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THERAPY IN PRACTICE

Management of Herpes Zoster and Post-Herpetic Neuralgia

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Abstract Herpes zoster and its sequela post-herpetic neuralgia (PHN) are conditions with significant morbidity. PHN is a chronic, debilitating neuropathic pain that can persist long beyond resolution of visible cutaneous manifestations. This paper provides practical guidelines for management of herpes zoster and PHN. For herpes zoster, antivirals should be started, preferably within 72 h of onset, to reduce the severity and duration of the eruptive phase and to reduce the intensity of acute pain. PHN can be treated with either topical or systemic agents. Topical lidocaine and capsaicin are effective. For patients with more severe pain, the following systemic agents can be considered (in decreasing order of recommendation): the anticonvulsants gabapentin and pregabalin, the tricyclic antidepressants amitriptyline, nortriptyline, and desipramine, and, lastly, the opioid analgesics tramadol, morphine, oxycodone, and methadone. For patients at high risk of developing PHN, early initiation of gabapentin or amitriptyline after the onset of herpes zoster is suggested. The new zoster vaccine has been shown to be effective in reducing the incidence of herpes zoster and PHN.

1 Introduction

Herpes zoster or shingles is caused by the varicella-zoster virus (VZV), also known as human herpes virus 3 (HHV 3). It results from reactivation of latent varicella infection within the sensory ganglia. The clinical form of the disease is characterized by a painful, unilateral vesicular eruption, which usually occurs with limited dermatomal distribution [1]. Early initiation of antiviral treatment reduces or eliminates serious disease-associated sequelae.

Herpes zoster-associated pain tends to resolve over time, but some patients suffer from post-herpetic neuralgia (PHN), a chronic, debilitating neuropathic pain that persists long beyond resolution of visible cutaneous manifestations.

This paper provides a practical overview of the treatment options available for management of patients with herpes zoster and PHN, focusing on the efficacy of the different therapeutic modalities. These modalities were assessed with regard to methodological quality of the respective studies and rated according to the well-known levels of evidence (Table 1). Recommendations were then graded according to the level(s) of evidence (Table 2).

2 Epidemiology

2.1 Herpes Zoster

Studies have shown that herpes zoster classically affects adults older than 50 years old [2–4], although it can occur in younger persons who had primary varicella infection within the first year of life. Individuals with a history of primary varicella have a 30 % lifetime risk of developing zoster [2], the severity and incidence of which increases substantially with age [3].

VZV is transmitted from person to person by direct contact or by inhalation of aerosols from vesicular fluid of skin lesions or infected respiratory tract secretions that are aerosolized [4].

The risk factors for developing herpes zoster are immunosuppression, advancing age, malignancy, chronic kidney or lung disease, disorders of cell-mediated immunity, for

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Table 1 Levels of evidence

Level of evidence	Type of study
Ia	Evidence obtained from a meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, for example comparative studies, correlation studies, and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Table 2 Grades of recommendation

Grade of recommendation	Levels of evidence	Definition
A	Ia, Ib	Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation
B	IIa, IIb, III	Requires the availability of well-controlled studies but no randomized clinical trials on the specific recommendation
C	IV	Requires evidence obtained from expert committed reports or opinions and/or based on the clinical experience of respected authorities. Indicates absence of directly applicable clinical studies of good quality

example infection with human immunodeficiency virus [5], and a family history of zoster. It occurs in approximately 20 % of healthy adults and 50 % of immunocompromised persons. In immunocompromised persons, the presentation of herpes zoster occurs earlier [6] and sometimes with atypical manifestations. There is a specific age-related decline in cell-mediated immunity to the VZV [7]. It is estimated that 50 % of patients who live to age 85 years will have an episode of herpes zoster [8].

2.2 Post-Herpetic Neuralgia

The incidence of PHN in herpes zoster patients is estimated to be 9–34 %. The major risk factors for PHN are older age, greater acute pain, greater rash severity, and ophthalmic location of the acute herpes zoster rash [9–13].

For patients who develop PHN, advanced age is associated with increasing severity and persistence of symptoms [14]. The risk of PHN is not increased in immunocompromised individuals [15].

