

# Management of Acute Herpes Zoster

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## Introduction

Acute herpes zoster (AHZ) or “shingles” is one of the most common neurological conditions worldwide. It occurs as a result of a reactivated varicella zoster virus (VZV) infection. Anaesthetists and pain specialists may find themselves consulted to manage the often severe and disabling pain of an acute episode. To prevent progression to post herpetic neuralgia (PHN), a potentially crippling persistent disorder, early intervention is imperative. The purpose of this paper is to review current guidelines for the acute management of AHZ.

## Incidence & Risk Factors

The incidence of AHZ ranges from 1.9 to 11.8 per 1000 person-years.<sup>1</sup> The risk factors for developing AHZ include increasing age and compromised immunity, often in association with malignancy, immunosuppressive therapy, or bone marrow and organ transplantation. Increasing age is the major risk factor, as ageing is associated with reduced cell mediated immunity to VZV. Other risk factors which have been implicated are genetic susceptibility, psychological stress and mechanical trauma.<sup>2</sup>

## Features

Typically, there is a prodrome of symptoms including malaise, headache or photophobia. Prior to the onset of the rash, there may also be abnormal sensations ranging from dysaesthesia to severe pain. The rash is normally painful, although the degree of pain may range from mild to severe. The pain may be constant or intermittent and the character may vary. Most commonly, thoracic or cranial dermatomes are involved unilaterally.

The rash is maculopapular and progresses to vesicular lesions which normally heal within two to four weeks. The pain usually resolves at this time, but in some patients it persists and can be refractory to treatment.

## Diagnosis

As the features are usually typical, the diagnosis is primarily a clinical one. If the rash is atypical or the patient is immunocompromised and the diagnosis is unclear, laboratory confirmation is recommended. This can be performed either by direct culture of VZV from skin vesicles or direct immunofluorescence assay. It is also

possible to perform polymerase-chain-reaction on tissue or fluid, such as cerebrospinal fluid in VZV meningitis. This is the most sensitive test for detecting VZV. If a direct culture is not possible, detection of IgM and IgA anti-VZV antibodies may also be helpful for the diagnosis in immune-compromised patients.

### Pathophysiology

AHZ infection is caused by the reactivation of dormant VZV from a primary chickenpox infection. The virus travels from the dorsal root ganglia by retrograde axonal transport to a particular dermatome. It is unknown why it only affects certain dermatomes. The reactivation is accompanied by inflammation of the skin and damage to the peripheral nerves. Sympathetic activation results in vasoconstriction and impaired intraneural blood flow, which causes nerve ischaemia.<sup>3</sup> This may lead to a combination of both nociceptive and neuropathic pain.

### Complications of AHZ

The most common complication of AHZ is PHN. Others include ophthalmic involvement (corneal ulceration, uveitis and conjunctivitis), Ramsay-Hunt syndrome, cerebral complications (meningoencephalitis), secondary bacterial infection and disseminated zoster with systemic involvement. Ophthalmic involvement requires early referral to an ophthalmologist, as early effective treatment has been shown to prevent further ocular complications.<sup>5</sup>

### Prevention

There is concern that childhood vaccination may increase the incidence of HZV in adults, as a result of decreased adult exposure to HZV with a resultant reduction in HZV immunity.<sup>4</sup> The Shingles Prevention Study is a five year multicentred trial involving more than 38,000 patients, to evaluate the efficacy of an adult VZV vaccine. Its aims are to establish whether such a programme would increase adult immunity and reduce the reactivation of the latent infection. The results are due in the near future.

### Management

Management guidelines for AHZ are summarized in Table 1. The aims are to:

1. Reduce complications of AHZ
2. Accelerate rash healing
3. Reduce acute pain
4. Reduce the risk of Post Herpetic Neuralgia (PHN).

**Table 1**  
Management guidelines and levels of evidence

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#### Key points

1. Early aggressive analgesia
2. Oral antiviral agent (Level 1)
3. Amitriptyline 25mg nocte or 10mg in elderly (Level 2)
4. Consider epidural LA & corticosteroids (Level 2)
5. Supportive therapy, explanation and advice

#### Suggested criteria for referral to a multidisciplinary pain service

1. Severe uncontrolled acute pain
  2. Persistent pain (>1 month duration)
  3. Presence of 3 or more risk factors for PHN
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### *Analgesics*

Early and effective analgesia to decrease acute pain and the risk of development of PHN is imperative. Pathogenic models of PHN suggest that early treatment of acute pain may prevent the initiation of the central mechanisms which lead to persistent pain.<sup>6</sup> A stepwise approach using the WHO analgesic ladder including NSAID and, if necessary, opioid analgesia should be used. Oral opioid analgesia should be administered in an immediate release preparation in the first instance.

### *Antiviral Treatment*

Antiviral agents are now a standard part of acute management. There is strong evidence that they reduce the duration and severity of acute herpes zoster pain<sup>7</sup> and the incidence of progression to PHN.<sup>8</sup> There is no clear difference in outcome between the different antiviral agents, although the newer agents have simpler dosing regimes, due to their improved oral bioavailability.

