CLINICAL REVIEW

Herpes zoster

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Herpes zoster is a clinical manifestation of the reactivation of latent varicella zoster virus infection. It is a cause of considerable morbidity, especially in elderly patients, and can be fatal in immunosuppressed or critically ill patients. The pain associated with herpes zoster can be debilitating, with a serious impact on quality of life, and the economic costs of managing the disease represent an important burden on both health services and society.[1] Here we provide an overview of the disease and a summary of "best practice guidance" for the management of herpes zoster and its sequelae.

What is herpes zoster and who gets it?

Herpes zoster, or shingles, is the painful eruption of a rash, usually unilateral, caused by the varicella zoster virus. Varicella zoster virus usually persists asymptomatically in the dorsal root ganglia of anyone who has had chickenpox, reactivating from its dormant state in about 25% of people to travel along the sensory nerve fibres and cause vesicular lesions in the dermatome supplied by that nerve.

Herpes zoster is more common in people with diminished cell mediated immunity. This includes elderly people, patients with lymphoma, those receiving chemotherapy or steroids, and people with HIV. In contrast to herpes simplex, precise triggers for herpes zoster are not known.

How common is herpes zoster in general practice?

Population based studies show that the incidence of herpes zoster rises with age from approximately 2-3/1000 patient years in people aged 50 to 8/1000 patient years in those aged 70 and over.[2] The average general practice of 1500 patients would therefore expect to have between three and five cases a year.

Sources and selection criteria

We searched Pubmed (2001-6) by using the terms "herpes zoster OR postherpetic neuralgia" with the limits "meta-analysis and randomised controlled trial." We searched all reviews in the Cochrane library with the same terms. We also reviewed recent recommendations made by an expert body on the management of herpes zoster sponsored by the International Association for the Study of Pain, the Neuropathic Pain Institute, and the VZV Foundation. We also drew heavily on published management guidelines from the British Infection Society, the International Herpes Management Forum, the German Dermatology Society, and the Quality Standards Subcommittee of the American Academy of Neurology

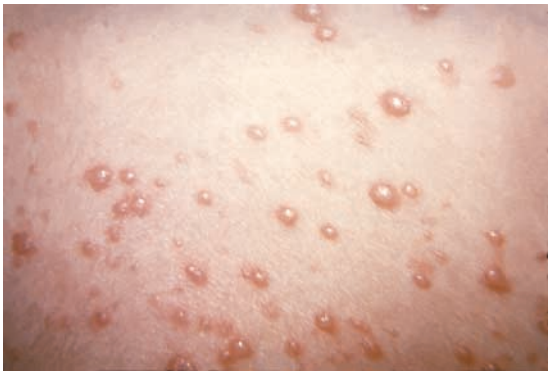
What are the clinical features?

Replication and transmission of the virus in the nerves and skin lead to the cardinal features of herpes zoster—pain and rash. In some people the rash is preceded by a prodromal phase lasting 48-72 hours or longer, consisting of throbbing pain and paraesthesia in the region of the affected sensory nerve. This may sometimes be confused with other acute medical conditions such as angina, cholecystitis, or renal colic, depending on the dermatome involved. The rash of herpes zoster is typically vesicular, affects a single dermatome, and lasts for three to five days before the lesions pustulate and scab (figure).

In immunocompetent patients, the most frequent site of reactivation is the thoracic nerves followed by the ophthalmic division of the trigeminal nerve (herpes zoster ophthalmicus), which can progress to involve all structures of the eye.[3] If the mucocutaneous division of the VII cranial nerve, which innervates the ear and side of the tongue, or the VIII cranial nerve is involved, the development of lesions in the ear, facial paralysis, and associated hearing and vestibulary symptoms are known as Ramsay Hunt syndrome. Herpes zoster may also cause facial nerve palsy without vesicles occurring in the external meatus. Other rare complications include encephalitis, myelitis, retinitis, and hemiparesis, all of which are more common in immunocompromised patients.[4]

How is herpes zoster diagnosed?

Herpes zoster can usually be diagnosed clinically. However, early zoster and zoster presenting in the sacral and cervical area may be difficult to distinguish from herpes simplex. In these cases, the diagnosis can be confirmed by sending swabs to the local virology laboratory, but treatment should not be delayed while waiting for test results. The top of the lesion should be lifted and a sterile swab used to rub the base of the lesion. The swab should then be wiped across a sterile glass side or over three wells on a Teflon coated slide. The slide should be air dried and sent to the laboratory for staining with immunofluorescent antibodies. The swab can also be placed



CDC

Rash of herpes zoster

in viral transport medium or sterile saline, which is suitable for transporting to the laboratory within the next one to three days for detection of viral DNA by polymerase chain reaction.

