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GUIDELINES

European consensus-based (S2k) Guideline on 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

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Abstract

Herpes zoster (HZ, shingles) is a frequent medical condition which may severely impact the quality of life of affected patients. Different therapeutic approaches to treat acute HZ are available. The aim of this European project was the elaboration of a consensus-based guideline on the management of patients who present with HZ, considering different patient populations and different localizations. This interdisciplinary guideline aims at an improvement of the outcomes of the acute HZ management concerning disease duration, acute pain and quality of life of the affected patients and at a reduction in the incidence of postherpetic neuralgia (PHN) and other complications. The guideline development followed a structured and pre-defined process, considering the quality criteria for guidelines development as suggested by the AGREE II instrument. The steering group was responsible for the planning and the organization of the guideline development process (Division of Evidence-Based Medicine, dEBM). The expert panel was nominated by virtue of clinical expertise and/or scientific experience and included experts from the fields of dermatology, virology/infectiology, ophthalmology, otolaryngology, neurology and anaesthesiology. Recommendations for clinical practice were formally consented during the consensus conference, explicitly considering different relevant aspects. The guideline was approved by the commissioning societies after an extensive internal and external review process. In this second part of the guideline, therapeutic interventions have been evaluated. The expert panel formally consented recommendations for the treatment of patients with HZ (antiviral medication, pain management, local therapy), considering various clinical situations. Users of the guideline must carefully check whether the recommendations are appropriate for the context of intended application. In the setting of an international guideline, it is generally important to consider different national approaches

and legal circumstances with regard to the regulatory approval, availability and reimbursement of diagnostic and therapeutic interventions.

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Conflicts of interest

Interests have been declared at various points of the guideline development by all participating professionals. The complete declarations of interests are published in methods report (online supplement).

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Scope and purpose of the guideline

The quality criteria for guidelines development as suggested by the Appraisal of Guidelines Research and Evaluation (AGREE II) Instrument[1] were incorporated into the development of the guideline. Detailed information on the scope, purpose and methods is reported in the methods report (online supplement).

Five strengths of recommendations were differentiated, expressed by wording and symbols (strong recommendation in favour, ↑↑/weak recommendation in favour, ↑/no recommendation, 0/weak recommendation against, ↓/strong recommendations against, ↓↓).[2] Table 1 shows wording, symbols and implications of each strength of recommendation. The percentage of agreement among the guideline's expert panel was noted and reported (≥50%, ≥75%, ≥90%).

This second part of the guideline is devoted to the treatment of patients who present with Herpes zoster (HZ). It is divided into three sections:

1 Antiviral medication [background texts and recommendations drafted by B. Marinović (lead author), A. F. Nikkels, A. M. Agius, Z. Bata-Csörgő, J. Breuer, G. E. Gross, R. Lapid-Gortzak, T. H. Lesser, U. Pleyer, P. Wutzler],
2 Pain management [background texts and recommendations drafted by M. Schäfer (lead author), R. Lapid-Gortzak (co-lead author), Z. Bata-Csörgő, G. E. Gross], and
3 Local therapy [background texts and recommendations drafted by M. Czarnecka-Operacz (lead author), A. F. Nikkels, A. M. Agius, R. Lapid-Gortzak, T. M. Lesser, U. Pleyer].

The final recommendations were formally consented by the expert panel of the guideline.

Antiviral medication

General considerations for an antiviral medication

In the absence of risk factors for complicated courses (see part 1 of the guideline), HZ usually is a self-limiting disease. Goals of treatment are to improve the outcomes concerning quality of life (QoL) of the affected patients, extent and duration of cutaneous symptoms and intensity and duration of acute zoster-associated

Table 1 Strength of recommendation – wording, symbols and implications (modified from Andrews *et al.*, 2013[2])

Strength	Wording	Symbols	Implications
Strong recommendation for the use of an intervention	'We recommend . . .'	↑↑	We believe that all or almost all informed people would make that choice. Clinicians will have to spend less time on the process of decision-making, and may devote that time to overcome barriers to implementation and adherence. In most clinical situations, the recommendation may be adopted as a policy.
Weak recommendation for the use of an intervention	'We suggest . . .'	↑	We believe that most informed people would make that choice, but a substantial number would not. Clinicians and health care providers will need to devote more time on the process of shared decision-making. Policy makers will have to involve many stakeholders and policy making requires substantial debate.
No recommendation with respect to an intervention	'We cannot make a recommendation with respect to . . .'	0	At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e.g. no reliable evidence data available, conflicting outcomes, etc.)
Weak recommendation against the use of an intervention	'We suggest against . . .'	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
Strong recommendation against the use of an intervention	'We recommend against . . .'	↓↓	We believe that all or almost all informed people would make a choice against that intervention. This recommendation can be adopted as a policy in most clinical situations.

pain (ZAP). Since postherpetic neuralgia (PHN) is the most frequent sequela of HZ, 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.

