. A recent review concluded that they were ineffective for this indication.[11]

Antiviral medicines are reported to reduce the duration of viral shedding and new lesion formation and accelerate rash healing time when given to patients in the early stages of shingles.[7] In a systematic review of evidence of antiviral treatment for post-herpetic neuralgia, four trials showed some evidence that patients with shingles treated with aciclovir within 72 hours of rash onset had a reduction in the incidence of acute pain (i.e. herpetic neuralgia) four weeks after the rash.[11]

Antiviral medicines have not, however, been conclusively shown to reduce the likelihood of patients with shingles developing post-herpetic neuralgia. A systematic review of evidence found that there was no significant difference in the incidence of post-herpetic neuralgia (pain persisting for at least 120 days after onset of rash) after four or six months in patients initially treated with either oral aciclovir or famciclovir compared to placebo.[11] The authors concluded that taking antiviral medicines within 72 hours of onset of rash, does not significantly reduce the subsequent incidence of post-herpetic neuralgia.[11]

Keeping in mind the limitations of treatment effectiveness, antiviral medicines may be considered for patients with:[6]

- Age > 50 years
- Ophthalmic involvement
- Immunocompromised status
- Atypical presentation of rash, e.g. shingles affecting the neck, limbs or perineum
- Moderate or severe pain
- Moderate or severe rash

Although likely to be most effective if given within 72 hours of rash onset, antiviral medicines may still be considered up to seven days after rash onset if the patient has an increased risk of severe shingles or complications, e.g. severe rash, severe pain, older age or immunocompromised.[6]

Oral aciclovir is first-line if antiviral treatment is given

Aciclovir 800 mg, five times daily, for seven days is the recommended first-line antiviral treatment for a patient with

shingles.[12] For patients with an estimated glomerular filtration rate (eGFR) of 10 – 25 mL/min/1.73m^2, the dose should be reduced to 800 mg, three times daily; 800 mg, twice daily, is appropriate for patients with eGFR < 10 mL/min/1.73m^2.[6]

Valaciclovir is an alternative antiviral

Valaciclovir is reported to have greater overall effectiveness than aciclovir as it produces higher levels of antiviral activity in blood.[7] Therefore, it may be a better alternative to aciclovir in patients at increased risk of complications, however, it is only subsidised for specific patients. The Special Authority criteria for valaciclovir in patients with shingles are:[12]

- Patients with a previous history of ophthalmic zoster and who are at risk of vision impairment **OR**
- Patients who are immunocompromised and valaciclovir treatment is to be no longer than seven days

The recommended dose for shingles is valaciclovir 1000 mg, three times daily, for seven days.[12] For patients with an eGFR between 30 – 50 mL/minute/1.73m^2, the dose should be reduced to 1000 mg, twice daily.[6]

N.B. Famciclovir is used in other countries as an antiviral treatment for shingles. This medicine is available in New Zealand, but is not subsidised and herpes zoster is not an approved indication.[12]

Treatment for patients who are immunocompromised

It is appropriate for patients with shingles who are immunocompromised to be managed in primary care if the rash is localised and they do not have systemic symptoms. VZV pneumonia, encephalitis and hepatitis are complications of shingles that are frequently reported in immunocompromised patients.[10] Specialist advice or referral should be sought immediately if:[6]

- The rash is severe, widespread or affecting multiple dermatomes
- Systemic symptoms are present
- The patient is severely immunocompromised, e.g. haematological malignancy, organ transplant recipient

Aciclovir is the recommended first-line antiviral treatment for shingles in patients who are immunocompromised, however, treatment should be given for ten days instead of seven.[6] Valaciclovir is an alternative.[6]

The role of corticosteroids

The role of corticosteroids in the treatment of shingles is even less clear than antiviral treatment. Oral corticosteroids are unlikely to significantly benefit the majority of patients with shingles and do not reduce the incidence of post-herpetic neuralgia. The decision on whether or not to prescribe must take into account the patient's individual risk of corticosteroid treatment.[6]

