



Guideline

DOI: 10.1111/ddg.14013

S2k guidelines for the diagnosis and treatment of herpes zoster and postherpetic neuralgia

AWMF registry number: 013–023, 2019
 Date of publication: 05/24/2019
 Valid until: 05/2024

**Gerd E. Gross^{1*}, Lisa Eisert^{2*}, Hans Wilhelm Doerr³,
 Helmut Fickenscher⁴, Markus Knuf⁵, Philip Maier⁶, Matthias Maschke⁷,
 Rainer Müller⁸, Uwe Pleyer⁹, Michael Schäfer¹⁰, Cord Sunderkötter¹¹,
 Ricardo N. Werner², Peter Wutzler¹², Alexander Nast²**

- (1) Department of Dermatology and Venereology, Rostock University Medical Center, Rostock, Germany
 (2) Charité – University Medicine Berlin, Corporate Member of Free University of Berlin, Humboldt University of Berlin, and Berlin Institute of Health, Department of Dermatology, Venereology und Allergy, Division of Evidence-based Medicine (dEBM), Berlin, Germany
 (3) Institute of Medical Virology, University Medical Center Frankfurt, Frankfurt (Main), Germany
 (4) Institute for Infectious Diseases, Christian Albrecht University and Schleswig-Holstein University Medical Center, Kiel, Germany
 (5) Dr. Horst Schmidt Hospital for Pediatric and Adolescent Medicine (Helios Kliniken), Wiesbaden, Germany
 (6) Department of Ophthalmology, Freiburg University Medical Center, Freiburg, Germany
 (7) Department of Neurology, Neurophysiology and Early Neurological Rehabilitation, Krankenhaus der Barmherzigen Brüder (Merciful Brothers' Hospital), Trier, Germany
 (8) Department of Otorhinolaryngology, Medical Faculty of the Carl Gustav Carus Technical University of Dresden, Dresden, Germany
 (9) Department of Ophthalmology, Charité – University Medicine Berlin, Berlin, Germany
 (10) Department of Anesthesiology and Surgical Intensive Care, Charité – University Medicine Berlin, Berlin, Germany
 (11) Department of Dermatology and Venereology, Halle University Medical Center, Halle (Saale), Germany
 (12) Department of Virology, Jena University Medical Center, Friedrich Schiller University, Jena, Germany

*The first two authors contributed equally to this publication.

Summary

The present guidelines are aimed at residents and board-certified specialists in the fields of dermatology, ophthalmology, ENT, pediatrics, neurology, virology, infectious diseases, anesthesiology, general medicine and any other medical specialties involved in the management of patients with herpes zoster. They are also intended as a guide for policymakers and health insurance funds. The guidelines were developed by dermatologists, virologists, ophthalmologists, ENT physicians, neurologists, pediatricians and anesthesiologists/pain specialists using a formal consensus process (S2k).

Readers are provided with an overview of the clinical and molecular diagnostic workup, including antigen detection, antibody tests and viral culture. Special diagnostic situations and complicated disease courses are discussed. The authors address general and special aspects of antiviral therapy for herpes zoster and postherpetic neuralgia. Furthermore, the guidelines provide detailed information on pain management including a schematic overview, and they conclude with a discussion of topical treatment options.

Preliminary comments

In order to promote circulation of these guidelines among the various medical specialties, the present article will also be published in *GMS Infectious Diseases*. The article is published under Creative Commons License CC BY.

1 Clinical Introduction

Herpes zoster (shingles) is caused by reactivation of the varicella zoster virus (VZV), which, after the initial infection, becomes latent and persists in sensory dorsal root ganglia and cranial nerve ganglia. While the abbreviated term “zoster” is commonly used in German-speaking countries, the internationally accepted designation is “herpes zoster” (in English as well as in French “herpès zoster”; “zoster” comes from the ancient Greek word for “belt”).

The primary infection with VZV predominantly occurs in childhood and usually presents with a generalized rash (chickenpox, varicella). One of the most common acute skin conditions, herpes zoster is a neurocutaneous viral disease that may occur at any age. However, its incidence shows a significant increase after the age of 50. Physicians of various specialties are routinely faced with challenging herpes zoster cases. This issue has been discussed at various interdisciplinary consensus meetings, both at the national and international level [1, 2].

The latency of VZV is attributable to the body's VZV-specific immune response. Whenever virus control is impaired, either due to aging processes (immune senescence) or a defect in cellular immunity, for instance, in the context of malignant lymphoma, HIV infection, or immunosuppressive therapy, latent VZVs may once again start to replicate. Herpes zoster as a consequence of prenatal VZV infection in neonates (without a fully competent immune system) constitutes a special case in this context. Subsequently, viral reactivation leads to inflammation and necrosis in one or more affected ganglia [3]. The characteristic unilateral dermatomal rash – referred to as shingles – usually develops three to five days after the onset of VZV reactivation.

Typical findings are a localized, unilateral eruption of grouped vesicles on an erythematous base. In 80 % of herpes

zoster cases, a prodromal stage precedes these cutaneous manifestations. Given the variable symptoms during this phase, including general malaise and usually mild-to-moderate pain in the area of the affected dermatome, misdiagnoses are not uncommon. Depending on the location, these may include cholecystitis, myocardial infarction, glaucoma, and others. This is particularly true for herpes zoster sine herpete. Following prodromal symptoms, this condition is characterized by dermatomal pain in the absence of herpes zoster lesions. Although the characteristic rash usually involves a single dermatome, it is not uncommon to find overlapping lesions that involve more than one segment. Multidermatomal herpes zoster affecting both sides of the body is a rare occurrence. Herpes zoster lesions predominantly develop in the thoracic region. With increasing age, there is an uptick in the incidence of cranial herpes zoster, which requires inpatient treatment if symptoms are severe. Even though the rash eventually resolves, patients may experience persistent and severe disease-related pain as a consequence of ganglionitis. By definition, pain that persists for more than three months is referred to as postherpetic neuralgia (PHN). For acute pain management, it is essential to distinguish whether the pain – irrespective of its onset – is nociceptive, neuropathic, or both nociceptive and neuropathic (see chapter 5.2.1). Persistent herpes zoster-associated pain is the most common disease complication. Similar to herpes zoster, PHN too is age dependent. While global incidence rates have been reported to range from 3–5 per 1,000 person-years (PY) [4], the age-specific incidence shows a steep increase after the age of 50⁺ with figures of 5/1,000 PY for individuals aged 50–60; 6–7/1,000 PY, for those aged 70–80; and up to 10/1,000 PY for people > 90 years [4]. In approximately 20 % of patients > 60 years, disease complications persist for more than one year [5]. Neurological complications of herpes zoster also include transient segmental paralysis, which may result in abdominal wall hernias and bladder dysfunction, as well as encephalitis and meningitis [6].

Ocular complications of herpes zoster comprise inflammation, keratitis, uveitis, glaucoma as well as acute and chronic retinal necrosis. These may be preceded by vasculitis or meningitis [7]. Cutaneous complications consist of

secondary bacterial infection and long-term persistence of skin lesions; immunocompromised patients may experience disseminated varicella-like skin and organ involvement [8]. Especially during the first four weeks after the rash, patients are at risk of vasculopathies and stroke [9, 10].

Herpes zoster occurs sporadically, with a lifetime prevalence of 25–50 % worldwide [11]. Disease frequency increases with age, both in people > 50 years as well as those with a compromised immune system, no matter if this is due to an illness or treatment related [12]. Between the ages of 10 and 49, the incidence of herpes zoster is four cases per 1,000 PY. After the age of 50, there is a steady increase to approximately 14 cases per 1,000 PY at the age of 75. Thereafter, the incidence remains stable [13]. Based on observations by Hope-Simpson in 1965 [14], individuals who reach the age of 85 develop herpes zoster at least once in their lifetime. Given the demographic changes and the increasing number of immunosuppressed individuals in Germany, it is expected that there will be a further increase in herpes zoster cases in the future. Currently, the number of new cases in Germany is estimated to be approximately 400,000/year. Based on estimates, that figure is thought to be approximately two million cases/year for the European Union. At least 10 % of all cases require hospitalization due to complications.

Available treatment strategies are aimed at alleviating pain during the acute disease phase, limiting the extent and duration of the rash, and preventing or mitigating chronic pain (such as PHN) as well as other acute and chronic complications. Treatment of acute herpes zoster consists of systemic antiviral chemotherapy, which should be started as early as possible, topical antiseptic therapy and rigorous pain management [6]. Systemic antiviral agents available include the nucleoside analogues acyclovir (given PO or IV), valacyclovir, famciclovir, and brivudine; the latter three drugs are given orally.

Acute herpes zoster-associated pain should be treated as early as possible in order to prevent potential pain chronicization. Based on pain intensity, treatment is administered according to the WHO's pain relief ladder, using nonsteroidal antiinflammatory drugs and, in some cases, opioids. Supplementary treatment with co-analgesics such as antidepressants and anticonvulsants is useful. PHN will frequently develop if said multimodal treatment is not provided consistently or even not at all (see chapter 5.2 and 5.3).

Given the rising number of individuals in Germany who have a compromised immune system due to age, illness, or treatment, there is a significant increase in the population risk for herpes zoster and PHN. In many cases, herpes zoster is associated with impaired quality of life, particularly in the elderly and those with an impaired immune system [15].

As herpes zoster and its complications pose a considerable health care challenge, prevention by vaccination is urgently

indicated. Moreover, the fact that VZV has been implicated to play a possible role in vasculopathies, stroke [9, 10], and giant cell arteritis [16] warrants continued and intense efforts to develop and widely use herpes zoster vaccines. The primary goal of herpes zoster vaccination is to inhibit VZV reactivation and thus to prevent herpes zoster, PHN, and other complications. Although approved in Germany, the German Standing Committee on Vaccination (*Ständige Impfkommission*, STIKO) does not generally recommend vaccination with the attenuated live vaccine Zostavax[®] due its limited efficacy and duration of action [17, 18].

In addition to Zostavax[®], which was approved a number of years ago, there is now a novel recombinant herpes zoster vaccine: Shingrix[®], an adjuvanted inactivated subunit vaccine. This vaccine contains the recombinant VZV glycoprotein E (VZV-gE) as VZV-specific antigen along with the adjuvant (immune booster) ASO1. Two doses of Shingrix[®] administered intramuscularly and given at a two-month interval (six months at most) are required. The vaccine boosts both the cellular and humoral immune response [19, 20].