Reactivation of varicella zoster virus in immunocompromised patients, especially those who have had bone marrow or solid organ transplants, may spread to involve the gut, liver, and other viscera. Although a typical rash is common, some cases present with abdominal pain and no evidence of rash. In the absence of rash, the diagnosis can be confirmed by measuring virus in the blood by polymerase chain reaction.[w1]

How serious is herpes zoster?

The rash is accompanied by severe pain, which, in some people, does not subside after healing but persists for months or years. This prolonged zoster associated pain, usually defined as pain persisting for more than four months after the rash has healed, is known as postherpetic neuralgia and is the most common complication of herpes zoster. The pain can be debilitating, exacerbated by the slightest touch, and lead to loss of employment, depression, and social isolation. Identification of patients at risk of developing postherpetic neuralgia is therefore crucial, as they stand to gain most from treatment. Several clinical and laboratory parameters have been suggested and evaluated as risk factors predicting postherpetic neuralgia (box 1), but they are by no means exhaustive.[5 6]

Health economic studies estimate that shingles and postherpetic neuralgia cost the United Kingdom up to £73.8m (€108m; $147m) a year. The main medical costs—drugs, visits to the general practitioner, and hospital admissions—equate to between £74 and £198 for each episode of acute herpes zoster and £777 for each episode of postherpetic neuralgia.[7] In patients aged under 65, acute herpes zoster is estimated to cost £526 per episode when the costs to wider society resulting from loss of productivity are also included.[8]

How is herpes zoster treated?

Many trials have compared interventions, concentrating on reductions in severity of pain as the key outcome measure. As zoster associated pain is a continuous spectrum ranging from the pain of the prodrome to the pain of established postherpetic neuralgia, considerable heterogeneity exists in the populations studied, making comparisons of the efficacy of agents across studies difficult. Also, as the severity of pain during an acute attack is an important predictor for the development and the severity of postherpetic neuralgia, interventions used during the acute phase may influence the outcome of interventions subsequently used to treat postherpetic neuralgia. Nevertheless, as clinicians are most likely to be confronted with either a patient with a herpes zoster rash or a patient with established postherpetic neuralgia, we will cover these two problems as separate entities.

What is effective treatment for an acute attack of herpes zoster?

Table 1 shows the drugs available for treating acute herpes zoster in immunocompetent adult patients.

Table 1 | Treatment of acute herpes zoster in immunocompetent adults

Drug	Dose/frequency	Treatment duration	Efficacy	Notes
Aciclovir	800 mg five times daily*	7-10 days	Reduces acute pain and development of PHN	Most effective if started within 72 hours of onset of rash
Famciclovir	750 mg daily* or 250 mg three times daily	7 days	Reduces acute pain and development of PHN	Most effective if started within 72 hours of onset of rash
Valaciclovir	1 g three times daily*	7 days	Reduces acute pain and development of PHN	Most effective if started within 72 hours of onset of rash
Brivudin	125 mg daily	7 days	Reduces acute pain and development of PHN	Licensed for treatment in Austria, Belgium, Germany, Greece, Italy, Luxembourg, and Spain
Prednisolone	60 mg daily initially, then taper dose	21 days	Reduces acute pain	Use only in combination with antivirals. Reduce dose to 30 mg after 7 days and to 15 mg after a further 7 days, then stop
Amitriptyline	25 mg daily	3 months	Reduces incidence of PHN; effect on acute pain uncertain	Use with care in elderly patients. An electrocardiogram should be done before treatment

PHN=postherpetic neuralgia.
*Dose given in *British National Formulary*.

Table 2 | Summary of evidence based treatments for established postherpetic neuralgia