Although subject to much debate, some reviews recommend that corticosteroids may be considered alongside antiviral treatment, to treat acute neuralgia associated with shingles.[3, 7] The United Kingdom's NICE guidance recommends that oral corticosteroids may be considered in the first two weeks following onset of rash, but only in patients with severe pain who are immunocompromised.[6]

A meta-analysis of aciclovir alone compared to aciclovir with corticosteroids failed to show a benefit of corticosteroids in improving quality of life or reducing post-herpetic neuralgia.[13]

Managing associated pain

A step-wise approach can be taken to treating both acute neuralgia and post-herpetic neuralgia, adjusted according to the severity of the patient's symptoms.

Almost all people with shingles will experience acute neuralgia. Paracetamol or a non-steroidal anti-inflammatory drug (NSAID) (unless contraindicated) is recommended first-line.[6] Treatment can then be stepped up as required, depending on the severity of symptoms (Table 1). Options for moderate to severe pain include codeine, tramadol, morphine, tricyclic antidepressants and gabapentin.[3]

Post-herpetic neuralgia occurs in up to one-third of patients with shingles.[3] It is treated the same as for other types of neuropathic pain (Table 1). In general, topical treatment such as capsaicin can be trialled in patients with mild pain or with contraindications to systemic treatment. If pain is moderate to severe, traditional treatments for neuropathic pain, including tricyclic antidepressants and gabapentin, can be trialled. If pain is still unmanaged, opioid analgesics may be considered, but referral to a pain management specialist may also be considered.[3]

Table 1: Medicines for treatment of acute and post-herpetic neuralgia[6, 12]

Medicine	Typical dose	Notes
Paracetamol	0.5 – 1 g, every 4 – 6 hours; maximum 4 g daily	Paracetamol can be combined with other medicines if required, e.g. codeine, tramadol
NSAIDs	Ibuprofen: 200 – 400 mg, three to four times daily; maximum 1200 mg daily Naproxen: 250 – 500 mg, twice daily; maximum 1000 mg daily	Be aware of contraindications and cautions for NSAID use, e.g. people with renal impairment, gastrointestinal ulcer
Codeine	15 – 60 mg, every 4 hours, as necessary; maximum 240 mg daily	If a patient requires a high dose of codeine or tramadol, pain relief may be better achieved with the equivalent dose of morphine
Tramadol	50 – 100 mg, up to every 4 hours; maximum 400 mg (300 mg for elderly) daily	
Topical capsaicin	0.075% cream (Zostrix HP): pea-sized amount rubbed in to affected area, 3 – 4 times daily	Topical capsaicin is indicated for use on healed lesions in patients with post-herpetic neuralgia, and is available fully subsidised (with endorsement for post-herpetic neuralgia). Topical capsaicin is not generally used for acute shingles rash as application to broken skin (i.e. burst vesicles) causes a painful burning sensation.
Tricyclic antidepressants	Nortriptyline: initially 10 mg, once daily at night, gradually increased if necessary N.B. Dose for patients with shingles should generally not exceed 75 mg daily Amitriptyline is an alternative	There is little difference in analgesic efficacy between TCAs, however, nortriptyline is usually better tolerated and less associated with sedation than amitriptyline,[6] therefore it is the preferred choice. TCAs are associated with anticholinergic adverse effects, e.g. dry mouth and blurred vision. TCAs should be used with caution in people with cardiovascular disease, and are contraindicated in people with arrhythmias. For further cautions see NZF.[12]
Gabapentin	300 mg, once daily on day 1, then 300 mg, twice daily on day 2, increasing to 1.8 g daily in 2 or 3 divided doses	Gabapentin is a second-line option for neuropathic pain. It is available fully subsidised under Special Authority, which requires that treatment with TCAs has been tried without success/tolerance. Doses need to be adjusted in patients with renal impairment (see NZF)[12] Pregabalin is an alternative to gabapentin for neuropathic pain in patients with shingles,[6] but is not subsidised (see NZF for further details).[12]

For further information on treatment of neuropathic pain, see "Pharmacological management of neuropathic pain", BPJ 16 (Sept, 2008).