In March 2018, this recombinant, adjuvanted inactivated subunit vaccine was approved in Germany for the prevention of herpes zoster and PHN in individuals \geq 50 years of age. In two approval studies (15,411 individuals aged \geq 50 years and more than 13,900 individuals aged \geq 70 years), the vaccine was effective in \geq 90 % of cases with respect to herpes zoster and in \geq 89 % of cases with respect to chronic pain and PHN. To date, there is continued effectiveness after more than four years [20]. Irrespective of patient age, it has been shown that cellular and humoral immune responses still persist after nine years [21]. Shingrix[®] has been available in Germany since May 2018. STIKO recommends the adjuvanted inactivated herpes zoster subunit vaccine for the prevention of herpes zoster and PHN in individuals \geq 60 years (standard vaccination).

Furthermore, STIKO recommends the adjuvanted inactivated herpes zoster subunit vaccine for herpes zoster and PHN in individuals \geq 50 years who are at greater risk of herpes zoster and PHN due to an increased overall health risk relating to an underlying medical condition or immunosuppression (indication-based vaccination). Both the effectiveness and safety in immunocompromised patients have been confirmed in multiple studies.

For individuals with an underlying medical condition – such as rheumatoid arthritis, chronic kidney disease, chronic obstructive pulmonary disease, or diabetes – who were included in the approval studies, stratified data analysis revealed no differences for these patient groups in terms of the vaccine's effectiveness compared with the overall effectiveness.

On March 7, 2019, the German Federal Joint Committee (*Gemeinsamer Bundesausschuss*, GBA) decided to add the inactivated subunit vaccine Shingrix[®] to the list of agents

covered by statutory health insurance funds for individuals > 60 years (and for immunocompromised individuals > 50 years).

2 Comments on how to use guidelines

Guidelines are systematically developed tools intended to assist physicians in standardized clinical situations. Only a limited number of such situations can be considered during guideline development. The recommendations contained in clinical guidelines are not legally binding; there may be specific situations in which deviation from these recommendations is appropriate or even required [22]. Implementation of guideline recommendations in specific clinical situations always requires that relevant individual circumstances (e.g., comorbidities, comedications, contraindications) be observed [23].

Medicine as a science is subject to continuous evolution. Guideline users are required to stay current with regard to any new developments that have occurred since the publication of the present guidelines. In addition, guideline users are advised to review the prescribing information and other important information issued by manufacturers in order to ensure that the recommendations provided are comprehensive and up-to-date. This applies to the implementation of any given intervention, contraindications and drug interactions to be observed, as well as approval status and cost coverage by health insurance funds.

3 Methods

The present guidelines were developed on the basis of the European guidelines “European consensus-based (S2k) Guideline for the Management of Herpes Zoster – guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV), Part 1: Diagnosis” [1] and “European consensus-based (S2k) Guideline for the Management of Herpes Zoster – guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology

and Venereology (EADV), Part 2: Treatment” [2]. The first author of the aforementioned source guidelines, Ricardo Werner, MD, has granted us permission to modify and partially use certain sections thereof.

The guidelines were developed on behalf of the German Herpes Management Forum (*Deutsches Herpes Management Forum*, DHMF) under the auspices of the Paul Ehrlich Society of Chemotherapy.

It is essential that physicians always assess and weight individual aspects relevant to the choice of treatment. The decision in favor or against a given treatment option is made on a case-by-case basis. These guidelines represent a decision guide based on scientific evidence that is intended to aid physicians in the choice of an appropriate treatment regimen and to facilitate optimal use of the chosen treatment option.

3.1 Development of recommendations: strength of recommendations, wording, and symbols

The guidelines were developed according to the methodological specifications issued by the Association of the Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.*, AWMF).

Rough drafts of the text and recommendations contained in the various guideline chapters were formulated by the authors and then circulated among the guideline group via email. The recommendations were graded according to their strength (Figure 1). Uniform wording was used in an effort to standardize the recommendations presented herein. Wording, symbols and comments on how to interpret the strength of a given recommendation are shown in Figure 1.

4 Diagnosis

4.1 Clinical diagnosis

Clinically, herpes zoster typically presents with a unilateral skin rash that is limited to one dermatome [14, 24, 25]. Individual lesions usually transition from erythematous

Passages requiring consensus		
The guideline group defined several particularly relevant passages as requiring consensus and adopted them at the consensus conferences. These passages are marked by gray boxes.		
The following wording was used to standardize the recommendations:		
↑↑	Is recommended	Strong recommendation in favor of a measure
↑	May be recommended	Recommendation in favor of a measure
→	May be considered	Open recommendation
↓	Cannot be recommended	Recommendation against a measure

Figure 1 Strength of recommendations – wording, symbols, and interpretation.

macules and papules to vesicles and pustules, eventually forming crusts after five to seven days. Typically, the lesions increase in number within 24 to 72 hours and spread across the affected dermatome in a radial fashion. Not always is a single dermatome affected in its entirety; depending on the site, however, adjacent dermatomes may also be involved. The lesions are usually associated with pain and abnormal sensations such as pruritus, paresthesia, dysesthesia, and numbness, which commonly precede the onset of skin manifestations by several days. The pain symptoms during the prodromal phase frequently give rise to a wide range of misdiagnoses, including myocardial infarction, cholecystitis, toothache, depending on the site affected [6, 26, 27]. Pain quality is often described as burning, stabbing, and pulsating (see chapter 9.2. [28–30]).

Local lymphadenopathy may be observed. Patients on anticoagulants or antiplatelet drugs and those on long-term corticosteroid therapy may develop hemorrhagic lesions. Herpes zoster most commonly affects thoracic dermatomes (55 %), followed by the trigeminal region (20 %) and cervical (11 %), lumbar (13 %), and sacral (2 %) dermatomes [24]. In some cases, there may be involvement of multiple adjacent or non-adjacent dermatomes; bilateral herpes zoster is very rare [31].

Studies in which the diagnosis was confirmed by lab tests have shown that the diagnosis of herpes zoster solely based on clinical evaluation has a specificity of 60–90 %, depending on severity and site. The differential diagnosis includes herpes simplex virus infections (HSV1 primarily in the head and neck region, HSV2 in the lumbosacral region in particular) as well as zosteriform dermatoses [6].

Given the availability of zoster-specific antiviral therapy and given the common practice today of administering adjuvant pain medication early on, timely confirmation of the diagnosis by laboratory tests is warranted (see below). This is especially true in cases in which

- the patient does not report a typical prodromal phase.
- the lesions involve more than one dermatome or cross the midline.
- a site other than the thoracic region is affected.
- the temporal course is atypical.

- the affected individual has a prior history of herpes zoster.
- the affected individual has received a VZV vaccine.

4.2 Molecular diagnostic workup

Molecular detection of VZV DNA from swabs is currently considered the gold standard in the diagnostic workup of VZV infections. If performed properly and under contamination-free conditions, modern real-time PCR has a sensitivity and specificity of nearly 100 %. Novel isothermal methods as well as helicase amplification techniques are still slightly inferior to classic PCR in terms of sensitivity and specificity [32–36]. It is recommended that sample collection be performed using either flocked swabs or nylon swabs in a stabilizing transport medium; these tools can usually be obtained from the laboratories. Fluid-filled vesicles are not required for the identification of VZV DNA from swabs. In general, reliable detection of viral DNA is also possible in the initial maculopapular stage and even from resolving lesions. If present, superficial crusts should be removed and swabs taken from the base of the lesions. The transport medium provided with the swabs allows for the samples to remain stable for several days and to be sent to the laboratory by regular mail.

In cases of suspected CNS involvement or CNS infection without skin involvement, VZV PCR is performed using cerebrospinal fluid (CSF). Suspected ocular herpes zoster may be confirmed by detecting VZV DNA in aqueous humor and, in some cases, from ocular swabs. Any suspicion of systemic infection with organ involvement requires the detection of VZV DNA in serum or plasma. In this context, quantitative PCR should preferably be used, given that low plasma/serum levels of VZV DNA may be found in localized disease, too (Table 1) [37].

4.3 Antigen detection

Direct antigen detection, which involves the detection of VZV proteins from swabs using fluorescence-labeled monoclonal antibodies, is significantly less sensitive and specific than molecular biology methods and is therefore no longer

Table 1 Diagnostic recommendations for herpes zoster; recommendations #1 and #2.

Recommendation		Recommendation	Consensus
#1	Laboratory confirmation is not required for herpes zoster cases with a typical clinical presentation.	Statement	91 %
#2	In all other cases, laboratory confirmation is recommended. Such diagnostic confirmation involves the use of VZV PCR or HSV-VZV PCR from swabs, aqueous humor, cerebrospinal fluid, serum or plasma.	↑↑	100 %

recommended [32, 33, 38, 39]. Moreover, successful antigen detection requires samples from fluid-filled vesicles and is only possible in the first few days after disease onset. The once common Tzanck smear (histological detection of intranuclear inclusion bodies) may be a useful clinical test for differentiating lesions not caused by herpesvirus, even though the sensitivity and specificity are significantly lower than virology methods. For the use of immunohistochemistry, see chapter 8.6 [40].

4.4 Antibody detection

While serological tests for VZV-specific IgM, IgG, and IgA antibodies by immunoassay are not suitable in the acute diagnosis of herpes zoster lesions, they may be useful in the workup of herpes zoster-like pain and zoster-associated (facial nerve) palsy. Over the course of the disease, there is a significant increase in anti-VZV IgG antibody levels. In addition, anti-VZV IgA and – less often – IgM antibodies may also be detected. Any measurements should be compared with baseline levels, given that subclinical viral reactivation too may cause an increase in antibody levels. A single serum sample is therefore only diagnostically useful if, based on the assessment of the laboratory, the measured antibody levels are exceptionally elevated [41, 42]. It should also be noted that reliable assessment of the serological course requires that the same laboratory method be used, ideally with duplicate measurements.

Detection of anti-VZV antibodies in CSF may be useful (provided there is an impaired blood-brain barrier), if the point in time for early detection of VZV DNA has been missed. This is also true for intraocular VZV detection from aqueous humor and, if necessary, from the vitreous body [43, 44].

