Herpes zoster infection is caused by a reactivation of the latent varicella zoster virus that causes chickenpox. It appears predominantly in older adults whose immunity for the virus has waned.

The natural course of the disease is usually favorable, and the symptoms disappear spontaneously within a few weeks. Some patients, however, have prolonged pain: post-herpetic neuralgia.

The diagnosis of acute zoster infection is made on the clinical signs including the appearance of rash. Post-herpetic neuralgia is described as sharp, burning, aching, or shooting constantly present in the dermatome that corresponds with the earlier rash.

The objectives of treating herpes zoster are: (1) acute pain reduction; (2) promotion of recovery of epidermal defects and prevention of secondary infections; and (3) reduction or prevention of post-herpetic neuralgia.

The objective of the treatment of post-herpetic neuralgia is primarily pain alleviation and improvement of the quality of life.

Early treatment of the infection and the pain is believed to reduce the risk for post-herpetic neuralgia. This persistent pain syndrome is difficult to treat. Antiepileptic drugs and tricyclic antidepressants are the first choice.

Interventional treatments, such as epidural injections of corticosteroids and local anesthetic drugs, have an effect on the acute pain but are of limited use in preventing post-herpetic neuralgia. When conservative treatment fails in providing satisfactory relief of post-herpetic neuralgia, a sympathetic block may be considered (2 C+); if this treatment provides unsatisfactory results, spinal cord stimulation may be considered, in a study context (2 C+).

Key Words: evidence-based medicine, herpes zoster, post-herpetic neuralgia, epidural injection, vaccination

INTRODUCTION

This review on herpes zoster and post-herpetic neuralgia (PHN) is part of the series “Evidence-Based Interventional Pain Medicine According to Clinical Diagnoses.” Recommendations formulated in this chapter are based on “Grading strength of recommendations and quality of evidence in clinical guidelines” described by Guyatt.
et al. and adapted by van Kleef et al. in the editorial accompanying the first article of this series (Table 1).

The latest literature update was performed in February 2010. Herpes zoster is a viral condition that appears mainly in older people. The incidence in the Dutch population is 3.4 per 1,000 people per year; in a population above 75 years, this amounts to 9.1 per 1,000 people per year. Approximately 20% of all people are affected by herpes zoster in their lifetime. In contrast to other herpes infections, herpes zoster relatively rarely relapses. Only a small percentage of patients are referred to the hospital by their family doctor, this mainly for the management of severe pain.

There is no consensus about the definition of PHN. It is usually defined as a zoster-related pain, which is still present 1 month after the development of the vesicles. Sometimes, however, this persists for a period of 3 to 6 months. In clinical trials, a cutoff pain intensity of 30 on a 100-point scale is used. Obviously, the definition used influences the reported incidents of PHN. This can vary from 10% to more than 50%. The risk for PHN increases with age. Figure 1 represents an estimated natural course of pain from herpes zoster and PHN.

Even though persistent serious pain occurs in a small percentage of herpes zoster patients, in those affected, it can have great consequences. Their quality of life is largely affected, not only directly by the pain, but also indirectly by fatigue, and diminished mobility and social contacts.

**PATHOPHYSIOLOGY**

Herpes zoster develops through reactivation of the varicella zoster virus (VZV), which infects people during childhood and leads to chicken pox (varicella). After recovery from chicken pox, the virus becomes latent in the sensory ganglia. The specific immunity to the virus gradually reduces with age, and the virus can overcome this defense. The virus disperses from the ganglia via the axon to the epidermis where it causes the characteristic unilateral rash of herpes zoster in one or, sometimes, a few dermatomes. The vesicles contain a virus and are therefore infectious to people who have not yet built up a natural defense. It is possible for grandparents with herpes zoster to be the source of chicken pox for one of their grandchildren. The reverse, however, is impossible. To the contrary, contact with chicken pox can reinforce the resistance against VZV, which reduces the risk for herpes zoster.

The pain from herpes zoster primarily develops because of inflammation of the sensory nerves.