Vaccination for prevention of shingles

Zostavax vaccination is available (unsubsidised) for protection against shingles. A 2012 meta-analysis showed that older adults who had received the zoster vaccine had a 50% reduced incidence of shingles compared with those who had a placebo vaccination.[16] The vaccine was most effective in people aged 60 – 69 years (64% reduced incidence of shingles).[16] A related meta-analysis was inconclusive as to whether zoster vaccination prevents post-herpetic neuralgia in patients who get shingles despite vaccination.[17]

A single dose of Zostavax may be considered for people aged over 50 years, irrespective of exposure to chicken pox or previous occurrence of shingles.[18] It is contraindicated for immunocompromised people, women who are pregnant, people with active untreated tuberculosis, and people with known anaphylactic reactions to any component of the vaccine.[12,18]

Zostavax contains the same live attenuated Oka strain as the varicella (chickenpox) vaccine, Varilrix,[12] however, vaccination with the varicella vaccine will not protect against reactivation of VZV. This is because the two vaccines are of different strengths – the shingles vaccine is up to 14 times more potent than the varicella vaccine.[8]

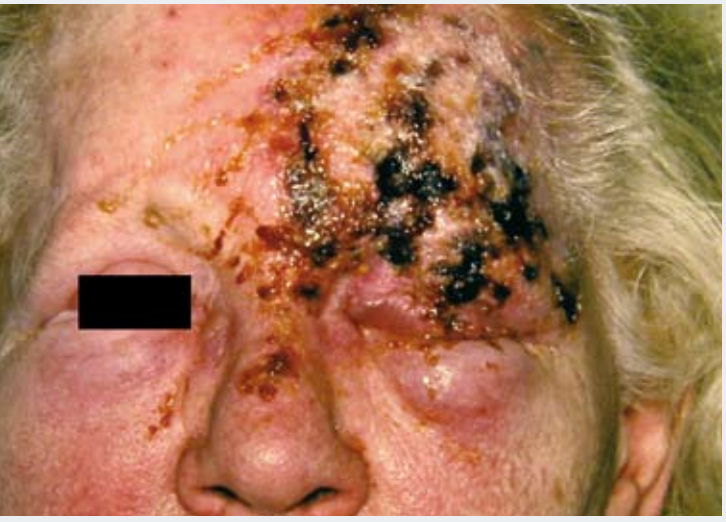

Figure 3: Herpes zoster ophthalmicus

(Supplied by Dermnet NZ)

Detecting and managing complications of shingles

Post-herpetic neuralgia is the most frequent complication

Post-herpetic neuralgia is defined as pain lasting for more than 120 days after onset of the shingles rash.[7, 11] Most cases resolve spontaneously, but pain can persist for several months or even years.[4, 11] In rare cases, post-herpetic neuralgia may first appear months to years after resolution of the acute shingles episode.[3] Often this is precipitated by a painful event, e.g. surgical procedure or tooth abscess,[3] and the patient may not connect the pain with their past shingles episode.