3 Clinical Features

Acute herpes zoster patients present with a painful vesicular rash with dermatomal distribution. Both acute herpes zoster and PHN can be severe with profound psychosocial dysfunction, causing impaired sleep, reduced appetite, and diminished libido [16, 17].

The symptoms of PHN can be intermittent or constant. The sensation can be aching, burning, itchy, sharp, or lancinating. Allodynia and hyperalgesia (increased sensitivity to pain) may be present.

Patients often have abnormal sensations, for example areas of anesthesia, deficits of thermal, tactile, pinprick, and vibration sensation, within the affected dermatomes [18]. The sensory deficits may extend beyond the dermatomal margins. It has been suggested that allodynia is most prominent in areas of relatively preserved sensation whereas spontaneous pain is felt predominantly within the area of lost or impaired sensation.

The point at which acute herpes zoster pain becomes PHN is controversial. PHN was traditionally defined as persistence of pain for more than one month after disappearance of the rash. However, some authors have preferred to classify the neuropathic pain according to the time lapse after onset of rash (Table 3) [19].

Rarely, PHN has been reported to occur months to years after resolution of the initial event [20]. These episodes occurred in the same distribution as the initial rash and were precipitated by a specific event, for example a surgical procedure or a tooth abscess.

4 Diagnosis and Investigations

The clinical features of herpes zoster are characteristic, including prodromal pain and/or itching with eruption of a

Table 3 Definition of type of neuropathic pain

Type of neuropathic pain	Temporal relationship of pain to rash
Acute herpetic neuralgia	Pain preceding or accompanying eruption of the rash that persists up to 30 days from its onset
Subacute herpetic neuralgia	Pain that persists beyond healing of the rash but which resolves within four months of onset
Post-herpetic neuralgia	Pain persisting beyond four months from initial onset of the rash

Table 4 Diagnostic tests in herpes zoster

Diagnostic test	Sensitivity (%)	Specificity (%)
VZV polymerase chain reaction	95	99
VZV direct immunofluorescent (IF) antigen staining	82	76
Virus culture	20	99

VZV varicella zoster virus

painful vesicular rash in a dermatomal distribution. The pain during the prodromal phase may mimic pain from other sources, for example trauma, myocardial ischemia, renal calculi, gallbladder, and dental diseases.

Serologic methods are not useful for an early diagnosis, because immunoglobulin (Ig) M and IgA antibodies specific for acute herpes zoster may be detected in approximately 60 % of patients only [21]. In the first five days of disease onset, specific IgM and/or IgA can be demonstrated in approximately 50 % of sera only. Two or more serum samples are necessary to detect a rise in IgA and/or IgG antibody titers [22]. A fourfold increase in IgG titer is useful for diagnosis when acute and chronic sera (e.g. four weeks apart) are compared. Serology is, however, useful when vesicle specimens are not available.

Table 4 shows the different diagnostic tests with their sensitivity and specificity [22]. These are helpful in atypical cases in which a definitive clinical diagnosis cannot be made.

5 Treatment of Acute Herpes Zoster

5.1 Antiviral Agents

Acute herpes zoster is treated with the antiviral agents aciclovir, valaciclovir, and famciclovir [23–26]. These antiviral agents are phosphorylated by viral thymidine kinase and cellular kinases to a triphosphate form that inhibits viral replication. The objectives of treatment are, primarily, to reduce the severity and duration of the herpes zoster eruptive phase and to reduce the intensity of herpes zoster pain in the acute phase and its effect on quality of life.

The systemic antiviral agent should be administered within 72 h of onset or if the patient is still developing new blisters. If presentation is more than 72 h after rash onset, consider antivirals if the risk of painful complications is high, for example, presence of pre-eruptive pain, severe pain, severe skin lesions, and neurologic complications in the initial phase, for example encephalitis [23].

A seven-day course of systemic antiviral agents (aciclovir, valaciclovir, and famciclovir) is generally recommended for uncomplicated cases [23]. There is, however, no consensus about whether it is beneficial to extend the duration of treatment for patients who still have new vesicles forming on the seventh day or for those who have cutaneous, neurologic, or ocular complications [27]. Topical antiviral agents have been shown to lack efficacy for herpes zoster [27].