4.5 Viral culture

The virus may be isolated in cultures of human diploid lung fibroblasts (WI-38 or MRC-5) or human retinal pigment epithelial (RPE) cells. Based on Koch's second postulate, this procedure was long considered to be the gold standard. Given the instability of this highly cell-associated herpesvirus, the sensitivity ranges from 20 % to 80 % under optimal conditions [32, 39, 45–47]. VZV production is significantly higher in RPE cell cultures [48]. VZV-induced cytopathic effects usually appear after three to eight days (average: 7.5 days) [46]. Shell vial cultures allow for the detection of specific viral antigens prior to

the onset of cytopathic effects [49]. Viral cultures are a useful option if replication-competent viral isolates are needed either for drug sensitivity tests or for molecular characterization. Given its low sensitivity and the greater diagnostic effort required, the significance of virus isolation in cell culture is today limited to special (clinical/scientific) questions.

4.6 Special situations

- *Herpes zoster ophthalmicus*, particularly the involvement of the nasociliary branch of the ophthalmic nerve clinically manifested as Hutchinson's sign (papulovesicles on the side and tip of the nose), is associated with a high complication rate. Herpes zoster ophthalmicus makes up approximately 10–20 % of all herpes zoster cases. Roughly one-half of these cases not only exhibit cutaneous lesions but commonly also keratitis, conjunctivitis, and uveitis [50, 51]. Important complications include delayed keratitis, scleritis, eyelid retraction, oculomotor nerve palsy, paralytic ptosis, secondary increase in intraocular pressure, optic neuritis, and acute retinal necrosis with the associated risk of bilateral blindness [43, 52]. The overall incidence of herpes zoster ophthalmicus was recently (2014, USA) reported to be 30.9 per 100,000 person-years (95 % confidence interval [CI]: 25.9–36.6), with an increase to 104.6 per 100,000 person-years (95 % CI: 79.0–135.9) in individuals \geq 65 years [53]. Ocular involvement associated with herpes zoster ophthalmicus may show a delay of more than four weeks. Approximately 10 % of patients with herpes zoster ophthalmicus develop keratitis and uveitis, which is associated with an increased risk of visual impairment [52, 54]. As (intra-) ocular involvement is common and may not be detected in the general physical examination, co-treatment by an ophthalmologist is recommended in herpes zoster cases with facial involvement. Not only does this ensure the required ophthalmologic follow-up but also allows for the treatment regimen to be adjusted accordingly (Table 2). The most accurate method to confirm intraocular involvement is the detection of VZV DNA [55, 56].
- *Herpes zoster oticus*: Herpes zoster oticus is characterized by involvement of cranial nerves VII and VIII. The diagnosis is usually made on clinical grounds. If there is any doubt about the viral etiology, virus detection is required. Based on the clinical presentation, specific

Table 2 Diagnostic recommendations for herpes zoster; recommendation #3.

Recommendation	References	Recommendation	Consensus
#3 In herpes zoster ophthalmicus, co-treatment by an ophthalmologist is recommended to rule out ocular involvement.	[52]	↑↑	100 %

neuro-otologic examinations should be performed, including pure tone audiometry, speech audiometry, stapedius reflex test, transient evoked otoacoustic emissions (TEOAE), brain stem evoked response audiometry (BERA), vestibular tests (coordination tests, videonystagmography, caloric reflex tests, video head impulse test, vestibular evoked myogenic potential). Characteristic clinical signs and symptoms include ear pain, impairment or loss of hearing (sensorineural hearing loss), vertigo, facial nerve palsy, and vesicular lesions on the auricle and in the auditory canal [57]. The Ramsay Hunt syndrome is defined as the presence of herpes zoster oticus in association with peripheral facial nerve palsy and possible impairment of other cranial nerves (V, IX, and X in some cases) [58–60]. Involvement of motor and sensory nerve fibers may cause facial muscle dysfunction, hearing loss, vertigo, sensory loss and disturbances in taste and lacrimation as well as nasal and salivary secretion [58, 61–63]. Cutaneous findings vary due to individual anastomoses between cranial and cervical nerves. Given the increased risk of severe complications [63], co-treatment by an ear, nose, and throat (ENT) specialist as well as by a neurologist is recommended, particularly if there is facial nerve and/or vestibulocochlear nerve involvement. Not only does this ensure the required ENT and neurological follow-up but also allows for the treatment regimen to be adjusted accordingly (Table 3) [60].

- *Herpes zoster sine herpette* is defined by the presence of unilateral dermatomal pain without cutaneous lesions in patients with virologic and/or serological evidence of

VZV infection. The most accurate method to confirm the diagnosis is the detection of rising anti-VZV IgG and IgM levels. Measurement of specific serum IgA levels may provide additional information, as they are also frequently elevated in acute infections, in some cases even earlier than IgM levels [59, 64, 65]. In herpes zoster sine herpette with facial nerve palsy, detection of VZV DNA can be done by PCR from nasopharyngeal swabs two to four days after the onset of facial nerve palsy or directly from plasma [66] (Table 4).

- *Atypical cutaneous manifestations* of herpes zoster that have been reported include verrucous [67], lichenoid [68], follicular [69, 70] and granulomatous [71] herpes zoster, as well as granulomatous angiitis [72–76]. In case of atypical cutaneous manifestations, it is recommended to take a diagnostic biopsy for virus detection by immunohistochemistry, in situ hybridization or PCR using unfixed tissue [77]. Concomitant serological tests for the presence of an active VZV infection may be useful. In case of ulcerating or oozing atypical cutaneous lesions, swabs may be taken for antigen detection or – even better – PCR (Table 5) [40].
- *Herpes zoster in children* is similar to adult disease. Pain is usually less pronounced [78–80].
- *Recurrent herpes zoster* is uncommon in immunocompetent patients. Over a period of eight years, it was observed in 6.2 % of patients; in immunosuppressed patients, that figure was 30 %. Overall, there is conflicting data with respect to herpes zoster recurrences [81–85].

Table 3 Diagnostic recommendations for herpes zoster, recommendation #4.

Recommendation	References	Recommendation	Consensus
#4 In herpes zoster oticus, co-treatment by an ENT specialist and a neurologist is recommended, particularly if there is facial nerve and/or vestibulocochlear nerve involvement.	[63]	↑↑	100 %

Table 4 Diagnostic recommendations for herpes zoster, recommendations #5, #6 and #7.

Recommendation	References	Recommendation	Consensus
#5 In case of suspected herpes zoster without skin manifestations, measurement of serum anti-VZV IgG, IgA, and IgM antibody levels may be recommended.	[64–66]	↑	100 %
#6 In case of suspected herpes zoster without skin manifestations and with facial palsy, testing for VZV DNA from nasopharyngeal swabs or saliva may be recommended two to four days after the onset of symptoms.		↑	100 %
#7 In case of suspected herpes zoster without skin manifestations, VZV PCR from plasma may be considered.		→	100 %

Table 5 Diagnostic recommendations for herpes zoster, recommendations #8, #9 and #10.

Recommendation	Recommendation	Consensus
#8	In case of atypical cutaneous manifestations, such as lichenoid, verrucous, granulomatous, and follicular lesions, a diagnostic biopsy (regular histology) is recommended.	↑↑ 100 %
#9	If herpes zoster is suspected based on histology, additional diagnostic tests using unfixed tissue, blood, and swabs are recommended.	↑↑ 100 %
#10	In case of suspected herpes zoster presenting with unclear ulcerated lesions, it may be recommended to take swabs for VZV PCR.	↑ 100 %

4.7 Complicated disease courses

4.7.1 Postherpetic neuralgia

The most common chronic sequela of acute herpes zoster is PHN, which is usually defined as pain that persists for three months or more after the skin lesions have resolved. Incidence and severity of PHN correlate with patient age, and show an increase after the age of 50 [13, 86, 87]. Herpes zoster ophthalmicus patients with keratitis or intraocular inflammation are at greater risk of developing PHN [86]. The following risk factors have been proposed to determine a patient's individual risk of PHN: female gender, age > 50 years, number of lesions > 50, cranial/sacral involvement, hemorrhagic lesions and prodromal pain [88]. Most patients affected by PHN experience steady improvement of their condition.

4.7.2 Disseminated herpes zoster and neurological complications

The occurrence of disseminated and/or confluent skin lesions is associated with a more severe disease course. The spectrum ranges from single-organ involvement with a good prognosis to multiorgan failure, a condition also referred to as visceral herpes zoster that frequently results in fatal outcomes despite high-dose intravenous antiviral therapy [89, 90].

There are several risk factors that may help identify patients at risk of developing severe herpes zoster and at increased risk of experiencing cutaneous and/or systemic dissemination as well as PHN. These include age > 50 years [13, 86, 91], moderate-to-severe prodromal or acute pain [86], immunosuppression [13, 91–93] including malignancies, blood disorders, HIV infection, organ or stem cell transplantation, as well as other immunosuppressive medications. There are also some clinical findings at disease onset that may indicate a greater risk of subsequent complications. These include satellite lesions (aberrant vesicles) [94], severe rash and/or involvement of multiple dermatomes or multisegmental herpes zoster [95] and simultaneous occurrence of lesions in different developmental stages, reduced overall health status,

meningeal or other neurological signs and symptoms. Table 6 provides an overview of risk factors associated with complicated disease courses. The expert panel recommends that patients with herpes zoster be specifically examined for the aforementioned signs and symptoms (Table 7).

Patients with herpes zoster of the head and neck region frequently experience asymptomatic CNS involvement [96], which is associated with pathological CSF findings in up to 60 % of cases [96]. Symptoms that have been reported to be associated with herpes zoster, especially in the elderly and in immunosuppressed patients, include encephalitis, meningoencephalitis, myelitis, cerebellitis, cerebrovascular disorders including zoster-associated vasculitis/vasculopathy, radiculitis, and Guillain-Barré syndrome [70, 82–84]. Vasculopathy refers to VZV infection of cerebral arteries, which may cause both ischemic and hemorrhagic strokes. In the first year after the onset of herpes zoster, the risk of having a stroke is increased by 30 % [9]. Patients with herpes zoster affecting the first branch of the trigeminal nerve have a 4.5-fold increased risk [76]. An entirely new approach may arise from reports that VZV antigens, VZV DNA and VZV viral particles can be found in the temporal arteries of patients with giant cell arteritis [73]. Confirmation of these findings might in the future result in affected patients being treated with both corticosteroids and systemic nucleoside analogues such as acyclovir [97].

Neurological complications of herpes zoster are quite common, especially in the elderly. Thus, even subclinical viral inflammation of CSF and CNS may cause confusion in multimorbid patients. Irrespective of the presence of neurological symptoms, it is recommended to have immunosuppressed patients and individuals > 80 years undergo neurological assessment (Table 8). Herpes zoster patients with acute focal neurological dysfunction or other neurological signs and symptoms should also be seen (and treated) by a neurologist (Table 10). If encephalitis or myelitis are suspected, or if there are signs of an acute stroke, patients should undergo cranial or spinal magnetic resonance imaging (MRI) including MR angiography of cerebral vessels.