Post-herpetic neuralgia usually occurs in the same dermatome as the rash, and is felt as a burning or shooting pain, itch, numbness or increased sensitivity to pain or touch.[3, 8] Patients often experience abnormal sensations in the affected dermatome (and sometimes extended beyond the margins), e.g. areas of anaesthesia, or lack of response to thermal, tactile, pinprick or vibration sensation.[3]

Post-herpetic neuralgia is the most frequent complication of shingles; estimates of prevalence range from 9 – 34% of patients with shingles.[3] However, age is the most important risk factor; it is estimated that 30% of patients aged over 80 years and 20% of patients aged 60 – 65 years experience post-herpetic neuralgia.[4] It is rare in patients aged under 50 years.[4] Increasing age is also associated with increasing severity of the post-herpetic pain.[3] Other risk factors for post-herpetic neuralgia include: severe pain when the shingles rash is present, greater severity of the rash and ophthalmic location of the rash.[3, 4]

Herpes zoster ophthalmicus

Herpes zoster ophthalmicus occurs when shingles affects the ophthalmic branch of the trigeminal nerve (the 5th cranial nerve). It is estimated to represent 5 – 25% of all cases of herpes zoster.[4, 14, 15] Patients with herpes zoster ophthalmicus should be urgently referred to a Ophthalmologist, particularly if they have visual symptoms, corneal epithelial defect on fluorescein examination or Hutchinson's sign (see: Best Practice Tip),[6] as it can lead to permanent vision loss and cranial nerve palsies.[4]

The symptoms and signs of herpes zoster ophthalmicus are the same as for shingles affecting other areas, but patients present with a periorbital distribution of the rash, and all parts of the eye innervated by the ophthalmic branch of the trigeminal nerve can be affected (Figure 3). A small number of patients may develop conjunctivitis, keratitis or uveitis.[14, 15]

For further information on investigating a patient with "red eye" see: "Causes, complications and treatment of a red eye", BPJ 54 (Aug, 2013).

Best Practice Tip: Hutchinson's sign refers to the presence of vesicular lesions on the nose due to involvement of the nasociliary branch of the trigeminal nerve.[14] Although uncommon, this sign gives a reliable prediction of ophthalmic complications in a patient with herpes zoster ophthalmicus.

Ramsay Hunt syndrome type II

Ramsay Hunt syndrome type II, also known as herpes zoster oticus, is a rare complication of shingles involving the geniculate ganglion of the facial nerve. A patient with Ramsay Hunt syndrome generally presents with lesions in the ear and side of the tongue and facial paralysis.[7] Other symptoms may include loss of taste and, if the vestibulocochlear nerve is affected, vertigo and tinnitus. Ramsey Hunt syndrome may initially be difficult to differentiate from Bell's palsy,[2] however, Bell's palsy is usually painless and does not affect the ear or tongue.

Other rare complications of shingles include encephalitis, myelitis, hemiparesis, pneumonia and meningitis.[4, 6]

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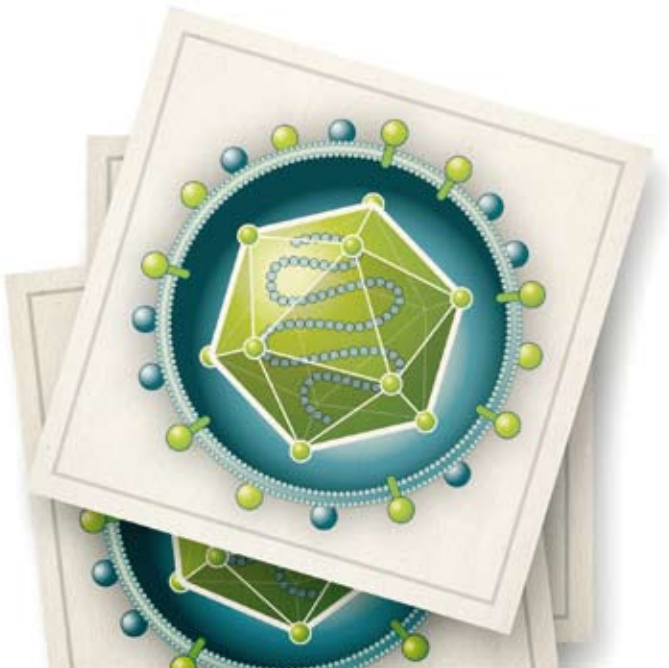

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