In ophthalmic herpes zoster, antiviral treatment is always recommended, even beyond 72 h of onset, unless contraindicated [23]. Patients should also be referred to an ophthalmologist to exclude ocular involvement. Early review is needed, especially if the conjunctiva is injected or there is a positive Hutchinson sign, defined as zoster lesions on the tip, sides, and root of the nose.

There are no systematic data suggesting superior efficacy of one antiviral over another. However, famciclovir and valaciclovir are expected to be more effective overall because of their higher and more reliable levels of antiviral activity in the blood and greater patient compliance with less frequent dosing [27]. Valaciclovir is comparable to famciclovir in accelerating resolution of herpes zoster-associated pain [28]. Table 5 shows the different antiviral drugs used for treatment of acute herpes zoster.

5.2 Pain Control

Because herpes zoster can be very painful, adequate pain control is important. Combination of antiviral therapy with effective relief of acute pain may lessen the risk of PHN, because severe acute pain is a risk factor for PHN.

To date, there are no published randomized, placebo-controlled trials of oral treatments for acute pain for patients with herpes zoster, although there have been recommendations for pain control according to the degree of pain [27]. (IV, C)

Table 5 Antiviral drugs for acute herpes zoster

Drug	Dosage	Comments	Most common adverse effects	Level of evidence, grade of recommendation
Aciclovir	PO 800 mg 5 times a day for 7–10 days; IV 10 mg/kg/dose 8-hourly for 7 days in severe infection or immunocompromised states	This drug has a lower bioavailability, hence the need for frequent dosing	Headache, nausea	Ia, A
Valaciclovir	PO 1,000 mg 3 times a day for 7 days	This is an oral prodrug of aciclovir with greater oral bioavailability	Headache, nausea	Ib, A
Famciclovir	PO 500 mg 3 times a day for 7 days	This is an oral prodrug of penciclovir	Headache, nausea	Ib, A

IV intravenous, *PO* per oral

For mild to moderate pain, consider prescribing paracetamol, NSAIDs, or tramadol. If pain is moderate to severe, opioids, for example morphine and oxycodone, can be given. If moderate to severe pain is not controlled with opioids, consider adding gabapentin or pregabalin, tricyclic antidepressants (TCAs), or corticosteroids. These medications are also used in PHN and will be elaborated in Sect. 6.2.

Corticosteroids reduce the pain of acute herpes zoster, accelerating lesion healing and return to daily activities. Oral prednisolone can be given at 1 mg/kg/day for seven days, followed by 0.5 mg/kg/day for seven days then 0.25 mg/kg/day for seven days [27]. Referral to a pain specialist for sympathetic and epidural neural blockade should be carried out if pain remains intractable with medications. (IV, C)

6 Treatment of Post-Herpetic Neuralgia (PHN)

PHN can be treated with topical or systemic agents. The treatment options are summarized in Table 6 and Fig. 1 shows a suggested therapeutic ladder for patients with PHN [29].

6.1 Topical Agents

6.1.1 Lidocaine

Lidocaine is believed to work by reducing the ectopic activity of sensory nerves. Its adverse effects are mainly limited to local reactions, for example erythema and itching. There is little systemic absorption.

A Cochrane review in 2007 analyzed three trials involving 182 topical lidocaine-treated participants and 132 controls. The authors concluded there is insufficient evidence to recommend topical lidocaine as a first-line agent for treatment of PHN with allodynia [30]. A separate meta-analysis in 2005 concluded there is evidence for use of a topical lidocaine 5 % patch for treatment of PHN [31]. (Ia, A)

Topical lidocaine is a good first-line agent for elderly patients where there is polypharmacy or contraindications to systemic agents. It is available as a lidocaine 2 or 10 % gel and as a lidocaine 5 % patch. Lidocaine 2 % gel should be applied to affected areas ≤4 times/day as needed. The maximum dose is 4.5 mg/kg and must not exceed 300 mg. Lidocaine 5 % patch (Lignopad®; Teikoku Seiyaku Co., Ltd, Kagawa, Japan) is used to cover the painful area and is applied once daily for up to 12 h within a 24 h period.