Many guidelines state that antiviral agents should be given within 72 hours to be effective. However, this restriction should not be applied to patients with later presentations of ophthalmic zoster. Standard regimens include valaciclovir 1000 mg tds, famciclovir 250 mg tds or acyclovir 800 mg five times a day, all for seven days. Intravenous acyclovir remains the drug of choice for immunocompromised individuals with disseminated infection. Oral antiviral drugs should be used for elderly patients, those with ophthalmic zoster infection and younger patients with severe pain.<sup>9</sup> The low incidence of adverse effects and the treatment cost with these drugs are offset by the benefits.

### *Antidepressants*

In a randomized controlled trial involving 72 patients, amitriptyline 25 mg given for 90 days during the acute phase of herpes zoster reduced the prevalence of PHN at 6 months by more than 50%.<sup>10</sup> However, the potential adverse effects of tricyclic agents, including postural hypotension, cardiac dysfunction, sedation and increased risk of glaucoma, need to be considered. These side effects are more likely in the elderly and the potential advantages need to be weighed against the risks on a case by case basis.

### *Anticonvulsants*

There is evidence that anticonvulsants are effective for PHN.<sup>11</sup> There have also been unpublished open studies looking at the effect of anticonvulsants such as gabapentin in the management of AHZ.

A large multicentred randomized controlled clinical trial, the “Shingles Trial of Oral Medication to Prevent Post-herpetic Neuralgia” (STOMP-PHN) is currently underway. The participants will receive antiviral therapy with famciclovir and will be randomized to receive opioid analgesics, anticonvulsant (pregabalin) or placebo. The aims of the trial are to establish whether pregabalin is effective for AHZ pain and if its use in the acute phase decreases the incidence of PHN.

### *Corticosteroids*

Corticosteroids in combination with antiviral therapy have been shown to accelerate the rate of healing and alleviation of acute pain. This was accompanied by improved quality of life, better sleep pattern and accelerated return to normal activities. However, there was no effect on the incidence or duration of PHN.<sup>12</sup>

Due to the potential for complications such as disseminated infection, corticosteroids are not recommended for the treatment of every case of acute herpes zoster. In addition, some patients, such as those with preexisting diabetes or gastritis, may be at a higher risk of developing complications to steroids. The drugs may be considered for otherwise healthy adults with moderate to severe pain and should always be used in conjunction with antiviral agents.<sup>13</sup>

Topical corticosteroids may be used for some ocular complications such as keratitis or uveitis.

#### *Sympathetic blockade, including epidurals*

The sympathetic nervous system plays an important part in mediating pain in AHZ. Epidural local anaesthesia provides sympathetic blockade increasing the intraneural blood flow which may reduce ischaemia and pain. They also block afferent transmission of the pain signal.<sup>14</sup> The use of epidural corticosteroids may decrease swelling-induced neuronal ischaemia,<sup>15</sup> thus reducing the incidence of PHN.

Kumar et al reviewed the use of epidural and other sympathetic blocks in the management of AHZ and PHN.<sup>16</sup> They found that 80% of trials involving AHZ showed a beneficial effect. However, there was a lack of good quality evidence for the use of sympathetic blocks alone. The evidence for the use of the combination of epidural local anaesthetic and steroid is based on a randomised controlled trial by Pasqualucci involving 600 patients with AHZ. There was a significant benefit both for acute pain and pain at one year.<sup>17</sup>

The PINE study is a multicentred trial in the Netherlands, which randomised 550 elderly patients with AHZ (rash <7 days) to receive either standard treatment (analgesia and antiviral) or epidural LA and steroid. The results, due to be published in 2005, should determine whether the use of epidural steroids reduces the incidence of PHN. Cost effectiveness and effect on quality of life are secondary outcome measures of this study.

#### *Topical agents*

Topical aspirin, suspended in a volatile substance such as chloroform, has been shown to reduce the pain of AHZ in several small studies.<sup>18</sup> However, such mixtures are potentially unstable and therefore are not used routinely.

Although topical lignocaine cream has been shown to be effective, there are practical difficulties in its application. Topical lignocaine 5% patch (Lidoderm) is reserved for the treatment of PHN and is not recommended for the management of AHZ, as use on non-intact skin may result in high blood concentrations of lignocaine from increased absorption.<sup>19</sup>

#### *Supportive therapy*

Patients should keep the lesions clean and dry to reduce the risk of secondary bacterial infection.<sup>21</sup> They should also be aware they will shed VZV for several days until the lesions are dry. They should therefore avoid contact with children or adults with no history of a previous VZV infection, pregnant women and immunocompromised individuals.

#### *Risk factors for PHN*

The overall risk is of developing PHN following AHZ is 10%, but is 50% in the presence of three or more risk factors including more advanced age, female sex,

presence of a prodrome, greater rash severity and greater acute pain.<sup>20</sup> Other studies have found ophthalmic involvement increases the risk.<sup>20</sup> PHN is often refractory to treatment and can lead to impaired physical, social and emotional functioning, including depression.

### Conclusion

Acute herpes zoster infection is an often painful condition which may progress to persistent pain. It is imperative to manage the symptoms early and aggressively. Evidence based management guidelines are useful for both the primary care physician and the specialist. The management of AHZ may affect the patient's outcome including future quality of life. Future studies should address the effect of management on both pain and quality of life.

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