Table 6 Risk factors for complicated disease courses in patients with herpes zoster.

Risk factor		Increased risk of ...
Herpes zoster of the head and/or neck region	Herpes zoster ophthalmicus	Intraocular involvement and complications [43, 52, 54], PHN [86, 88], neurological involvement/long-term sequelae [96]
	Herpes zoster oticus	Vestibulocochlear sequelae [63], neurological involvement/long-term sequelae [96]
	Herpes zoster affecting other facial or cervical dermatomes	Neurological involvement/long-term sequelae [96]
Herpes zoster with moderate-to-severe prodromal or acute disease-associated pain		PHN [86, 88]
Herpes zoster with severe skin lesions and/or signs of cutaneous dissemination	Aberrant vesicles, hemorrhagic and/or necrotic lesions, mucosal involvement, multisegmental herpes zoster, generalized herpes zoster	PHN [86, 88], neurological involvement/long-term sequelae [91], visceral dissemination
Herpes zoster with signs of CNS involvement		Long-term neurological sequelae; complicated disease courses with fatal outcomes, stroke
Herpes zoster with signs of visceral involvement		Complicated disease courses with fatal outcomes
Herpes zoster in the elderly		PHN [13, 86, 88], cutaneous dissemination [13], neurological involvement/long-term sequelae [13, 91]
Herpes zoster in immunosuppressed patients (malignancies, blood disorders, HIV infection, status post organ or stem cell transplantation, and individuals on immunosuppressive medication)		Recurrent herpes zoster [81], atypical manifestations, cutaneous, neurological and/or visceral dissemination [13, 91–94], acyclovir-resistant herpes zoster [100, 101]
Herpes zoster in patients with severe predisposing skin diseases (e. g., atopic dermatitis)		Cutaneous dissemination

Encephalitis or meningoencephalitis are rare complications seen in approximately 0.25 % of herpes zoster patients. Compared with HSV encephalitis or the initial infection with VZV, the condition typically presents with only mild disturbances of consciousness and confusion – especially in patients > 80 years. Signs and symptoms suggestive of meningeal involvement include headache, mild stiffness of the neck and fever. Focal neurological signs such as hemiparesis or brain stem symptoms and seizures are rare and usually indicative of vasculopathy, another potential complication. If encephalitis is suspected, imaging studies (preferentially cMRI) and a lumbar puncture including VZV PCR should

be performed immediately. Manifest encephalitis requires that patients be closely monitored in an intermediate or intensive care unit until there is clinical improvement. Moreover, these patients frequently require follow-up rehabilitation treatment, in particular for any cognitive deficits. Sole meningeal involvement (meningitis) may also be associated with cognitive deficits, albeit significantly less often than in the context of bacterial meningitis [98]. Both encephalitis and meningitis should be treated with intravenous acyclovir for 10–14 days. Additional administration of corticosteroids is not useful, as there are no studies that provide evidence for their effectiveness.

Table 7 Diagnostic recommendations for herpes zoster, recommendations #11 and #12.

Recommendation	References	Recommendation	Consensus
#11	[94, 95]	↑↑	100 %
#12	[13, 86, 91–93, 102] [63]	↑↑	100 %

Table 8 Diagnostic recommendations for herpes zoster, recommendations #13 and #14.

Recommendation	Recommendation	Consensus
#13	↑↑	100 %
#14	↑↑	100 %

It has been shown that herpes zoster is an independent risk factor for vascular disorders, in particular stroke, transient ischemic attacks, and myocardial infarction [88–90]. It is therefore recommended to pay close attention to any acute cardiac and cerebrovascular symptoms (Table 9). Recent studies indicate that VZV reactivation causes both vasculopathy and vasculitis. Large, medium and small arteries may be affected. Patients with herpes zoster-associated vasculitis/vasculopathy may – even without prior signs of CNS involvement – present not only with sudden onset of focal neurological deficits such as hemiparesis, but also with nonspecific symptoms including confusion, cognitive deficits, and seizures [99]. In cases of suspected VZV vasculopathy, patients should undergo cranial MRI and MR angiography; if necessary, this should include vessel wall imaging. Close monitoring in an intermediate care/stroke unit or intensive care unit is required for the first 24 hours at least. Depending on the

clinical presentation and any possible improvement, patients should receive follow-up (neurological) rehabilitation treatment. Treatment of herpes zoster-related vasculitis should include not only intravenous acyclovir but also corticosteroids (at least 1 mg/kg until there is clinical improvement).

The most severe acute complication for immunosuppressed patients with herpes zoster is systemic VZV dissemination. Fortunately, this is a rare event. It is recommended that clinicians rule out associated complications such as pneumonia, hepatitis, disseminated intravascular coagulation and signs of CNS involvement in these patients if they show acute deterioration of their overall condition (Table 10).

4.8 Screening for (occult) risk factors

Herpes zoster is considered to be an indicator disease for HIV infection. Various reports have shown an increased prevalence

Table 9 Diagnostic recommendations for herpes zoster, recommendation #15.

Recommendation	References	Recommendation	Consensus
#15	[103–105]	↑↑	100 %

Table 10 Diagnostic recommendations for herpes zoster, recommendation #16.

Recommendation	Recommendation	Consensus
#16 In patients with herpes zoster and concomitant deterioration of their overall condition, it is recommended to rule out associated complications such as pneumonia, hepatitis, disseminated intravascular coagulopathy or CNS involvement.	↑↑	100 %

Table 11 Diagnostic recommendations for herpes zoster, recommendation #17.

Recommendation	References	Recommendation	Consensus
#17 Testing for HIV is recommended in herpes zoster patients younger than 50 years of age.	[106–108, 112–114]	↑↑	89 %

Table 12 Diagnostic recommendations for herpes zoster, recommendation #18.

Recommendation	References	Recommendation	Consensus
#18 For herpes zoster cases with a typical clinical course, screening for malignancy is not recommended.	[110, 111]	↓	100 %

of HIV positivity in herpes zoster patients. This is especially true for patients with involvement of multiple dermatomes or recurrent herpes zoster, and in the presence of other risk factors for HIV infection [106–109]. Younger patients (< 50 years) with herpes zoster are recommended to be tested for HIV, in particular those with widespread multidermatomal involvement, recurrent herpes zoster, lesions in different disease stages, and individuals with other risk factors for HIV (Table 11).

It remains a matter of debate whether patients should be screened for malignancy solely based on the diagnosis of herpes zoster. In a large cohort of herpes zoster patients, the incidence rates of various malignancies were investigated. Standardized incidence rates were not increased in this patient group [110]. By contrast, a retrospective controlled cohort study showed a hazard ratio (HR) of 2.43 (95 % CI 2.21–2.66) for the risk of developing a malignancy in patients with a prior history of herpes zoster [111]. Given these conflicting findings and based on clinical consensus, the expert panel does not recommend cancer screening based solely on the diagnosis of herpes zoster (Table 12).

4.9 Other specific situations

Resistance of VZV infections to acyclovir has been defined either as the absence of a clinical response or positive virus detection on systemic antiviral therapy for 10–21 days [100, 101]. In particular, this phenomenon has been reported for VZV infections in immunocompromised patients, especially following hematopoietic stem cell transplantation [67, 115–117].

Phenotypical assessment of acyclovir resistance *in vitro* has been considered the gold standard for resistance testing. However, *in vitro* tests are not ubiquitously available and VZV isolation in cell culture has low sensitivity. Genotyping of VZV is faster method and may also provide information about the emergence of acyclovir-resistant VZVs during long-term treatment.

Unlike HSV [118], the natural and acyclovir resistance-associated polymorphisms of VZV thymidine kinase (TK) and polymerase have been insufficiently defined and are therefore not yet available for diagnostic purposes [101, 118–120]. VZV genotyping is restricted to specialized laboratories.

Herpes zoster may also be caused by reactivation of VZV vaccine strains that persist in neurons after VZV vaccination. Genotyping of viral DNA is useful in distinguishing wild-type viruses from vaccine strains [121, 122].

4.10 Hygienic measures in hospitals

In general, immunocompetent herpes zoster patients do not excrete infectious viral particles via the oropharynx, thus precluding transmission by droplets or aerosols [123].

The fact that some studies found replication-competent VZVs in the saliva of both healthy individuals and herpes zoster patients is – given the low infectious dose – irrelevant in terms of contagiousness. This is in line with the assessment by the German Commission for Hospital Hygiene and Infection Prevention (*Kommission für Krankenhaushygiene und*

Table 13 Recommendation for isolating herpes zoster patients, recommendation #19.

Recommendation	References	Consensus
<p>#19 Current recommendation by the RKI guidebook “Varicella and Herpes zoster”</p> <p>“The German Commission for Hospital Hygiene and Infection Prevention (<i>Kommission für Krankenhaushygiene und Infektionsprävention</i>, KRINKO) recommends that patients with herpes zoster be isolated in single rooms until all lesions have become crusted.”</p> <p>If single-room isolation is not feasible and following individual risk assessment, it may be considered to have patients share a room with other patients if the latter have documented immunity to VZV.”</p>	[124]	100 %

Infektionsprävention, KRINKO). According to KRINKO, viral transmission occurs exclusively by direct or indirect contact with herpes zoster lesions, which remain infectious until all vesicles have become crusted. VZVs can usually not be cultivated from crusted lesions.

In this context, the guidebook “Varicella and Herpes zoster” (*Varizellen und Herpes zoster*) issued by the Robert Koch Institute states: “With strict adherence to basic hygiene and with cooperative patients, the likelihood of transmission can be reduced by completely covering all lesions”. KRINKO recommends that patients with herpes zoster be isolated in single rooms until all lesions have become crusted. If single-room isolation is not feasible and following individual risk assessment, it may be considered to have patients share a room with other patients if the latter have documented immunity to VZV [124]. In these cases, it is not required to wear protective clothing when entering the room. However, such clothing is required when handling patients whose vesicles have not yet become crusted. It is essential to prevent any viral transmission to immunocompromised patients (Table 13).

In immunosuppressed patients with disseminated herpes zoster, the expert panel considers it possible for the virus to spread by aerosols and would follow the same procedures as for varicella.