6.1.2 Capsaicin

Capsaicin releases substance P, a neuropeptide, from sensory nerve fibers (C and Aδ fibers). Substance P depletion desensitizes nociceptive terminals. Side effects are mainly limited to local reactions, for example itching, burning sensation, soreness, and erythema at the site of application. There is little systemic absorption

It is available as capsaicin 0.05 % ointment, which should be applied to affected areas ≤4 times/day as needed. Other formulations are capsaicin 0.075 % cream and 8 % patch (Qutenza®). Qutenza® has effects lasting up to 12 weeks after a single 60-min application and has been approved in both the European Union and the USA for localized therapy of PHN [32].

A Cochrane review in 2009 analyzed six studies using either a low-dose capsaicin 0.075 % cream or single application of a high-dose 8 % patch for chronic neuropathic pain. The authors concluded that both forms of capsaicin provide pain relief, but there were insufficient data to estimate the degree of benefit [33]. A separate meta-analysis in 2005 concluded there is evidence for use of topical capsaicin for treatment of PHN [31]. (Ia, A)

Table 6 Summary of treatment options in post-herpetic neuralgia

Treatment	Recommendations	Level of evidence, grade of recommendation
Topical lidocaine	Consider topical treatment if pain is mild or when systemic agents are contraindicated	Ia, A
Topical capsaicin	Consider topical treatment if pain is mild or when systemic agents are contraindicated	Ia, A
Anticonvulsants	Typically used as the first-line systemic agent	
Gabapentin		Ia, A
Pregabalin		Ia, A
Tricyclic antidepressants	Indicated for patients who have failed anticonvulsants or have contraindications to taking anticonvulsants	
Amitriptyline		Ia, A
Nortriptyline		Ia, A
Desipramine		Ib, A
Opioid analgesics	When prescribing morphine or oxycodone, caution must be exercised for patients with renal impairment. Limitations of opioid use include development of dependence and tolerance	
Tramadol		Ib, A
Morphine		Ib, A
Oxycodone		Ib, A
Methadone		Ib, A

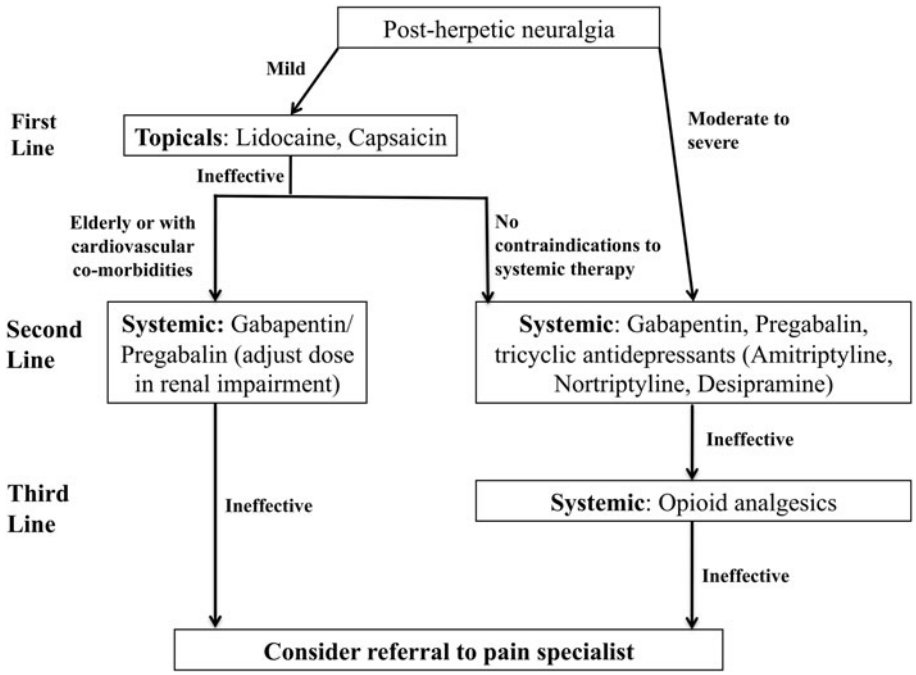

Fig. 1 Suggested therapeutic ladder for treatment of post-herpetic neuralgia

6.2 Systemic Agents

6.2.1 Anticonvulsants

6.2.1.1 Gabapentin Gabapentin is efficacious [31] and safe and therefore good as a first-line agent. It works by binding to the α2δ subunit of voltage-gated calcium ion channels to reduce influx of calcium ions into presynaptic nerve terminals. This inhibits the release of nociceptive neurotransmitters, for example glutamate and substance P.