The pathophysiology of PHN is not fully understood yet. In any case, two processes play a role: sensitization and deafferentation. Peripheral sensitization develops because inflammatory mediators, such as substance P, histamines, and cytokines reduce the stimulus threshold of nociceptors. Central sensitization is related to an increasingly stronger response from nerve cells in the occipital horn to continuous stimulation by nociceptive C fibers. Deafferentation can develop through the rep-
lication of the virus in the cell and/or the subsequent inflammatory reaction. The swelling accompanying the inflammation can compress the sensory ganglion in the intervertebral foramen, resulting in ischemia and nerve tissue damage. In addition, Schwann cell activation may play a role.

I. DIAGNOSIS

I.A HISTORY

Patients with herpes zoster report unilateral symptoms in the dermatome that corresponds with the affected spinal ganglion. In addition to pain, there are paresthesias, dysesthesias, and pruritus. Likewise, general malaise, fever, and headache may occur. These symptoms usually begin as a prodrome a few days before the rash occurs.

The dermatome-related pain is described as burning, throbbing, numbing, and itching.

Patients with post-herpetic neuralgia describe the pain as being sharp, burning, aching, or shooting that is constantly present in the dermatome that corresponds with the earlier rash. Stimulation-induced pain, allodynia, and hyperalgesia are often present. Wearing clothes can be very unpleasant or even painful for these patients.

I.B PHYSICAL EXAMINATION

During the acute phase, the patient shows the typical rash with redness, papules, and vesicles in the painful dermatome. Healing vesicles show crust formation. The rash is generally unilateral and does not cross the midline of the body. Concomitant sensory defects such as hypesthesia, hyperalgesia, or allodynia frequently occur. Motor defects are rare. The painful area can increase in size and exceed the limits of the affected dermatome with PHN.

I.C ADDITIONAL TESTS

Additional laboratory testing, such as polymerase chain reaction (PCR), can establish or rule out the presence of herpes simplex virus when there is an atypical presentation of epidermal rash and relapsing rash in the same area.

A strong increase of antibody titer can establish the so-called zoster sine herpete if dermatome-related pain is present without vesicles.

I.D DIFFERENTIAL DIAGNOSIS

During the prodromal phase and depending on the dermatome involved, there is a long list of possible differential diagnoses, such as coronary artery disease, pleurodynia, costochondritis (Tietze’s syndrome), pericarditis, cholecystitis, acute abdominal diseases, disk diseases, nerve diseases, and myofascial pain. The diagnosis of herpes zoster is usually easy to establish as soon as the rash is visible. However, in 10% to 20% of the cases, it turns out that the clinical diagnosis of herpes zoster cannot be confirmed with serology or PCR. The distinction from herpes simplex is somewhat difficult in young people. In contrast to herpes zoster, with herpes simplex, the rash can cross the midline of the body, and the symptoms can relapse. Contact dermatitis and
epidermal rash resulting from food poisoning also must be ruled out. The diagnosis of PHN is established based on medical history and physical examination. Scarring or vitiligo is often visible. If no vesicles are seen or documented, the distinction between PHN and other neuropathic pain syndromes cannot be established. The therapeutic consequences of this are, however, minimal.

II. TREATMENT OPTIONS
The objectives of treating herpes zoster are: (1) the reduction of severity and duration of the pain; (2) the promotion of recovery of epidermal defects and prevention of secondary infections; and (3) the reduction or prevention of PHN.

The objective of the treatment of PHN is primarily pain alleviation and—directly related to that—an improvement of the quality of life.

II.A CONSERVATIVE MANAGEMENT
Pharmacological Treatment of Herpes Zoster

Antiviral Medicines. Antiviral medicines, such as acyclovir, famcyclovir, or valacyclovir, should be started as quickly as possible after the onset of clinical signs. A review regarding the efficacy of this treatment showed that antiviral treatment, provided it starts within 72 hours after the development of the vesicles, accelerates the healing of the vesicles by approximately 1 to 2 days. It is, however, doubtful if antiviral treatment can prevent PHN. There were four systematic reviews published with different conclusions. Antiviral medicines reduce, at most to a slight degree, the incidence and duration of PHN.