5 Treatment

5.1 Antiviral agents

5.1.1 General aspects of antiviral agents

In patients without risk factors for complications, herpes zoster usually is a self-limiting disease. Treatment objectives include the improvement of outcomes in terms of the quality of life (QoL) of affected patients, duration and extent of cutaneous symptoms, as well as intensity and duration of acute zoster-associated pain. Given that postherpetic neuralgia is the most common sequela of herpes zoster, reducing its

incidence is a major secondary treatment goal. In immunosuppressed or otherwise susceptible patients, treatment goals extend to reducing the incidence and intensity of accompanying complications [125, 126].

In controlled trials, a reduced duration of skin lesions as well as duration and severity of zoster-associated pain was demonstrated for systemic treatment with acyclovir [127–130] and famciclovir [131] compared with placebo. A meta-analysis of four placebo-controlled trials showed a statistically significant superiority of oral acyclovir over placebo with respect to time until cessation of pain [132]. Results from controlled randomized trials suggest the superiority of valacyclovir over acyclovir as regards duration and/or severity of zoster-associated pain [133, 134]. In these studies, no statistically significant differences were seen for the duration of skin lesions. No statistically significant differences with respect to the duration of pain and skin lesions were found in controlled randomized trials comparing famciclovir with acyclovir [135, 136], brivudine with acyclovir [137], and valacyclovir with famciclovir [138]. In another randomized controlled trial, famciclovir was superior to acyclovir with respect to duration of pain if the famciclovir dose was doubled [139]. Another randomized controlled trial investigating valacyclovir versus famciclovir showed statistically significantly earlier pain reduction with famciclovir [140].

Quality of life (QoL) as central patient-reported outcome (PRO) has been addressed only in a limited number of clinical studies. Given the reduction in duration and intensity of acute herpes zoster-associated pain, it is presumed that antiviral therapy may have positive effects on patients’ quality of life. However, this presumption is not based on scientific observations.

In a systematic review, it was shown that – compared with placebo – neither acyclovir nor famciclovir statistically significantly reduced the incidence of postherpetic neuralgia four to six months after the onset of acute herpes zoster [141].

Brivudine and acyclovir were compared in the context of a follow-up survey to a previously conducted randomized

controlled trial [137], showing a significantly lower incidence of PHN following brivudine than after acyclovir treatment [142]. In another randomized controlled trial that compared brivudine with famciclovir, there were no statistically significant intergroup differences with respect to the prevalence and duration of pain [143]. Other randomized controlled trials found no statistically significant differences between valacyclovir and acyclovir [144] nor between famciclovir and acyclovir [145].

Controlled studies of antiviral medications have also been conducted in immunocompromised patients: One randomized controlled trial compared the efficacy of intravenous acyclovir and placebo in immunocompromised patients with localized or disseminated herpes zoster, showing acyclovir to be superior in reducing the incidence of complications (including cutaneous and visceral dissemination) [146]. Another randomized controlled trial of 48 immunocompromised patients that compared intravenous acyclovir with oral brivudine found no statistically significant difference with regard to cutaneous or visceral dissemination [147]. Compared with vidarabine, acyclovir was statistically significantly superior in preventing cutaneous dissemination, duration of pain, and healing of skin lesions [148].

Standard antiviral treatment for herpes zoster currently recommended includes the four orally effective nucleoside analogues acyclovir, valacyclovir, famciclovir, and brivudine as well as acyclovir for IV treatment (Table 14). In line with previous guidelines [6, 149], the expert panel recommends initiation of systemic antiviral therapy for the patient groups listed in Table 15 (recommendation #20, Table 15). Given the relatively low risk of adverse effects associated with antiviral agents, systemic antiviral therapy should also be considered in patients at low risk of sequelae or complicated disease courses (recommendation #21, Table 15).

Based on consensus, intravenous administration of acyclovir is recommended in patients presenting with complicated herpes zoster or at risk of a complicated disease course (recommendation #22, Table 16).

Factors that may be crucial in terms of which oral antiviral agent to choose are listed in Table 17 (recommendation

#23). There is no conclusive evidence as to the superiority of valacyclovir, famciclovir, and brivudine over oral acyclovir with respect to different outcomes. While brivudine is beneficial in that it requires only once-daily dosing, it is not available in all countries. Acyclovir is the least expensive agent. Brivudine is contraindicated in immunosuppressed patients and, due to possible life-threatening drug interactions, also in patients who have been treated with drugs containing 5-fluoropyrimidine (e.g., 5-fluorouracil, flucytosine) in the past four weeks.

According to the prescribing information of the various drugs, renal function-related dose adjustment is required for acyclovir, valacyclovir, and famciclovir. For these agents, creatinine levels should be checked at the onset of treatment in patients with known or suspected chronic kidney disease (Table 18).

Given the lack of trials investigating the initiation of antiviral therapy more than 72 hours after the onset of skin lesions, there is no evidence that would warrant such a recommendation. Based on consensus and in keeping with existing guidelines [6, 149], it is recommended to initiate antiviral therapy at a later point in time – if any of the conditions listed in recommendation #25 are met – in cases in which it was not possible to start systemic treatment within the first 72 hours after the onset of skin lesions (Table 19).

Trials investigating prolonged antiviral therapy beyond seven days revealed no clinically relevant differences [133] or additional benefit compared with standard treatment [150]. The duration of antiviral therapy should be extended until no more vesicular lesions appear. If vesicles occur within a period of more than seven days, the diagnosis should be reassessed and viral resistance to the antiviral medication should be considered.

5.1.2 Special situations

- *Chronic kidney disease:* For herpes zoster patients with chronic kidney disease, we recommend brivudine (if oral treatment is indicated) or intravenous acyclovir (if

Table 14 Summary of duration and dosage of standard antiviral therapy for herpes zoster.

Agent	Individual dose	Frequency of intake/administration	Duration
Valacyclovir PO	1,000 mg	Three times daily	7 days
Acyclovir PO	800 mg	Five times daily	7 days
Acyclovir IV*	8–10 mg/kg	Three times daily	7–10 days
Famciclovir PO	250 mg	Three times daily	7 days
Brivudine PO	125 mg	Once daily	7 days

*Herpes zoster in immunocompromised patients and other patients at increased risk of a severe disease course (see Table 16).

Guideline S2k guidelines zoster and postherpetic neuralgia

Table 15 Treatment recommendations for herpes zoster, recommendations #20 and #21.

Recommendation	References	Recommendation	Consensus
#20 Systemic antiviral therapy is recommended for the following patient groups: <ul style="list-style-type: none"> ▶ Herpes zoster in patients aged 50 and older, regardless of site ▶ Herpes zoster of the head and neck region ▶ Herpes zoster regardless of site with <ul style="list-style-type: none"> – associated moderate-to-severe pain – hemorrhagic or necrotic lesions – multisegmental involvement – aberrant vesicles/satellite lesions – mucocutaneous involvement ▶ Herpes zoster in immunosuppressed patients ▶ Herpes zoster in patients with predisposing skin diseases (for example, atopic dermatitis) ▶ Herpes zoster in children and adolescents on long-term topical corticosteroid treatment 	[127, 128, 130, 131, 133–140, 146–148]	↑↑	100 %
#21 In patients under the age of 50 with herpes zoster of the extremities or the trunk and no evidence of a complicated disease course, systemic antiviral therapy may be considered.		→	100 %

Table 16 Treatment recommendations for herpes zoster, recommendation #22.

Recommendation	Recommendation	Consensus
#22 In patients with herpes zoster and a complicated disease course or those at risk of a complicated disease course, intravenous antiviral therapy is recommended. This includes the following patient groups: <ul style="list-style-type: none"> ▶ Herpes zoster of the head and neck region, especially in elderly patients ▶ Herpes zoster with hemorrhagic/necrotic lesions, multisegmental involvement, aberrant vesicles/satellite lesions, mucosal involvement, or generalized herpes zoster ▶ Herpes zoster in immunosuppressed patients ▶ Herpes zoster with signs of visceral or CNS involvement (including vasculitis) 	↑↑	100 %

Table 17 Treatment recommendations for herpes zoster, recommendation #23.

Recommendation	Recommendation	Consensus
#23 In patients without indication for intravenous acyclovir therapy, it is recommended to use shared decision making with respect to the use of oral acyclovir, valacyclovir, famciclovir, or brivudine. Aspects to be observed include dosing frequency, costs, contraindications, comorbidity, and drug interactions.	↑↑	100 % <i>One abstention from voting</i>

Table 18 Treatment recommendations for herpes zoster, recommendation #24.

Recommendation	Recommendation	Consensus
#24 In patients with known or suspected chronic kidney disease, it is recommended to check creatinine levels at the start of oral antiviral therapy with acyclovir, famciclovir or valacyclovir.	↑↑	100 %

Table 19 Treatment recommendations for herpes zoster, recommendations #25 and #26.

Recommendation	Recommendation	Consensus
#25 It may be recommended to initiate antiviral therapy as early as possible within 72 hours after the onset of symptoms. In the following cases, initiation of systemic antiviral therapy may be recommended even at a later point in time: <ul style="list-style-type: none"> ▶ as long as new vesicles appear ▶ in patients with signs of cutaneous, visceral, or neurological dissemination ▶ in case of herpes zoster ophthalmicus or herpes zoster oticus ▶ in all immunosuppressed patients 	↑	100 %
#26 In patients with uncomplicated herpes zoster (classical presentation, unilateral thoracic or lumbar involvement, under the age of 50, without signs of a disease complicated course) who consult a physician more than 72 hours after the onset of cutaneous symptoms, initiation of systemic antiviral therapy may be considered.* *Due to divergent opinions among the guideline group members, this recommendation was adopted by majority consensus of only 60 %. In the aforementioned setting, 40 % of guideline group members would not recommend initiation of systemic antiviral therapy.	→	60 %

intravenous treatment is indicated) given at a dose adjusted to renal function (Table 20). This recommendation is based on consensus among the expert panel and on the fact that brivudine is less dependent on renal excretion than other systemic antiviral agents. Inpatient treatment with acyclovir allows for close monitoring of renal function during treatment.