In terms of pharmacokinetics, gabapentin is slowly absorbed, with a peak at 3–4 h after the dose. It is not metabolized by the liver and does not affect hepatic enzymes. There are no drug interactions because gabapentin is not bound to plasma proteins. There is a non-

linear relationship between plasma concentration and increasing dose.

Gabapentin is started at 300 mg daily, with an increase of 300 mg every day as needed for pain relief. The recommended dose range is 1,800–3,600 mg/day. A daily dose greater than 1,800 mg is not generally of greater benefit. Pain relief occurs as early as one week after the start of the treatment. The common side effects are somnolence (frequent), dizziness, and transient peripheral edema. (Ia, A)

6.2.1.2 Pregabalin Pregabalin has been used for treatment of a variety of acute and chronic painful conditions. A recent Cochrane review revealed significantly greater substantial benefit when it was used to treat PHN [34]. Pregabalin is a structural analog of γ-aminobutyric acid (GABA). Its bioavailability is greater than that of gabapentin (90 versus 33–60 %) and it is rapidly absorbed with a peak achieved at 1 h post-dose. Its plasma concentration increases linearly with increasing dose.

The initial dose is 150 mg/day in divided doses (75 mg twice daily or 50 mg three times daily) and it may be increased to 300 mg/day within one week, depending on tolerability and effect. Further dose titration (to 600 mg/day) after 2–4 weeks may be considered for patients who do not experience sufficient pain relief, if they are able to tolerate pregabalin. The maximum dose is 600 mg/day. The side effects of pregabalin include giddiness, somnolence, dry mouth, weight gain, and peripheral edema. It usually has fewer dose-related adverse events than gabapentin because of the lower doses used. (Ia, A)

6.2.2 Tricyclic Antidepressants (TCAs)

The mechanism of action of TCAs involves blockade of neuronal uptake of noradrenaline and serotonin, thereby potentiating inhibition of spinal neurons involved in nociceptive perception. They also block α-adrenergic receptors and sodium channels. This is useful in PHN, in which damaged primary afferents develop adrenergic sensitivity and generate ectopic impulses, which are very susceptible to sodium-channel blockade.

The side effects of this class of medication include excessive sedation, cognitive impairment, dry mouth, constipation, sexual dysfunction, and orthostatic giddiness. They are contraindicated for patients with cardiovascular disease and should be used with caution for patients with glaucoma, urinary retention, and high risk of suicide. In the elderly population, in which PHN is most prevalent, therapy with TCAs is often contraindicated because of cardiovascular disease or poorly tolerated because of the side effects.

6.2.2.1 Amitriptyline Amitriptyline is started at a low dose of 10 mg every night, with gradual small increments, up to 100 mg every night. (Ia, A)

6.2.2.2 Nortriptyline The initial dose is 10–25 mg at bedtime and the dosage may be increased by 25 mg/day weekly, if tolerated. The usual maintenance dose is 30–75 mg daily in divided doses, or a single night dose. It is as effective as amitriptyline. (Ia, A)

6.2.2.3 Desipramine Desipramine has been compared with amitriptyline and fluoxetine in a randomized, double-blind, parallel design trial and was shown to provide superior satisfactory relief for 80 % of those treated [35]. The initial dose is 10–25 mg/day with an increase in dose every 3 days until the desired effect is achieved. The usual effective dose is 50–150 mg/day, with a maximum dose of 150 mg/day. This is given for three weeks then tapered off. (Ia, A)

6.2.3 Opioid Analgesics

There is evidence to support the use of opioids [31]. Opioids modulate pain via the various opioid receptors (μ, κ, δ and nociceptin (orphanin FQ peptide receptor)) located both within the central nervous system and the peripheral afferent nerve terminals. Morphine acts on μ-opioid receptors. Opioid receptors are coupled to inhibitory G-proteins and activation of these receptors leads to closure of voltage-gated calcium channels, stimulation of potassium efflux leading to hyperpolarization, and reduced cyclic adenosine monophosphate production. This results in reduced neuronal cell excitability and hence reduced transmission of nociceptive impulses.