In controlled trials, a reduced duration of skin symptoms and duration or severity of ZAP could be demonstrated for the systemic application of aciclovir[3–6] and famciclovir[7] when compared to placebo. A meta-analysis of four placebo-controlled trials of oral aciclovir could demonstrate statically significant superiority over placebo regarding time to cessation of pain.[8] Results from RCTs suggest superiority of valaciclovir over aciclovir considering duration and/or severity of ZAP.[9,10] In these studies, no statistically significant differences were seen for the resolution of cutaneous symptoms. No statistically significant differences regarding pain cessation and resolution of skin symptoms were seen in RCTs comparing famciclovir with aciclovir,[11,12] brivudin with aciclovir[13] and valaciclovir with famciclovir.[14] One RCT, contrary to the previously mentioned trials, demonstrated superiority of famciclovir when compared to aciclovir regarding cessation of pain. However, this difference only occurred in the 500 mg famciclovir group and was of questionable clinical significance.[15] Another RCT, contrary to the previously mentioned trial on valaciclovir vs. famciclovir, found a statistically significant earlier reduction in pain with famciclovir.[16]

QoL, as a central patient-reported outcome, was only addressed in a very limited number of trials. Due to the reduction in the duration and intensity of acute ZAP, it is presumed that an antiviral therapy may positively affect QoL. This presumption, however, is not based on scientific observations.

A systematic review demonstrated that neither aciclovir nor famciclovir statistically significantly reduced the incidence of PHN 4–6 months after the onset of acute HZ when compared to placebo.[17] Brivudin was compared with aciclovir in a survey study follow-up of a previously conducted RCT,[13] which found a significantly lower incidence of PHN after brivudin than after aciclovir treatment.[18] In an RCT comparing brivudin with famciclovir, however, no statistically significant between-group differences with respect to pain prevalence and duration were seen.[19]

Regarding ocular complications of HZ ophthalmicus, pain duration and resolution of cutaneous symptoms, systemic application of aciclovir was favourable when compared to topical application of aciclovir in an RCT.[20] No statistically significant differences were seen in RCTs of valaciclovir vs. aciclovir[21] and famciclovir vs. aciclovir.[22]

Controlled studies on antiviral medication have also been conducted in immunocompromised patients: One RCT compared the efficacy of intravenous aciclovir and placebo in immunocompromised patients with localized or disseminated HZ; here, aciclovir was superior considering a reduced incidence of complications (including cutaneous and visceral dissemination).[23] Another RCT in 48 immunocompromised patients, comparing intravenous aciclovir with oral brivudin did not find statistically significant differences regarding cutaneous or visceral dissemination.[24] When compared to vidarabine, aciclovir was statistically significantly superior in preventing cutaneous dissemination, time until cessation of pain and healing of skin symptoms.[25]

Based on consensus and in line with previous guidelines,[26,27] the expert panel recommends the initiation of an antiviral medication in the presence of any of the conditions listed in