Corticosteroids. A large randomized study compared the effect of acyclovir with that of a combination of acyclovir and prednisolone. A significantly better pain reduction was gained in the first 2 weeks for the group that was treated with prednisolone.

Another study compared the effect of acyclovir–prednisolone, acyclovir–placebo, prednisolone–placebo, and placebo–placebo. The patients who received prednisolone alone or in combination with acyclovir had 2.3 times more chance of being free of pain after a month in comparison with the patients who did not receive prednisolone. The corticosteroid treatment, however, had no influence on the healing of the rash. A Cochrane review studied the effect of oral, intramuscular, or intravenous corticosteroid administration during the acute phase of herpes zoster for the prevention of PHN 6 months after the acute infection. Inadequate evidence was found to determine if corticosteroids are safe and effective in the prevention of PHN.

Analgesics. There are no studies that evaluate the effect nonsteroidal anti-inflammatory drugs (NSAIDs) and/or paracetamol. Clinical experience has shown that these analgesics reduce acute pain. Opioids are effective in reducing acute herpes zoster pain.

Local Anesthetics. Clinical evidence and a single randomized controlled trial (RCT) show that topical lidocaine was effective without significant side effects.

Adjuvant Analgesics. A small placebo-controlled study showed that amitriptyline (25 mg a day taken for 90 days in the evening) during the acute phase of herpes zoster reduced the risk of PHN by 50%. Another study showed that gabapentin reduced acute herpes zoster pain.

Pharmacological Treatment of PHN
To a great extent, the pharmacological treatment of PHN is the same as that for other neuropathic pain syndromes. However, a number of randomized controlled studies, meta-analyses, and systematic reviews mainly concentrate on PHN. The key findings are summarized below, although in the U.S.A., formally only lidocaine patch, pregabalin, gabapentin, and 8% capsaicin patch are approved by the Food and Drug Administration (FDA) for this indication.

Tricyclic Antidepressants. The most frequently used and investigated tricyclic antidepressant is amitriptyline. The collective data from different RCTs show a number needed to treat (NNT) of 2.6 in order to obtain significant pain relief. The most important products in the group of tricyclic antidepressants in addition to amitriptyline are nortriptyline and desipramine. All of these medicines provide comparable results.

Antiepileptics. The effect of gabapentin with PHN was extensively investigated. A meta-analysis of two RCTs estimated a collective NNT of 4.4. In these studies, the average daily doses ranged from 1,800 mg to 2,400 mg. An RCT compared gabapentin in doses up to 3,600 mg a day with placebo and found a significant pain reduction in the active group. Pregabalin is assumed to have a mechanism of action comparable to gabapentin. The only difference is that...
pregabalin is better absorbed with linear kinetics, making it easier to titrate. There are no meta-analyses regarding the effect of pregabalin, but different RCTs show that pregabalin, in daily doses of 150 to 600 mg, relieve pain better than placebo.

**Tramadol.** A placebo-controlled study, in which 127 patients with PHN were treated with long-acting tramadol with a mean dose of 275 mg per day for 6 weeks, showed significant pain reduction and improvement of quality of life.

**Opioids.** The role of opioids in the treatment of neuropathic pain was controversial for a long time. It has now been shown that oral and intravenous administration of opioids provide significant alleviation of neuropathic pain. The analgesic effect of oxycodone for the treatment of PHN was evaluated in a double-blind randomized crossover study. The oxycodone treatment resulted in a significantly better reduction of pain (alldynia, steady state pain, and paroxysmal spontaneous pain).

An NNT of 2.7 was found for the opioid treatment in an RCT. These data imply that opioids can be useful in the treatment of PHN.

**Local Treatments**

**Local Anesthetics.** The 5% lidocaine patch was investigated for the treatment of PHN. An RCT and two open-label studies suggest a positive effect when the patch is applied to the most painful area. A Cochrane review concluded that there is inadequate evidence to recommend topical lidocaine as first-line treatment for PHN, although some clinicians prefer lidocaine patch as first-line treatment.