The limitations of opioid use arise from physical dependence and development of analgesic tolerance. Side effects of opioids include constipation, cardiorespiratory depression, sedation, nausea/vomiting, and histamine release. Referral to a pain specialist for expert management should be considered if the stronger opioid medications are needed.

6.2.3.1 Tramadol Tramadol is a synthetic, centrally acting analgesic with both opioid and non-opioid analgesic activity. Its effects arise via inhibition of noradrenaline reuptake and stimulation of serotonin (5-hydroxytryptamine; 5-HT) release at the spinal level. It is dosed at 100–400 mg/day, in divided doses, not more often than 4-hourly. (Ib, A)

6.2.3.2 Morphine The starting dose of oral morphine (controlled release) is 10 mg at night and the dose is

increased twice weekly till maximum pain relief is achieved or dose-limiting side effects occur. The maximum dose is 200 mg/day and it can be given at 10–30 mg every 12 h as needed [36]. For intravenous morphine [37], the target dose is 0.3 mg/kg over 1 h, up to a maximum of 25 mg. This should be administered to an inpatient with cardiorespiratory monitoring. (Ib, A)

6.2.3.3 Oxycodone (Controlled-Release) Controlled-release oxycodone has greater efficacy than placebo [38]. The dose is 10 mg twice daily, up to a maximum of 60 mg/day. The mean dose needed is 45 mg/day. Oxycodone has the advantage of less frequent dosing compared with oral morphine. (Ib, A)

6.2.3.4 Methadone (Controlled-Release) Dosing starts at 5 mg every night and is increased till maximum pain relief is achieved or occurrence of dose-limiting side effects, to a mean dose of 15 mg/day. There is no significant renal elimination, hence this drug is safe for patients with renal failure. A randomized, double-blind study of patients with chronic cancer pain showed that methadone did not have superior analgesic efficacy to morphine as a first-line strong opioid [39]. (Ib, A)

6.2.4 Other Therapies

Other therapies have been used for treatment of PHN but were either inefficacious or results were discrepant. These drugs include carbamazepine, topical benzydamine, some *N*-methyl-D-aspartate (NMDA) receptor antagonists, for example memantine or dextromethorphan, lorazepam, fluphenazine, mexiletine, and cyclo-oxygenase (COX)-2 inhibitors [29, 40, 41].

7 Prevention of Post-Herpetic Neuralgia

7.1 Effective Strategies

7.1.1 Zoster Vaccine

The zoster vaccine (Zostavax®) is a one-dose, high-potency, live-attenuated vaccine that boosts VZV-specific cell-mediated immunity. It was licensed in the USA in 2006 for adults aged 60 years and older. In a large study involving 38,546 patients aged 60 years or older, the vaccine's efficacy was demonstrated in its ability to reduce the burden of illness of herpes zoster by 61.1 %, the incidence of PHN by 66.5 %, and the incidence of herpes zoster by 51.3 % [42].

In 2011, the US FDA approved the expanded age range of the vaccine to include adults aged 50–59 years [43]. This approval was based on the results of a multicenter study conducted in USA and four other countries, comprising 22,000 participants aged 50–59 years, where the vaccine reduced the risk of developing herpes zoster by 70 % compared with placebo [43].

The Shingles Prevention Study demonstrated the efficacy of the vaccine through four years post-vaccination. The Short-Term Persistence Substudy subsequently demonstrated the persistence of vaccine efficacy five years post-vaccination with regard to incidence of herpes zoster and burden of illness of herpes zoster; efficacy beyond five years is uncertain [44]. (Ib, A)

7.1.2 Gabapentin

An uncontrolled, open-label study included 133 patients who received 1,000 mg valaciclovir hydrochloride three times daily for 7 days plus gabapentin at an initial dose of 300 mg/day, titrated up to a maximum dose of 3,600 mg/day, started within 72 h of onset of vesicular rash [45]. The patients received 4–8 weeks of gabapentin, with continuation beyond four weeks for patients who reported a pain score of more than 3 after four weeks. The overall incidence of zoster pain at six months was 9.8 %.