- *Herpes zoster ophthalmicus*: Involvement of the skin supplied by the nasociliary nerve (Hutchinson's sign) is considered the main criterion for ophthalmological referral. Ocular involvement occurs in up to 85 % of affected patients. The eye may be affected even in the absence of the Hutchinson's sign. Visual impairment, eye pain, photophobia, and reduced corneal sensitivity are indicative of ocular involvement. All patients with herpes zoster ophthalmicus/herpes zoster of the first branch of the trigeminal nerve should be immediately started on acyclovir IV (8–10 mg/kg for 7–10 days) and referred to an ophthalmologist to rule out ocular involvement. The treatment

regimen for herpes zoster ophthalmicus and the requirement for ophthalmological follow-up should be determined by an ophthalmologist. In general, the treatment recommendations outlined above also apply to herpes zoster ophthalmicus. Acute retinal necrosis as complication of herpes zoster ophthalmicus constitutes an ophthalmological emergency and should be treated under close supervision by an ophthalmologist. Given that acute retinal necrosis is rapidly progressive and may spread to the contralateral eye, immediate intravenous induction therapy followed by oral antiviral therapy for 3–4 months is indicated (Table 21). Prolonged treatment is recommended to protect the contralateral eye [151, 152]. Additional use of systemic corticosteroids in patients with acute retinal necrosis is subject to controversial debate as regards the proper initiation. A starting dose 0.5–1.0 mg/kg of prednisolone per day for the first 7–10 treatment days may be recommended [152, 153]. We recommend the use of topical and systemic corticosteroids for supplementary

Table 20 Treatment recommendations for herpes zoster, recommendation #27.

Recommendation	Recommendation	Consensus
#27 In patients with impaired renal function, it is recommended to use oral brivudine (if oral antiviral treatment is indicated) or intravenous acyclovir (if intravenous antiviral treatment is indicated; criteria see above) given at a dose adjusted to renal function.	↑↑	100 % <i>One abstention from voting</i>

Table 21 Treatment recommendations for herpes zoster, recommendations #28 and #29.

Recommendation	References	Recommendation	Consensus
#28 In patients with acute retinal necrosis (as complication of herpes zoster ophthalmicus), systemic antiviral induction therapy with intravenous acyclovir (10 mg/kg three times daily for 7–10 days)* followed by oral acyclovir (800 mg five times daily) or oral valacyclovir (1,000 mg three times daily) for 3–4 months* is recommended. *Potentially required dose adjustment must be observed.	[151, 152, 155]	↑↑	100 %
#29 In patients with acute retinal necrosis (as complication of herpes zoster ophthalmicus), topical and systemic corticosteroids may be recommended for supplementary anti-inflammatory treatment.	[152, 153]	↑	100 %

anti-inflammatory treatment (Table 21). Caution is warranted when using corticosteroids without concomitant antiviral therapy, as this may promote viral replication and trigger acute retinal necrosis [154].

- *Herpes zoster oticus*: The treatment strategy for herpes zoster oticus with involvement of the facial nerve and/or vestibulocochlear nerve, ear pain, and vertigo should be determined by an ENT specialist and a neurologist [60]. The expert panel recommends combination treatment using intravenous acyclovir and corticosteroids (Table 22). It has been reported that herpes zoster oticus with severe pain and cranial nerve palsy can be successfully managed with systemic antiviral therapy consisting of intravenous acyclovir followed by oral acyclovir for another one to two weeks [57, 156, 157]. Corticosteroids are still considered the best treatment option for viral inflammation of the facial nerve [158]. The efficacy of corticosteroid treatment is based on the reduction of the inflammatory edema and the resultant decompression of the facial nerve within the facial canal in the petrous portion of the temporal bone [62, 159, 160]. Combination treatment is more effective in restoring facial nerve function following herpes zoster oticus [161–165] and seems to be associated with a more favorable prognosis [166]. With respect to corticosteroid dosing, the reader is referred to the AWMF guidelines “Idiopathische Fazialisparese (Bell’s Palsy)”, S2k guidelines, registry no.

030-013 [167]. In addition, patients require sufficient pain medication for the usually severe neuralgiform pain as well as antivertigo agents if they experience vertigo. It is recommended to refer patients to a neurologist and an ENT specialist if there is incomplete healing/defective healing of the facial nerve despite appropriate treatment.

- *Pregnancy*: Given the lack of systematically assessed data on the safety of antiviral agents during pregnancy, it is recommended to use these drugs with caution, carefully weighing potential risks and therapeutic benefits. In the absence of any risk factors for a complicated disease course, systemic antiviral therapy is not recommended in pregnant women with herpes zoster (Table 23). Both a large population-based, retrospective controlled cohort study and another study that included registry data found no increased risk of birth defects in children whose mothers had been exposed to acyclovir during pregnancy. For other antiviral agents (valacyclovir and famciclovir), the number of cases was too small to draw any conclusions [168, 169]. Use of acyclovir may therefore be recommended in pregnant women with risk factors for a complicated disease course, if the potential therapeutic benefits for the mother outweigh the potential risk for the fetus (Table 23).
- *Children*: Given the lack of safety data for the use of systemic antiviral agents in children, it is recommended to use these drugs with caution, carefully weighing

Table 22 Treatment recommendations for herpes zoster, recommendation #30.

Recommendation	References	Recommendation	Consensus
#30 In patients with herpes zoster oticus and facial nerve involvement (Ramsay Hunt syndrome), severe pain and/or paralysis of multiple cranial nerves, it is recommended to administer combination treatment consisting of intravenous acyclovir and systemic corticosteroids.	[161, 166]	↑↑	100 %

Table 23 Treatment recommendations for herpes zoster, recommendations #31 and #32.

Recommendation	References	Recommendation	Consensus
#31		↓	90 %
In the absence of risk factors for a complicated disease course, systemic antiviral therapy cannot be recommended during pregnancy.			
#32	[168, 169]	↑↑	100 %
During pregnancy, systemic antiviral therapy is only recommended for complicated disease courses. In such cases, acyclovir is recommended.			

Table 24 Treatment recommendations for herpes zoster, recommendations #33 and #34.

Recommendation	Recommendation	Consensus
#33	↓	100 %
In the absence of risk factors for complications, systemic antiviral therapy cannot be recommended for children with herpes zoster (see Table 6).		
#34	↑	100 %
In the presence of risk factors for a complicated disease course, systemic antiviral therapy may be recommended for children with herpes zoster, if the therapeutic benefits outweigh any potential risks.		

potential risks and benefits of antiviral therapy. In general, childhood herpes zoster is associated with lower morbidity than adult disease [78, 79]. In the absence of risk factors, systemic antiviral therapy is not recommended in children (Table 24). Initiation of systemic antiviral therapy may be considered in children, if there are risk factors for a complicated disease course (Table 6) and if the potential therapeutic benefits outweigh any potential risks (Table 24).

- *Recalcitrant/chronic herpes zoster lesions:* Clinically, VZV infections that do not respond to acyclovir treatment administered for 10 to 21 days may be considered to be acyclovir resistant [100, 101]. This phenomenon is particularly common in patients presenting with verrucous lesions [67]. In cases of acyclovir resistance, treatment with an alternative antiviral agent, for example, brivudine, or with another thymidine kinase-dependent antiviral agent (famciclovir) may be attempted. In a small retrospective case series of immunosuppressed patients with acyclovir-resistant herpes zoster, a response to intravenous foscarnet treatment was observed [100, 170]. There have also been anecdotal reports of acyclovir-resistant VZV strains responding to cidofovir [171–173]. Neither drug is approved for the treatment of herpes zoster. Given the potentially severe adverse effects associated with foscarnet and cidofovir, these agents should only be used in very severe cases and after consulting with virologists and pharmacists. Moreover, the risk-benefit ratio must be thoroughly discussed with the patient. As regards chronic herpes zoster lesions, the reader is referred to a review by Wauters et al. (2012) [67] about chronic mucocutaneous herpes zoster lesions.

5.2 Pain management

5.2.1 Introduction

Herpes zoster is typically associated with acute pain in the affected dermatomes. It is essential to properly characterize the pain (Table 25). On the one hand, patients experience “wound pain” (nociceptive pain) that occurs as a result of the acute immune response. On the other hand, axonal spread of VZVs leads to concomitant inflammation, which also causes pain (acute herpes zoster neuralgia/neuropathic pain). By definition, dermatomal pain that persists for more than three months after the cutaneous herpes zoster lesions have resolved is referred to as postherpetic neuralgia (PHN).

Acute zoster-associated pain occurs in > 95 % of patients older than 50 years of age; 60–70 % of patients continue to experience persistent pain one month after disease onset; 40 % of patients consider their pain to be severe [178, 179].

Table 25 Recommendation for distinguishing the types of pain associated with herpes zoster, recommendation #35.

Recommendation	Recommendation	Consensus
#35	↑↑	100 %
It is recommended to strictly distinguish between nociceptive and neuropathic pain.		

Table 26 Definition of nociceptive and neuropathic pain.

1. Nociceptive pain	2. Neuropathic pain
<ul style="list-style-type: none"> ▶ Caused by the local inflammatory response during the occurrence of lesions (wound pain) ▶ Pain that is caused by actual or imminent damage of non-neuronal tissue and that is attributable to activation of nociceptors [174] 	<ul style="list-style-type: none"> ▶ Acute herpes zoster neuralgia (axonal spread of the virus and migration of immune cells; subsequent inflammation and degeneration of sensory neurons [175]) ▶ Pain caused by damage to or a disorder of the somatosensory nervous system [174] <hr/> <ul style="list-style-type: none"> ▶ Postherpetic neuralgia (by definition, pain that persists for three months after acute herpes zoster lesions have resolved; caused by significant damage to peripheral neuronal structures and central changes in the spinal cord; chronic pain disorder with pain sensitization) <hr/> <ul style="list-style-type: none"> ▶ Typically presents with prodromal symptoms (dermatomal pain that precedes vesicular lesions by 2–28 days) <hr/> <ul style="list-style-type: none"> ▶ Four distinct types of pain can be distinguished; they frequently occur in combination: <ol style="list-style-type: none"> a. persistent burning, lancinating pain b. short episodes of shooting, neuralgiform pain c. dynamic tactile allodynia (very severe pain to touch, often spreading to adjacent segments) d. paresthesia (for example, burning or stabbing), dysesthesia (altered or painful sensitivity to touch), or hyperesthesia (excessive or prolonged response to painful stimuli) [176, 177]

5.2.2 Assessment of pain intensity

Pain intensity should be assessed using a validated assessment scale (for example, visual analog scale [VAS] or numeric rating scale [NRS]) [180, 181] (Table 27). In addition, validated assessment tools may be used to determine neuropathic pain characteristics (Douleur Neuropathique 4 [DN4], PainDETECT [PD-Q], or Leeds Assessment of Neuropathic Symptoms and Signs [LANSS]) [180, 181] and quality of life (SF36 or its short version SF12) [180, 181].