**Capsaicin.** A 6-week study with parallel groups followed by a 2-year open follow-up study showed that 0.075% capsaicin cream provides pain alleviation in 64% of the patients after 6 weeks in comparison with 25% of the patients who received placebo. The application must take place three to four times a day and is often accompanied by local irritation and an unpleasant burning sensation, which can be a threat to treatment compliance. A single administration of a patch with 8% capsaicin on a lidocaine-pretreated skin proved effective in a large RCT.

**Other Treatments**

A number of other treatments are used, such as NMDA receptor antagonists, ketamine, topical NSAIDs and tricyclic antidepressants, Botox, vincristine iontophoresis, homeopathy, and acupuncture. There is, however, little evidence that justifies evaluation of the efficacy of these therapeutic options.

**Combination Treatments**

The different medicinal treatments are typically investigated and addressed individually. However, there is a tendency to implement more than one therapeutic class simultaneously in order to achieve an additive or synergistic effect. In a crossover trial with 41 patients, there was better analgesia with a combination of gabapentin and morphine in lower dosages than with monotherapy using either of these products alone.

**II.B INTERVENTIONAL MANAGEMENT**

**Epidural and Paravertebral Injection**

Several studies have shown that epidural injections of corticosteroids with or without local anesthetics reduce the pain during the acute phase. The question is, however, if this treatment prevents PHN. An Italian study with 600 herpes zoster patients older than 55 years with a visual analog scale greater than 70 compared repeated injections of bupivacaine and methylprednisolone by way of an epidural catheter with intravenous prednisolone and acyclovir. The epidural injections were repeated every 3 to 4 days (for a maximum of 3 weeks) until the patient was free of pain. Analysis after 1 year of the 485 patients who completed the study showed an incidence of 22% of PHN in the group that received intravenous acyclovir and prednisolone, and 1.6% of PHN in the group that received epidural bupivacaine and methylprednisolone. However, in view of the risk of major endocrinological adverse effects, this is not regular practice.

In many countries, it is more common to administer an epidural injection without a catheter. In a multicenter study in the Netherlands, 598 patients age 50 or over with herpes zoster below dermatome C6 were studied to see if a single interlaminar epidural injection of bupivacaine (10 mg) and methylprednisolone (80 mg) had any supplemental value over the standard treatment with antiviral medicines and painkillers. The epidural injection provided a reduction in pain for 1 month after the development of vesicles, but there was no long-term effect, such as the prevention of PHN.
Interlaminar epidural injection was used in this randomized study. The transfominal technique with radiography is an alternative approach to the epidural space where dispersion of the medication to the affected ganglion would possibly be better. A difficulty with this technique, especially in the thorax, is that the affected dermatome cannot be determined with certainty, which causes one to easily treat at a level too high or too low. There is no research of the efficacy of this technique for herpes zoster. Theoretically, a technique, which requires the needle position and the dispersion of the medication to be monitored, should preferably be executed under radiographic control. The value of epidural injections for the treatment of existing PHN has also not been investigated.

A recent single-center study randomized 132 herpes zoster patients to either standard therapy of oral antivirals and analgesics, or a series of 4 paravertebral injections of bupivacaine and methylprednisolone in addition to standard therapy. After 12 months, the incidence of PHN after paravertebral injections was 2% compared with 16% after standard therapy alone. The authors of the latter study concluded that a series of paravertebral blocks seemed to be effective in preventing PHN but that a larger multicenter trial was needed.

**Intrathecal Injection**

A Japanese study of 277 patients with PHN reported a clearly positive effect from 4 weekly intrathecal injections of 60 mg of methylprednisolone dissolved in lidocaine 3%. Complications such as hypotension, symptoms of nerve root irritation, and arachnoiditis were not reported. The authors received much criticism, and the treatment is scarcely applied. Confirmation of the results in an independent second study is necessary.