Table 2 Health question 2, Antiviral medication, Recommendations #18 and #19

Recommendation		Supporting literature	Strength	Consensus
#18	**We recommend** treating the following patient subgroups with an antiviral medication: -HZ of any localization in patients ≥50 years of age -HZ of the head and/or neck area -HZ of any localization with • moderate to severe zoster-associated pain • haemorrhagic or necrotizing lesions • >1 segment involved • aberrant vesicles/satellite lesions • involvement of mucous membranes -HZ in immunocompromised patients -HZ in patients with severe predisposing skin diseases (e.g. atopic dermatitis) -HZ in children and adolescents under long-term treatment with salicylic acid or corticosteroids	Clinical consensus; Tyring *et al.* 1995[7]; McKendrick *et al.* 1986[3]; Huff *et al.* 1988[4]; Wood *et al.* 1988[5]; Beutner *et al.* 1995[9]; Lin *et al.* 2001[10]; Shen *et al.* 2004[11]; Shafran *et al.* 2004[12]; Wassilew *et al.* 2003[13]; Tyring *et al.* 2000[14]; Degreef *et al.* 1994[15]; Ono *et al.* 2012[16]; Balfour *et al.* 1983[23]; Wutzler *et al.* 1995[24]; Shepp *et al.* 1986[25]	↑↑	≥90%
#19	In patients younger than 50 years of age who present with HZ of the trunk or extremities, without being at risk of or displaying signs of a complicated course, **we suggest** initiating an antiviral medication.		↑	≥90%

recommendation #18 (Table 2). Due to the relatively low risk of complications associated with an antiviral medication, the initiation of an antiviral medication should also be considered in patients who are at low risk of sequela or a complicated course (Table 2).

Based on consensus, an antiviral therapy using intravenous aciclovir is suggested in patients who present with complicated HZ or who are at risk of a complicated course (conditions specified in recommendation #20, Table 3).

Although limited evidence suggests superior efficacy of valaciclovir, famciclovir and brivudin over orally administered aciclovir regarding different outcomes, this evidence was not consistently reproduced. Brivudin offers the advantage of a reduced dosing frequency. However, other factors should also be considered in choosing among an antiviral medication (Table 4). Costs are the lowest for aciclovir. Brivudin is not available in all countries. It is contraindicated for immunosuppressed patients and patients who have been treated with 5-fluoropyrimidine drugs (e.g. 5-fluorouracil, flucytosine) within the last 4 weeks due to possible life-threatening drug interactions.

Adaptation of dosages to the renal function according to the product information is necessary for aciclovir, valaciclovir and famciclovir. For these agents, creatinine should be checked in patients with known or suspected renal insufficiency at the time of treatment initiation (Table 5).

Due to the lack of trials evaluating the initiation of a systemic antiviral medication more than 72 h after onset of the rash, there is no evidence basis to recommend the administration of antivirals in this setting. Based on consensus and as recommended in guidelines previously,[26,27] we suggest an initiation of an antiviral medication at a later point in time in the presence of any of the conditions listed in recommendation #23 (Table 6), if treatment within 72 h after the onset of cutaneous symptoms was not possible.

There are few trials evaluating whether an extended period of intake of antivirals provides benefit over the standard administration for 7 days. These trials found no clinically relevant difference[9] or a benefit of questionable clinical importance with prolonged treatment.[28] Antiviral medication should be prolonged until no more vesicular lesions appear. If vesicle formation extends to more than 7 days, the diagnosis should be reassessed and resistancy to the antiviral medication considered.

Specific situations

Renal function impairment For HZ in patients with renal function impairment, we suggest initiating an antiviral medication with brivudin in the case of indication for oral treatment or with intravenous aciclovir with dosage adaptation in the case of indication for intravenous treatment as defined above (Table 7). This recommendation is based on consensus among the expert panel and on the reasoning that brivudin is relatively less dependent on renal excretion than other antiviral agents and intravenous

Table 3 Health question 2, Antiviral medication, Recommendation #20

Recommendation		Supporting literature	Strength	Consensus
#20	**We suggest** using intravenous aciclovir in patients who present with complicated HZ or who are at risk of a complicated course. This includes the following patient groups: -HZ of the head and/or neck area, particularly in elderly patients -HZ with haemorrhagic/necrotizing lesions, >1 segment involved, aberrant vesicles/ satellite lesions, involvement of mucous membranes or generalized zoster -HZ in immunocompromised patients -HZ with signs of visceral or central nervous system involvement (dosage escalation up to 15 mg/kg bodyweight 3x/d possible, treatment for up to 21 days)	Clinical consensus	↑	≥90%

Table 4 Health question 2, Antiviral medication, Recommendation #21

Recommendation		Supporting literature	Strength	Consensus
#21	In patients who do not present with an indication to initiate an intravenous treatment with aciclovir, **we suggest** shared decision-making with respect to using oral aciclovir, valaciclovir, famciclovir or brivudin, taking e.g. practicability (dosage frequency), costs, contraindications, comorbidity and drug interactions into consideration.	Clinical consensus	↑	≥90%

Table 5 Health question 2, Antiviral medication, Recommendation #22

Recommendation		Supporting literature	Strength	Consensus
#22	**We suggest** checking creatinine in patients with known or suspected renal insufficiency at the time of initiation of an antiviral medication with aciclovir, famciclovir or valaciclovir.	Clinical consensus	↑	≥90%

(in-patient) treatment with aciclovir allows for close examinations of the renal function during the course of treatment.