Further tools may be used to assess response to treatment (for example, minimum and maximum pain over the

course of the last 24 hours, pain intensity during movement, satisfaction with pain management (NRS: 0 = not satisfied, 10 = very satisfied; Table 28). At the European level, said assessment tools were recently validated for acute postoperative pain [182].

5.2.3 Treatment of herpes zoster-associated pain

While there are numerous publications addressing postherpetic neuralgia [76, 146], the evidence for managing acute herpes zoster-associated pain is scarce.

Table 27 Recommendations for pain management in herpes zoster; recommendations #36 and #37.

Recommendation	References	Recommendation	Consensus
#36 It is recommended to assess pain using a validated pain intensity scale, such as the visual analog scale or the numeric rating scale (0 = no pain, 10 = worst pain imaginable).	[180, 181]	↑↑	100 %
#37 Additional assessment tools (questionnaires) may be recommended in select patients, as described in the background text.	[180, 181]	↑	100 %

Table 28 Recommendations for pain management in herpes zoster, recommendation #38.

Recommendation	References	Recommendation	Consensus
#38 Assessment of patient satisfaction with pain management may be recommended (NRS: 0 = not satisfied to 10 = very satisfied).	[180, 181]	↑	100 %

Table 29 Recommendations for pain management in herpes zoster, recommendation #39.

Recommendation	Recommendation	Consensus
#39 Early treatment of herpes zoster-associated pain using systemic analgesics is recommended.	↑↑	100 %

Apart from improving functional status and health-related quality of life, controlling acute herpes zoster-associated pain is believed to reduce the risk of postherpetic neuralgia, even though there are no controlled trials that would support this assumption. Unlike postherpetic neuralgia, acute herpes zoster-associated pain should preferentially be treated with systemic analgesics and not with topical agents (Table 29). In this context, it should be borne in mind that the painful sensations are in part caused by neuroinflammation [183, 184].

As antiepileptic agents are characterized by delayed onset of action (dose titration phase), treatment of purely neuropathic pain should initially also include NSAIDs and opioids according to the WHO pain relief ladder [187]. Following the onset of action of the antiepileptic drugs, it should be attempted to reduce the pain medication (first opioids, then non-opioid analgesics) (Figure 2).

In case of uncertainty as to whether the acute pain is purely nociceptive or whether there is also a neuropathic component, antiepileptic drugs may be considered, as they have been shown to be moderately superior to placebo for acute herpes zoster-associated pain (Tables 30 and 31) [188].

The positive effects of both pregabalin and gabapentin on neuropathic pain has been confirmed in trials and meta-analyses [189–192]. The term postherpetic neuralgia is not consistently used across studies and frequently also encompasses pain during the acute disease phase. Pregabalin has the advantage of allowing more rapid incremental dose increase and of being available as tablets for easier oral dosing. As these drugs take several days to achieve effective plasma levels, use of analgesic agents should not be delayed.

Except for initial fatigue and vertigo, gabapentin and pregabalin are well tolerated, and there are no known severe drug interactions. The following aspects should be observed

during treatment with antiepileptic agents (gabapentin, pregabalin):

- careful monitoring of blood glucose levels in diabetic patients (in some patients, adjustment of the insulin dose may be required at the start of treatment),
- monitoring of pancreatic enzymes during the dose titration phase,
- gabapentin and opioids mutually affect the other's effectiveness as well as adverse effects (somnolence, sedation, respiratory depression),
- gradual tapering of gabapentin and pregabalin (over the course of seven days due to the risk of withdrawal seizures).

Antidepressants inhibit the reuptake of norepinephrine and/or serotonin in the spinal cord, resulting in elevated transmitter levels that subsequently inhibit nociceptive spinal transmission. In addition, these agents block voltage-dependent sodium channels and have indirect sympatholytic effects [193–195]. A serotonin and norepinephrine reuptake inhibitor, amitriptyline has been most extensively studied. It suppresses all types of pain: spontaneous burning pain, shooting pain, and evoked pain. The mean dose required for pain relief is lower than that required for its antidepressant effect. It will take several days to two weeks for pain reduction to set in [196]. The occurrence of xerostomia indicates that the target dose has been reached – at least in terms of treating depression. Persistent fatigue indicates that the dose is too high. Relatively selective norepinephrine reuptake inhibitors, such as desipramine, have fewer anticholinergic side effects and are associated with a lower degree of sedation. Selective serotonin reuptake inhibitors, such as fluoxetine and paroxetine, are characterized by a favorable side effect profile. Unfortunately, most controlled studies have demonstrated no or only minor analgesic effects. Important adverse effects include orthostatic hypotension (due to sympatholytic effects), sedation (caused by histamine receptor inhibition), urinary retention, memory impairment, arrhythmia, and xerostomia (anticholinergic effect). Contraindications are AV-block, heart failure, angle-closure glaucoma, pyloric stenosis, and prostatic hyperplasia. All patients should therefore have an EKG prior to treatment. In case of first-degree AV block, it is recommended to consult a cardiologist or at least to ensure that these patients have an EKG on a weekly basis (there have been cases

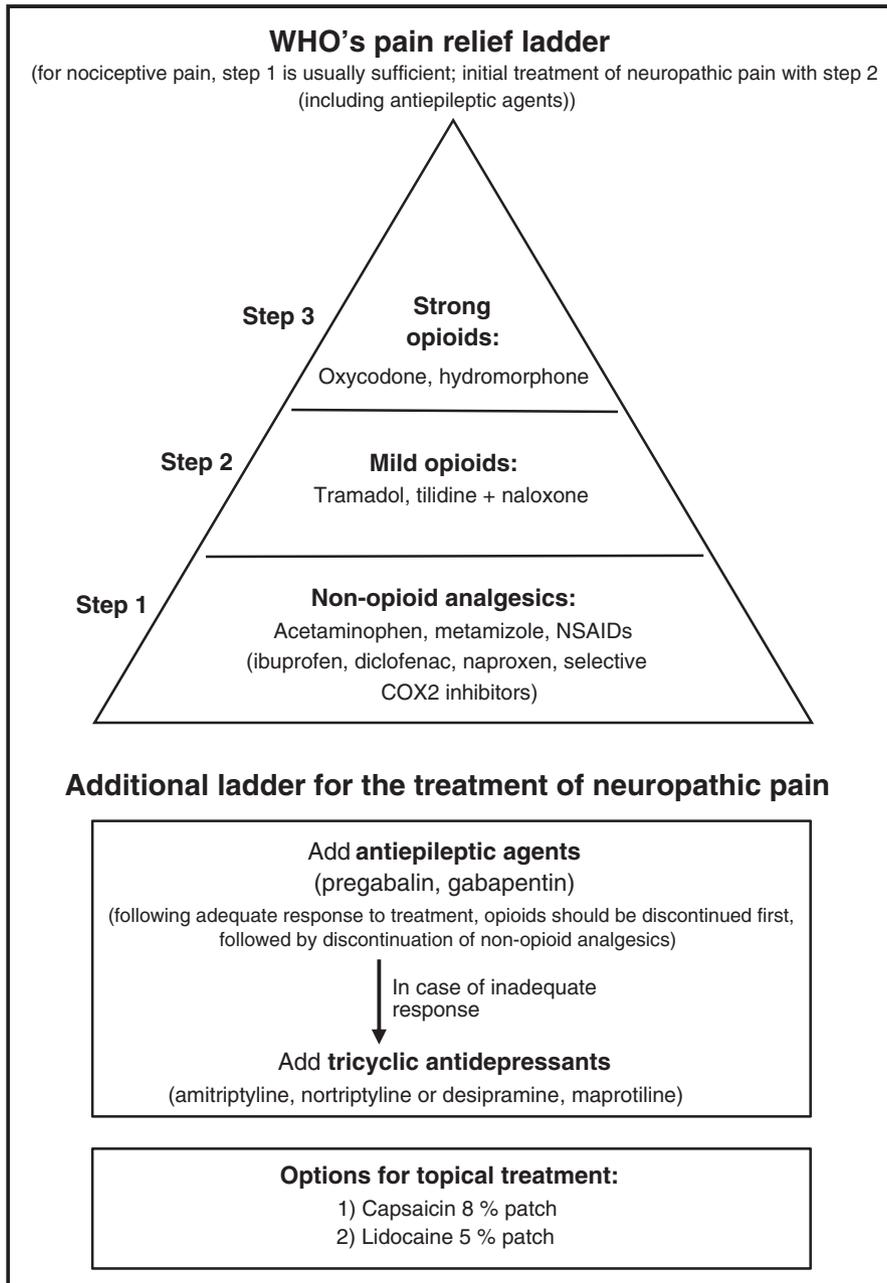


Figure 2 Pain management in patients with herpes zoster.

in which first-degree AV block progressed to third-degree AV block within one week, or in which patients even required a pacemaker due to asystole). If the dose exceeds 100 mg/d, it is recommended that patients undergo regular EKG and drug blood level monitoring, particularly elderly individuals. Moreover, there may be an increased risk of hemorrhage if these drugs are given in combination with factor Xa inhibitors (apixaban). The reason for this is the fact that the latter agents (indirectly) also inhibit thrombin-induced platelet aggregation, and inhibition of serotonin reuptake using SSRIs/SNRIs likewise interferes with platelet aggregation.

Capsaicin is another option for treating neuropathic pain after the vesicles and erosions have healed. An agonist of the vanilloid receptor on primary afferent nociceptive nerve fibers, capsaicin (8 %) is available as a patch formulation. One-time application of this agent causes massive calcium influx into the cell, resulting in pronounced nociceptor excitation followed by spontaneous burning pain. Chronic application leads to degradation of nociceptive nerve endings in the skin associated with reversible loss of function [197, 198]. However, open application of capsaicin 0.025–0.075 % cream has been shown to have only minor effects in patients

Table 30 Recommendations for pain management in herpes zoster, recommendations #40 and #41.