**Sympathetic Nerve Block**

The value of a sympathetic nerve block for the treatment of acute herpes zoster is described mainly in retrospective studies. A small, randomized study compared bupivacaine administration with physiological saline solution. A review concluded that based on the retrospective data, there was evidence that sympathetic nerve block reduced the duration of acute herpes zoster pain.

The influence of sympathetic nerve block on the risk for the development of PHN can be somewhat derived from the retrospective studies that investigated the acute phase. The results are difficult to interpret, because the time of the initial sympathetic nerve block and the evaluation criteria differ.

Sympathetic nerve block for the treatment of PHN was evaluated mainly in retrospective studies as well. In a few studies, a reduction in pain was noted initially, but this effect was not maintained for the longer term. There is inadequate evidence for a long-term effect from sympathetic nerve block for PHN.

**Spinal Cord Stimulation**

Twenty-eight consecutive patients suffering PHN refractory to pharmacological treatment received spinal cord stimulation. The majority of these patients had serious underlying pathology such as cardiovascular, respiratory, endocrine conditions, or cancer. A long-lasting alleviation of pain, the duration of which was not reported in the publication, was obtained in 23 patients, and the pain medication could be reduced or even completely terminated (inclusion criterion was a positive response to a sympathetic nerve block). This study has various weak points including the absence of a comparative treatment group, which is certainly most important. The type of patient suggests, however, that randomization was difficult for ethical and practical reasons.

**Other Interventional Treatments**

The effect on herpes zoster and PHN from subcutaneous injections, transcutaneous nerve stimulation, percutaneous nerve stimulation, and pulsed and conventional radiofrequency has not been established. There is minor anecdotal evidence for the efficacy of these techniques, and the risk for complications, such as exacerbation of the pain, is unknown. There are no controlled studies.

### II.C COMPLICATIONS OF INTERVENTIONAL MANAGEMENT

**Complications of Epidural and Paravertebral Injections**

Complications of injections include hematoma or abscess, but the risk is low. Corticosteroids can cause a temporary depression of the adrenal cortex. At the time of injection, cellular immunity has already reached its peak because the intervention takes place at least a few days after the onset of the condition. Therefore, an increased risk for the dissemination or spread of the infection because of the immnosuppressive activity of corticosteroids is not expected. The risk for infarction of the spinal cord by accidental intra-arterial injection exists with the transfominal epidural method. It is known that application of methylprednisolone at cervical levels is associated with increased risk.
particles may cause an embolic process in the spinal cord. Pneumothorax is a risk with paravertebral injection.

**Sympathetic Nerve Block Complications**

Vasodilatation occurs in extremities when sympathetic nerves are blocked. This can be accompanied by hypotension. The establishment of an intravenous access before treatment is recommended. Intermittent blood pressure should be measured in the recovery room. Intravenous crystalloids can potentially be administered depending on the blood pressure.

Orthostatic hypotension may occur when standing up quickly. After the recovery period, it is recommended that the patient take additional oral fluids during the first 24 hours. Another infrequent complication is damage to the ilioinguinal nerve; more frequently (5% to 10%), the genitofemoral nerve is injured. This can cause neuropathic deafferentation pain.

**Complications of Spinal Cord Stimulation**

Spinal cord stimulation and the potential complications have been described in the article on complex regional pain syndrome (CRPS) of this series.\(^\text{42}\)

**II.D EVIDENCE FOR INTERVENTIONAL MANAGEMENT**

The available evidence for interventional pain management techniques is summarized in Table 2

**III. RECOMMENDATIONS**

An epidural injection of corticosteroids with local anesthesia can be used in patients with pain caused by herpes zoster that has been inadequately reduced by pharmacological treatment. Monitoring of the correct needle position with radiography has a theoretical benefit compared with a “blind” technique. Effectiveness and safety of transforaminal epidural corticosteroid injections for patients with herpes zoster have not been investigated and should subsequently only be performed as part of a study. A series of paravertebral injections of corticosteroids with local anesthetics every second day for a week can be an alternative. A sympathetic nerve block can also be considered, particularly during the acute stage, but has no advantage over epidural corticosteroid with or without local anesthetic.