Drug class and supporting studies	Study design	Measure of treatment effect (95% CI)
Tricyclic antidepressants		
Amitriptyline *v* placebo[w6]	Double blind, placebo controlled, crossover trial	ARR=65%; NNT=1.6 (1.2 to 2.4)
Amitriptyline *v* lorazepam and placebo[w7]	Randomised, placebo controlled, multi-armed, crossover trial	NNT=3.2 (2.1 to 6.6)
Amitriptyline *v* nortriptyline[w8]	Randomised, double blind, placebo controlled, crossover trial	NA
Amitriptyline *v* maprotiline[w9]	Randomised, double blind, crossover trial	NNT=32 for amitriptyline
Desipramine *v* benztropine[w10]	Randomised, active placebo controlled trial	ARR=63%; NNT=1.6 (1.1 to 2.6)
Anticonvulsants		
Gabapentin *v* placebo[w11]	Randomised, dose titrated, double blind, placebo controlled trial	NNT=2.2 (1.7 to 3.0); NNH=10.3
Gabapentin *v* placebo[w12]	Randomised, dose titrated double blind, placebo controlled trial	ARR=29.5%; NNT=5.3 (3.6 to 10.2); NNH=11.2
Pregabalin *v* placebo[w13]	Randomised, placebo controlled trial	NNT=3.3 (2.3 to 5.9); NNH=3.7
Opioids		
Oxycodone *v* placebo[w14]	Double blind, placebo controlled, crossover trial	ARR=65%; NNT=2.5 (1.7 to 5.1); NNH=38
Morphine or methadone *v* nortriptyline/ desipramine and placebo[w15]	Double blind, placebo controlled, crossover trial	NNT=3 (2 to 5.5) for opioids; NNT=6.2 (3.2 to 294) for tricyclics
Tramadol *v* placebo[w16]	Randomised, placebo controlled trial	NNT=4.7 (2.9 to 19)
Topical lidocaine, aspirin, and capsaicin		
Lidocaine gel *v* placebo[w17]	Randomised, double blind, placebo controlled, crossover trial	NA
Lidocaine polyethylene patch *v* placebo[w18]	Enriched enrolment, randomised, double blind, placebo controlled trial	NNT=2 (1.4 to 3.3)
Aspirin cream *v* indometacin cream, diclofenac cream, and placebo[w19]	Randomised, double blind, placebo controlled, crossover trial	ARR=32%; NNT=3 (1.7 to 26.1)
Capsaicin *v* placebo[w20]	Randomised, double blind, placebo controlled trial	NNT=3.2 (2.1 to 6.3)

ARR=absolute risk reduction; NA=not available; NNH=number needed to harm; NNT=number needed to treat.

Systemic antivirals

Meta-analyses and randomised controlled trials suggest that the oral antiviral agents aciclovir, famciclovir, and valaciclovir started within 72 hours of the onset of rash reduce both the severity and the duration of acute pain,[9 10] as well as the incidence of postherpetic neuralgia.[11 12] The nucleoside analogue brivudin has been shown to be as effective as famciclovir but superior to aciclovir in both healing acute lesions and reducing postherpetic neuralgia.[13-15] The pharmacokinetics of oral antivirals differ considerably, so the patient's ability to adhere to a multiple dosing regimen should be considered when selecting an agent for treatment. Antiviral treatment is effective at an early stage when viral replication is still occurring. It should be given to patients who present within 72 hours of the onset of rash and to those aged over 50 with new vesicle formation or complications whenever they present.[16 17] Published guidelines advise that herpes zoster ophthalmicus should always be treated with antivirals and the advice of an ophthalmologist sought.[17] Likewise, visceral herpes zoster requires prompt admission to hospital and use of intravenous aciclovir (10 mg/kg, eight hourly).[17]

Corticosteroids

The addition of oral prednisolone to aciclovir treatment has been shown to reduce pain, speed healing of lesions, and enable a more rapid return to daily activities.[18] Coadministration of steroids and antivirals should therefore be considered for older patients with appreciable pain who do not have a contraindication to steroids (such as diabetes or peptic ulcer disease). Expert opinion also supports the use of steroids in the

Box 1 | Risk factors for development of postherpetic neuralgia after an attack of herpes zoster

- Advanced age (>50 years)
- Female sex
- Presence of a prodrome
- Severe or disseminated rash
- Severe pain at presentation (visual analogue score >5)
- Polymerase chain reaction detectable varicella zoster virus viraemia

Box 2 | Complications of herpes zoster ophthalmicus

- Conjunctivitis, episcleritis, and scleritis
- Keratitis, iridocyclitis
- Choroiditis, papillitis
- Oculomotor palsy
- Retinitis
- Optic atrophy

treatment of acute idiopathic facial palsy in combination with aciclovir.[17]

Although oral steroids are of benefit in the acute attack, they have not been shown to have an effect on preventing postherpetic neuralgia.[12] Likewise, a single dose of epidural methylprednisolone combined with a local anaesthetic is a useful addition to antiviral treatment for resolution of acute pain but has no effect on the development of postherpetic neuralgia.[19] Repeated administration of epidural steroids combined with continuous infusion of anaesthetic for up to 21 days has been shown to reduce postherpetic neuralgia,[20] but the risks and practicalities of interventions that need epidural administration remain to be resolved. The role of steroids in the management of herpes zoster is controversial, and the results of a systematic review of their efficacy in postherpetic neuralgia are awaited.[w2]

Tricyclic antidepressants

Tricyclic antidepressants have been widely used in the management of chronic neuropathic pain conditions.[w3] Use in the acute phase of herpes zoster in elderly patients has been evaluated in a randomised placebo controlled trail of amitriptyline. Effects on reduction of acute pain were not evaluated, but a reduction in the prevalence of postherpetic neuralgia at six months was reported in the amitriptyline treated group.[21] Although this trial provides some evidence for the efficacy of tricyclic antidepressants in preventing postherpetic neuralgia, antivirals were also given but only at the attending physicians' discretion. If prescribed, tricyclic antidepressants should be used with caution, especially in elderly patients, in whom anticholinergic side effects may precipitate acute confusion or cardiac arrhythmias.