Recommendation	References	Recommendation	Consensus
#40 Analgesic treatment of nociceptive pain based on the WHO's pain relief ladder is recommended (Figure 2). <i>Mild pain intensity:</i> NSAIDs or other non-opioid analgesics <i>Moderate pain intensity:</i> combination of non-opioid analgesics and mild opioids <i>Severe pain intensity:</i> combination of non-opioid analgesics and strong opioids	[185] [6, 181, 186]	↑↑	100 %
#41 In case of protopathic/neuropathic pain, additional treatment with incremental doses of gabapentin or pregabalin (antiepileptic agents) is recommended; if necessary, this may be combined with an antidepressant (for example, amitriptyline) *The aforementioned antidepressant and antiepileptic agents are not approved for the treatment of acute herpes zoster-associated pain. However, severe pain at disease onset usually also has a neuropathic component.		↑↑	100 %

Table 31 Recommendations for pain management in herpes zoster, recommendations #42 and #43.

Recommendation	Recommendation	Consensus
#42 If neuropathic pain does not adequately respond to treatment based on the WHO pain relief ladder, it is recommended to modify the treatment regimen after 2–4 weeks.	↑↑	100 %
#43 In such cases, it may be recommended to add tricyclic antidepressants (for example, amitriptyline); in case of localized pain and after the skin lesions have healed, capsaicin or lidocaine patches may be recommended.	↑	100 %

with postherpetic neuralgia. The cream must be applied 3–4 times daily for 4–6 weeks to achieve the desired effect on nociceptors (2.5 g or 7.5 g of a capsaicin 1 % extract mixed with cold cream to yield 100 g) (Table 31) [199].

In the 2017 update of a Cochrane review [200, 201] (on neuropathic pain and “postherpetic neuralgia”), all studies showed capsaicin to alleviate pain, which was associated with improved sleep and improved quality of life [200, 201].

A key adverse effect is the severe burning sensation in the area of application, caused by the initial excitation of afferent nerve fibers. As a result, many patients discontinue treatment prematurely, before capsaicin can exert its desensitizing effect. Cooling of the skin prior to application of the capsaicin patch will significantly reduce the burning sensation [202]. It is therefore essential that patients be thoroughly informed about this (only) transient adverse effect.

Based on Cochrane reviews and given the lack of high-quality studies, lidocaine 5 % patches cannot be recommended as first-line pain medication for postherpetic neuralgia [203] or neuropathic pain in general [204]. However, as studies do provide evidence for a certain degree of pain

relief, the expert panel recommends lidocaine patches as second-line treatment after capsaicin.

The treatment goal with respect to herpes zoster-associated pain should be optimal pain relief or at least pain reduction down to a level tolerable for the patient. Patients with acute herpes zoster-associated pain are recommended to be followed up beyond the resolution of skin lesions. In case of persistent intolerable pain, it is recommended to refer patients to a pain specialist (Tables 32 and 34).

5.2.3.1 Risk factors for severe neuropathic pain or postherpetic neuralgia (PHN)

The circumstances stated below are commonly associated with neuropathic pain or postherpetic neuralgia (PHN). If present, prophylactic (pain) management may be considered [30, 102]. The individual risk of postherpetic neuralgia may be estimated based on various prognostic factors as proposed by Meister et al. in 1998 [88]: female gender, age > 50 years, number of lesions > 50, cranial/sacral involvement, hemorrhagic lesions, and dermatomal pain during the prodromal phase.

Table 32 Recommendations for pain management in herpes zoster, recommendation #44.

Recommendation	Recommendation	Consensus
#44 In case of persistent pain despite pain management (four weeks after the resolution of skin lesions), co-treatment by a pain specialist is recommended.	↑↑	100 %

Table 33 Recommendations for topical treatment of herpes zoster, recommendation #45.

Recommendation	Recommendation	Consensus
#45 Stage-adjusted topical treatment, may be recommended. This includes antiseptic gels for crusted vesicles, and cooling, antiinflammatory or antiseptic solutions for fresh vesicles.	↑	100 %

Table 34 Recommendations for topical treatment of herpes zoster, recommendation #46.

Recommendation	Recommendation	Consensus
#46 Topical antiviral therapy for cutaneous herpes zoster cannot be recommended.	↓	100 %

Factors reported by other studies include age > 50 years and pain with a severity of $\geq 4/10$ NRS [205], or

- moderate-to-severe prodromal or acute pain,
- immunosuppression (including leukemia, HIV infection, malignancy, immunosuppression in patients following stem cell transplantation and other transplantations, some autoimmune diseases; according to Forbes et al. 2016 [86], this also includes smokers and patients with diabetes),
- severe cutaneous involvement (for example, > 50 vesicles) or hemorrhagic lesions [86, 206].

In the presence of risk factors, antiepileptic agents such as gabapentin (given at specified doses) have also been used for prophylaxis. Previous (low-quality) studies have yielded conflicting results (positive in an uncontrolled open study in combination with valacyclovir in patients with acute herpes zoster [205]; not significant in a controlled prospective study, also in combination with valacyclovir [207]); at least one study is still ongoing [208]. Prophylactic use of gabapentin may be considered in patients with acute herpes zoster and risk factors for prothopathic pain (Table 26) (for example, age > 50 years and one of the aforementioned circumstances); such treatment should be initiated as early as possible (within the first three days after the onset of skin lesions), in addition to antiviral therapy.

For further details, see Appendix 10.1 of the long version of these guidelines at www.awmf.org.

5.2.3.2 Treatment options for persistent pain (postherpetic neuralgia)

A recently published meta-analysis showed that the use of nerve blocks – with local anesthetics and/or corticosteroids

– within three weeks after the onset of herpes zoster was able to significantly reduce the incidence of postherpetic neuralgia at three, six, and twelve months [209] (nine studies, 1,645 patients). Additional subgroup analysis revealed that epidural and paravertebral nerve blocks in particular as well as their repeated administration – as opposed to single blocks – resulted in a significant decrease in the incidence of postherpetic neuralgia [209].

These results are supported by a recent retrospective analysis of 227 patients with herpes zoster-associated pain. This study showed that the combination of standard systemic treatment and epidural nerve block was up to five times more likely to result in successful pain treatment and up to three times more likely to result in complete remission than standard treatment alone; this applied to both acute and chronic herpes zoster-associated pain [210]. However, it should be noted that administration of epidural nerve blocks requires the expertise of experienced anesthesiologists and/or pain specialists.

5.3 Topical treatment

5.3.1 General considerations

There are no studies and thus there is no sufficient evidence that would support the recommendation for topical treatment of acute herpes zoster, with the exception of herpes zoster ophthalmicus (see respective chapter) and topical treatment of neuropathic pain discussed in chapter 5.2.3.

Topical treatment is not expected to provide any clinically relevant antiviral effect, at least there are no randomized placebo-controlled trials demonstrating the effectiveness of

Table 35 Recommendations for topical treatment of herpes zoster, recommendations #47 and #48.

Recommendation		Recommendation	Consensus
#47	For herpes zoster ophthalmicus, it is recommended to supplement systemic treatment with five-times daily application of topical acyclovir preparations (for example, acyclovir 3 % eye ointment) to the affected eye.	↑↑	100 %
#48	For herpes zoster ophthalmicus with disciform keratitis, endo-theliitis, or anterior uveitis, additional application of topical corticosteroids – under close supervision by an ophthalmologist – is recommended.	↑↑	100 %

topical agents (Table 33). Topical treatment should therefore have the following goals, if at all achievable:

- promoting the healing process (for example, by softening and loosening crusts),
- prevention of bacterial infection,
- subjective relief during the acute stages, and
- targeted pain management (see chapter 5.2.3).

Topical treatment should be adjusted to the disease stage. Options include cooling, antiinflammatory or antiseptic solutions for fresh vesicles, and antiseptic gels for removing scabs from crusted lesions.

In general, our experience with the antiseptic and scab-removing effects of polyhexanide-containing gels (hydrophilic polyhexanide 0.04 % or 0.1 % gel, NRF [New German Formulary] 11.131) has been positive. The water content in these gels promotes the degrading activity of skin proteases. We therefore recommend these topical agents for crusted herpes zoster lesions (expert opinion).

While drying and astringent effects are not conducive to wound healing, some may believe (without evidence) that dehydration or altering of the wound environment (from moist to dry) might prevent infection and – consequently – impaired wound healing.

Topical agents to which such characteristics are attributed and that are perceived as having alleviating properties are more likely to exert their effects through their cooling (sterile saline 0.9 %) or antiinflammatory (for example, compresses soaked in black tea, applied for 15–20 minutes six times daily) properties. These agents may be applied as long as they do not make the skin too dry. While the application of astringent zinc oxide lotion is common practice at some centers, we advise against it, as this prevents unobstructed assessment of the lesions. The intended cooling effect may also be achieved by other means.

Cooling and antiseptic effects can be achieved with mild antiseptics, such as polyhexanide 0.02 or 0.04 % solution (NRF 11.128) and octenidine solution (octenidine dihy-

drochloride 0.1 % in *DAC Basiscreme* [vehicle cream] or, alternatively, according to NRF 11.145 with propylene glycol and water but without prednicarbate, Table 34) [211].

5.3.2 Topical treatment in special situations

What constitutes the optimal treatment strategy for herpes zoster ophthalmicus with ocular involvement remains subject to controversial debate, given that a number of randomized controlled trials have shown conflicting results. In one randomized controlled trial investigating the efficacy of topical acyclovir versus betamethasone in herpes zoster-associated keratouveitis, ocular symptoms resolved significantly more rapidly and recurrences were less common in the acyclovir group [212]. In another trial, the time to resolution of ocular inflammation was longer in the acyclovir group than in the corticosteroid group [213]. Based on consensus, the expert panel recommends five-times daily application of acyclovir eye ointment to the affected eye (Table 35), particularly in cases of VZV-associated dendritic keratitis.

The mainstay of treatment for disciform keratitis, endo-theliitis, and anterior uveitis are topical corticosteroids (including subconjunctival administration) in combination with systemic antiviral therapy (Table 35). Corticosteroids should be used with caution and under close ophthalmological supervision, as disease progression may result in thinning and even perforation of the cornea, secondary glaucoma, and superinfection of reactivated dendritic keratitis [214]. Use of topical corticosteroids should be avoided in cases of epithelial involvement in order to prevent epithelial lesions from potentially spreading.

As regards herpes zoster oticus, there is no evidence from trials that would support specific topical treatment.

6 Appendix

Please refer to the long version of the guidelines at www.awmf.org.

7 Handling of conflicts of interest

Please refer to the long version of the guidelines at www.awmf.org.

Correspondence to

Alexander Nast, MD, PhD
Charité – University Medicine Berlin, Department of
Dermatology, Venereology and Allergy
Division of Evidence-Based Medicine (dEBM)
Charitéplatz 1
10117 Berlin, Germany
E-mail: alexander.nast@charite.de