The authors concluded that the combination of gabapentin and valaciclovir administered acutely reduces incidence of PHN [45]. Of note, this study only enrolled patients at high risk of PHN, i.e. those over 50 years of age with an initial pain score of at least 4 on a 10-point Likert scale. However, there was no control group and the authors compared the incidence with that in historic controls described in a meta-analysis of six randomized controlled trials (RCTs) of antiviral agents used in the treatment of acute zoster [46]. (IIb, B)

7.1.3 Amitriptyline

A randomized, double-blinded, placebo-controlled trial of amitriptyline 25 mg daily was performed on 72 patients older than 60 years diagnosed with herpes zoster [47]. In combination with an antiviral drug, preemptive treatment of PHN with amitriptyline 25 mg reduced the prevalence of PHN by more than half at six months post zoster. (Ib, A)

7.1.4 Transcutaneous Electrical Nerve Stimulation (TENS)

Kolsek [48] reported a retrospective observational study analyzing 102 medical records. Transcutaneous electrical nerve stimulation (TENS) therapy comprised placement of two patches on the skin at the affected dermatome: one patch in the paravertebral region, another patch on the other side, along the nerve. The patches were placed for 30 min five times per week for 2 or 3 weeks and connected to a low output (1–5 mA) electrical generator and

stimulated at frequencies ranging from 20 to 40 Hz. Patients treated only with TENS had no PHN, 28.6 % of patients treated with antiviral drugs had PHN. Less analgesic drugs were prescribed to patients treated only with TENS. The authors concluded that TENS may be a safe adjunct or even alternative to antiviral drugs for treatment of acute herpes zoster with prevention of PHN. (III, B)

7.2 Strategy with Uncertain Benefit

7.2.1 Narrowband Ultraviolet B

Seventeen patients with PHN in a study with an intention-to-treat analysis received narrowband ultraviolet B 3 times per week for a total of 15 sessions or until pain disappeared [49]. They were followed up for three months after cessation of therapy. More than 50 % improvement was achieved for 6 (35 %) and 8 (47 %) patients at the end of the treatment session and at three months follow-up, respectively. Complete pain relief was achieved in 58 % and 83 % of patients at one and three months follow-up, respectively. However, no comparison was made with historic data. (IIb, B)

7.3 Strategies not Proven to be Effective

7.3.1 Antiviral Therapy

A Cochrane review in 2009 analyzed all randomized and quasi-RCTs for antiviral treatment given within 72 h after the onset of herpes zoster [50]. Five trials evaluated oral aciclovir and one trial evaluated oral famciclovir. The authors concluded that oral aciclovir did not significantly reduce the incidence of PHN. There was insufficient evidence from RCTs to determine whether other antiviral treatments prevent PHN. (A, Ia)

7.3.2 Corticosteroids

A Cochrane review in 2010 concluded that corticosteroids given acutely during zoster infection are ineffective in preventing PHN [51]. Corticosteroids have been recommended to relieve the zoster-associated pain in the acute phase of the disease. (A, Ia)

8 Summary of Recommendations

Antivirals should be started early, preferably within 72 h of onset of herpes zoster, to reduce the severity and duration of the herpes zoster eruptive phase and to reduce the intensity of herpes zoster pain in the acute phase and its impact on quality of life. There is good evidence for the agents aciclovir (Ia, A), valaciclovir (Ib, A), and famciclovir (Ib, A).

PHN can be treated with topical or systemic agents. Topical lidocaine and capsaicin are effective (Ia, A). For patients with more severe pain, the following systemic agents can be considered (in decreasing order of recommendation): anticonvulsants including gabapentin (Ia, A) and pregabalin (Ia, A), the TCAs amitriptyline (A, Ia), nortriptyline (A, Ia), and desipramine (Ib, A), and, lastly, the opioid analgesics tramadol (Ib, A), morphine (Ib, A), oxycodone (Ib, A), and methadone (Ib, A).

For patients at high risk of developing PHN, early initiation of gabapentin (IIb, B) or amitriptyline (Ib, A) after the onset of herpes zoster is suggested.

Finally, the zoster vaccine is effective in reduction of the incidence of herpes zoster and PHN (Ib, A).

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