Ophthalmic HZ The treatment strategy in case of HZ ophthalmicus and necessity for an ophthalmologic reassessment should be determined by an ophthalmologist. Generally, treatment recommendations as specified above apply. Acute retinal necrosis (ARN) as complication of HZ ophthalmicus is an ophthalmic emergency that has to be managed under close supervision of an ophthalmologist. Since ARN is rapidly progressive and may spread to the contralateral eye, it requires immediate treatment with an intravenous induction and oral treatment continuation of antivirals for 3–4 months (Table 8). The prolonged treatment is recommended in order to prevent involvement of the second eye.[29,30] The additional use of systemic corticosteroid in these patients is still controversial in respect to its appropriate initiation. A loading dose of 0.5–1.0 mg/kg/day of corticosteroids (prednisolone) for the first 7–10 days of treatment has been suggested.[30,31] We suggest using topical and systemic corticosteroids as adjunctive anti-inflammatory treatment (Table 8). Caution should be taken to use corticosteroids in the absence of antiviral medication, since this may promote viral replication and even initiate ARN.

Otic HZ The treatment strategy in the case of HZ oticus with involvement of the facial nerve (i.e. Ramsay Hunt syndrome) or with severe pain and cranial nerve palsies should be determined by an otorhinolaryngologist. The expert panel suggests initiating a combination therapy of intravenous aciclovir and oral corticosteroids (Table 9). Corticosteroids are still considered the best treatment in viral inflammatory processes of the facial nerve.[32] In HZ oticus with severe pain and cranial nerve palsies, intravenous aciclovir followed by oral treatment for 1–2 weeks has been used with success.[33–35] Combination treatment is more effective in restoring facial nerve function after HZ oticus[36] and seems to offer better prognosis.[37]

Pregnancy Due to the lack of systematically assessed data on the safety of antiviral medications during pregnancy, careful consideration of possible harms and benefits is recommended. In the absence of the risk of complications (see part 1 of the guideline), we suggest against initiating an antiviral medication

Table 6 Health question 2, Antiviral medication, Recommendations #23 and #24

Recommendation		Supporting literature	Strength	Consensus
#23	**We suggest** initiating antiviral medication as early as possible, within 72 h after the onset of symptoms, or at a later time -as long as new vesicles appear in patients at risk of a complicated course or with manifest complications -in patients with signs of cutaneous, visceral or neurological dissemination -in the case of HZ ophthalmicus or HZ oticus -in all immunocompromised patients	Clinical consensus	↑	≥90%
#24	**We suggest against** initiating an antiviral medication in patients who have 'uncomplicated' HZ (classical, unilateral thoracic or lumbar HZ in patients younger than 50 years of age, without signs of a complicated course) who present >72 h after the onset of skin symptoms.	Clinical consensus	↓	≥90%

Table 7 Health question 2, Antiviral medication, Recommendation #25

Recommendation		Supporting literature	Strength	Consensus
#25	In patients with renal function impairment, **we recommend** using oral brivudin (if oral antiviral medication is indicated) or intravenous aciclovir with dosage adaptation (if intravenous treatment is indicated as defined above).	Clinical consensus	↑↑	≥90%

Table 8 Health question 2, Antiviral medication, Recommendations #26 and #27

Recommendation		Supporting literature	Strength	Consensus
#26	In patients who present with acute retinal necrosis (as complication of HZ ophthalmicus), **we recommend** induction treatment with intravenous aciclovir (10 mg/kg bodyweight 3x/d for 7–10 days)* followed by oral aciclovir (800 mg 5x/d for 3–4 months)*. *Dosage adaptation may be necessary	Wong *et al.* 2013[30]; Pleyer *et al.* 2015[29]	↑↑	≥90%
#27	In patients who present with acute retinal necrosis (as complication of HZ ophthalmicus), **we suggest** to use topical and systemic corticosteroids as adjunctive anti-inflammatory treatment.	Wong *et al.* 2013[30]; Tibbetts *et al.* 2010[31]	↑	≥75%