Other agents

Although opioid analgesics and non-steroidal anti-inflammatory drugs are widely used in the management of acute pain syndromes, only the opioids oxycodone and tramadol have been subjected to formal trials in herpes zoster. Oxycodone reduces acute pain, but evidence for the prevention of postherpetic neuralgia is lacking; conversely, tramadol is efficacious in established postherpetic neuralgia but has not been studied for acute treatment.[22] A randomised controlled trial has recently shown that a single 900 mg dose of the anticonvulsant gabapentin reduces acute pain in herpes zoster.[23]

Management of acute ophthalmic zoster

Herpes zoster affecting the first division of the trigeminal nerve is particularly aggressive and must be treated with antivirals, even if more than 72 hours have elapsed since onset. Oral antiviral agents should be accompanied by topical antiviral cream applied to the eye and corticosteroids where appropriate.[17 w4] Box 2 shows the complications of acute ophthalmic zoster.

What is effective treatment in established postherpetic neuralgia?

An expert subcommittee of the American Academy of Neurology has done a systematic review of treatments for established postherpetic neuralgia.[w5] Several recommendations were made, the strength of the evidence supporting them was ranked, and where possible absolute risk reduction rate, number needed to treat, and number needed to harm were calculated. Tricyclic antidepressants, the anticonvulsants gabapentin and pregabalin, controlled released oxycodone or morphine sulphate, and lidocaine patches were all classed as moderately to highly effective. Some evidence of efficacy was also found for topical capsaicin and aspirin creams and for intrathecally administered methylprednisolone. Non-drug treatments such as transcutaneous electrical stimulation and acupuncture were also evaluated and found to be ineffective. Table 2 summarises the supporting evidence.

Can we prevent herpes zoster?

A live attenuated vaccine derived from the oka strain of varicella zoster virus has been shown to be highly effective in preventing primary varicella in children and was introduced into the US vaccination programme in 1996. A reduction in the number of cases of primary varicella zoster virus could have a major impact on the incidence of zoster in both the short term and longer

ADDITIONAL EDUCATION RESOURCES

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Resources for patients

Ramsey Hunt Organisation (www.ramsayhunt.org/)—This support group provides both general information and an online discussion forum for patients with Ramsay Hunt syndrome and neuropathic pain

VZV Research Foundation (www.vzvfoundation.org/)—Dedicated to combating all diseases caused by varicella zoster virus by providing research funding and educational material

American Academy of Family Physicians. Shingles patient information sheet (www.aafp.org/afp/20000415/2447ph.html)—A useful information sheet on shingles and its complications

After Shingles (www.aftershingles.com/index.html)—Extensive website providing advice for both patients and carers on the treatment of shingles and postherpetic neuralgia

SUMMARY POINTS

Herpes zoster and postherpetic neuralgia are common causes of debilitating neuropathic pain

Systemic antiviral agents reduce both the acute pain of herpes zoster and the incidence of postherpetic neuralgia

Corticosteroids, tricyclic antidepressants, gabapentin, and opioids reduce acute pain and may have additional effects on the reduction of postherpetic neuralgia

Tricyclic antidepressants, gabapentin, opioids, and lidocaine patches are effective in established postherpetic neuralgia

Large scale vaccination of children and older adults may have an important impact on the incidence of herpes zoster and postherpetic neuralgia

term. Although the eradication of primary varicella would also lead to the eradication of herpes zoster, the cell mediated immunity responsible for suppression of latent infection needs to be repeatedly boosted by exposure to wild type virus circulating in the community. Concern exists that a reduction in the number of childhood cases of varicella could lead to a short term increase in herpes zoster in latently infected people. Early analyses of the incidence of herpes zoster in the United States after introduction of the vaccination programme have yet to support this theory.[24] A large clinical trial of varicella zoster virus vaccine in adults aged over 60 in an attempt to boost waning immunity was recently reported.[25] The vaccine was found to be highly effective at reducing both the number of cases of herpes zoster and the incidence of postherpetic neuralgia, suggesting that this may be an extremely useful intervention for reducing the burden of herpes zoster disease.

Ongoing research

Herpes zoster and postherpetic neuralgia will remain important clinical problems for the foreseeable future. Several areas need further research, some of which are being tackled in ongoing studies. These include the development of biomarkers to identify people at risk of developing postherpetic neuralgia and clinical trials to determine exactly who should be treated when presenting more than 72 hours after onset of the rash. Research on the molecular pathogenesis of varicella zoster virus and mechanisms underlying latency will help in the design of more effective antiviral agents and inactivated (non-infectious) vaccines for use in immunocompromised patients.

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