Sympathetic nerve block can be considered for patients suffering from PHN refractory to conservative treatment. For patients who have inadequate pain control with sympathetic nerve block, spinal cord stimulation can be considered. Considering the degree of invasiveness and the costs of this treatment, it should preferentially be performed in a study context.

**III.A VACCINATION**

The observation that herpes zoster mainly appears in older patients (> 50 years) and that the reduced immunity is accompanied by an increased risk for herpes zoster stimulated research into a common factor in this risk population: This proved to be a reduced VZV-specific immune response. In addition, it was also observed that contact with children with varicella increased the immunity for varicella zoster. Theoretically, the immunity of adults for VZV is increased by a booster vaccination. With this method, the incidence of herpes zoster infections and, consequently, PHN is reduced.

The shingles prevention study included 38,456 adults who, at random, received a zoster vaccine or placebo. The participants in the study were followed for an average duration of 3.13 years after vaccination.\(^\text{7}\) The vaccination reduced the burden of illness in a significant way, which is a composite end point consisting of the incidence of herpes zoster, duration, and intensity of the pain. The burden of illness was 61.1% lower in the vaccination group compared with placebo. The incidence of PHN in the active group was 66.5% lower than in the placebo group. These findings certainly provide hope and place the prevention plan first in the treatment algorithm.

In an editorial on the prevention by epidural injection of postherpetic neuralgia in the elderly study that was described above, Baron and Wasner\(^\text{37}\) proposed the algorithm (Figure 2).

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**Table 2. Summary of Evidence for Interventional Pain Management**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Evaluation</th>
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<tbody>
<tr>
<td>Interventional pain treatment of acute herpes zoster</td>
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<tr>
<td>Epidural injections</td>
<td>$B+$</td>
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<tr>
<td>Sympathetic nerve block</td>
<td>$C+$</td>
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<tr>
<td>Prevention of PHN</td>
<td></td>
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<tr>
<td>One-time epidural injection</td>
<td>$B-$</td>
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<tr>
<td>Repeated paravertebral injections</td>
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<tr>
<td>Sympathetic nerve block</td>
<td>$C+$</td>
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<tr>
<td>Treatment of PHN</td>
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<td>Epidural injections</td>
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<td>Sympathetic nerve block</td>
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<tr>
<td>Intrathecal injection</td>
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<tr>
<td>Spinal cord stimulation</td>
<td>$C+$</td>
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</tbody>
</table>

PHN, post-herpetic neuralgia.
III.B CLINICAL PRACTICE ALGORITHM

Figure 3 illustrates the clinical practice algorithm for the management of PHN.

III.C TECHNIQUE(S)

For the description of epidural injection, the reader is referred to the following chapters: cervical radicular, thoracic pain, and lumbosacral radicular pain. Sym pathetic nerve block is described in the chapter on CRPS.

IV. SUMMARY

Herpes zoster is a condition that mainly affects older people. Its course is usually favorable, and the symptoms disappear spontaneously within a few weeks. Some patients, however, have prolonged pain: PHN. This persistent pain syndrome is difficult to treat. Interventional treatments, such as epidural injections of corticosteroids and local anesthetic drugs, have an effect on the acute pain but are of limited use in preventing PHN.

ACKNOWLEDGEMENTS

This review was initially based on practice guidelines written by Dutch and Flemish (Belgian) experts that are assembled in a handbook for the Dutch-speaking pain physicians. After translation, the article was updated and edited in cooperation with U.S./international pain specialists.

Figure 2. Algorithm for pharmacological prevention and treatment of post-herpetic neuralgia (from: Baron and Wasner, with the publisher’s permission).

Figure 3. Practice algorithm for anesthesiological treatment of post-herpetic neuralgia. VAS, visual analog scale.
The authors thank Arno Lataster for review and control of anatomical terminology and José Geurts and Nicole Van den Hecke for coordination and suggestions regarding the article.

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