Table 9 Health question 2, Antiviral medication, Recommendation #28

Recommendation		Supporting literature	Strength	Consensus
#28	In patients with HZ oticus with involvement of the facial nerve (Ramsay Hunt syndrome) or with severe pain and multiple cranial nerve palsies, **we suggest** combination therapy of intravenous aciclovir with systemic corticosteroids.	de Ru *et al.* 2011[36]; Coulson *et al.* 2011[37]	↑	≥90%

Table 10 Health question 2, Antiviral medication, Recommendations #29 and #30

Recommendation		Supporting literature	Strength	Consensus
#29	In the absence of the risk of complications, **we suggest against** initiating an antiviral medication in pregnant women.	Clinical consensus	↓	≥90%
#30	**We suggest** the initiation of an antiviral medication in pregnant women in the presence of risk factors for complicated courses of disease, if potential benefits to the mother outweigh the potential risks to the foetus. In this case, aciclovir should be used preferentially.	Clinical consensus, Pasternak *et al.* 2010[38]; Reiff-Eldridge *et al.* 2000[39]	↑	≥90%

Table 11 Health question 2, Antiviral medication, Recommendations #31 and #32

Recommendation		Supporting literature	Strength	Consensus
#31	In the absence of the risk of complications, **we suggest against** initiating an antiviral medication in children.	Clinical consensus	↓	≥90%
#32	**We suggest** the initiation of an antiviral medication in children in the presence of risk factors for complicated courses of disease, if potential benefits of the treatment outweigh the potential risks.	Clinical consensus	↑	≥90%

in pregnant women who present with HZ (Table 10). In a large population-based retrospective controlled cohort study and in a study including data from registries, the risk of birth defects in children whose mothers had been exposed to aciclovir was not increased. For other antiviral agents (valaciclovir and famciclovir), the number of cases was too small to draw conclusions.[38,39] Therefore, the initiation of an antiviral medication in pregnant women using aciclovir may be suggested in the presence of risk factors for complicated courses of disease, if potential benefits to the mother outweigh the potential risks to the foetus (Table 10).

Children Due to the lack of data on the safety in children, we recommend careful consideration of possible harms and benefits of an antiviral medication. Generally, HZ in children presents with less morbidity than HZ in adults.[40,41] In the absence of the risk of complications (see part 1 of the guideline), we suggest against initiating an antiviral medication in children (Table 11). The initiation of an antiviral medication in children is suggested in the presence of risk factors for complicated courses of disease, if potential benefits outweigh the potential risks (Table 11).

Therapy refractory/chronic HZ lesions Clinical resistance of VZV infections to aciclovir should be considered in the case of treatment failure of drug therapy for at least 10–21 days,[42,43] particularly in patients presenting verrucous VZV infections.[44] When aciclovir resistance occurs, treatment with alternative medications, e.g. with brivudin or another TK-dependent antiviral agent (famciclovir) may be required. In small retrospective case series of immunocompromised patients with aciclovir-resistant HZ, a response to intravenous foscarnet therapy has been observed.[42,45] Anecdotal reports exist which demonstrate responses of aciclovir-resistant VZV strains to cidofovir.[46–48] Both agents are not licensed for the treatment of HZ. They should only be used in very severe cases, with caution due to the risk of severe adverse effects, and only following discussion with virologists, pharmacists and intensive discussion of the risk–benefit balance with the patient. In the case of chronic HZ lesions, we refer to a review article by Wauters *et al.* (2012)[44] on chronic mucocutaneous HZ lesions.

Acute pain management

Introduction

HZ rash is often preceded and accompanied by continuous or episodic sensory sensations such as pain, paresthesia (e.g. burning and tingling), dysaesthesia (altered or painful sensitivity to touch), allodynia (pain associated with non-painful stimuli) or hyperesthesia (exaggerated or prolonged response to painful stimuli).[49,50] Acute ZAP occurs in ≥95% of patients aged >50 years, and 60–70% of patients continue to have persistent pain 1 month after the episode, 40% of those considering it severe.[51,52] While there is abundant literature on PHN,[53,54] evidence on the treatment of acute ZAP is scarce.

Assessment of pain

Pain intensity should be assessed by a validated assessment scale [e.g. Visual Analog Scale or Numeric Rating Scale (NRS)][55,56] (Table 12). Additionally, validated assessment tools may be used to assess neuropathic pain characteristics [Douleur Neuropathique 4 (DN4), PainDETECT (PD-Q) or Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)][55,56] and QoL [SF36 or short form SF12].[55,56]

Further tools may be used to assess response to treatment [e.g. minimum and maximum pain during the last 24 h, pain intensity during movement and satisfaction with pain management (NRS, 0, not satisfied to 10, very satisfied)][55,56] (Table 13). Such tools have been recently validated for acute post-operative pain Europe wide.[57]

Treatment of acute zoster-associated pain

Apart from improving functional status and health-related QoL, controlling acute ZAP is presumed to reduce the risk of PHN, although evidence from controlled studies to support this presumption is not available. Distinct to the treatment of PHN, acute ZAP should preferentially be treated by systemic analgetics and not by local agents (Table 14). It should be taken into account that a process of neuroinflammation is, in part, responsible for the painful sensations.[58,59]

Analgetic treatment of acute ZAP should follow the three-step WHO pain ladder[60] as based on the severity of pain (Table 15) and the individual considerations: in situations of mild pain intensity, NSAIDs or other non-opioids are appropriate; with moderate pain, non-opioids in combination with weak opioid analgetics might be sufficient; with severe pain, non-opioids combined with strong opioids may be required.[27,55,61] Treatment should start according to the severity of pain and not follow a time-consuming stepwise approach.[61] Because of the neuropathic component of pain, tricyclic anti-depressant (e.g. amitriptyline) or anti-epileptic drugs (e.g. gabapentin, pregabalin) may be added as supplement to the basic analgetic treatment.[60,62] Effective plasma concentrations are reached after several days and thus, the basic analgesic treatment should not be postponed. The mentioned anti-depressants and anti-epileptic drugs may not be approved for the indication of acute ZAP treatment.

Table 12 Health question 3, Pain management, Recommendations #33 and #34

Recommendation		Supporting literature	Strength	Consensus
#33	**We recommend** assessing pain intensity by a validated pain assessment scale, e.g. Visual Analog Scale, Numeric Rating Scale (0 = no pain, 10 = worst possible pain).	Clinical consensus, Erlenwein *et al.*, 2016[55]; Haanpää *et al.*, 2011[56]	↑↑	≥90%
#34	**We suggest** using additional tools (questionnaires) in selected patients as described in the background text.	Clinical consensus, Erlenwein *et al.*, 2016[55]; Haanpää *et al.*, 2011[56]	↑	≥90%

Table 13 Health question 3, Pain management, Recommendation #35

Recommendation		Supporting literature	Strength	Consensus
#35	**We suggest** assessing patients' satisfaction with pain management (NRS: 0 = not satisfied to 10 = very satisfied).	Clinical consensus, Erlenwein *et al.*, 2016[55]; Haanpää *et al.*, 2011[56]	↑	≥75%

NRS, Numeric Rating Scale.

Table 14 Health question 3, Pain management, Recommendation #36

Recommendation		Supporting literature	Strength	Consensus
#36	**We recommend** an early initiation of acute ZAP treatment, using systemic analgesics.	Clinical consensus	↑↑	≥90%

ZAP, zoster-associated pain.

Table 15 Health question 3, Pain management, Recommendation #37

Recommendation		Supporting literature	Strength	Consensus
#37	**We recommend** analgesic treatment of HZ pain according to the WHO pain ladder[60] and, if pain severity at baseline is moderate-to-severe or other risk factors for PHN are present, consider supplementing with an anti-depressant (e.g. amitriptyline) or anti-epileptic (e.g. gabapentin, pregabalin) drug*. *The mentioned anti-depressants and anti-epileptic drugs may not be approved for the treatment of acute zoster-associated pain.	Clinical consensus	↑↑	≥90%

PHN, postherpetic neuralgia.

Supplementing pain medication should be considered if pain severity at baseline is moderate-to-severe or other risk factors for PHN are present (Table 15). The individual risk for PHN may be estimated taking various prognostic factors into account as suggested by Meister *et al.* 1998[63]: female gender, age >50 years, number of lesions >50, cranial/sacral localization, haemorrhagic lesions and dermatomal pain in the prodromal phase.

Treatment of ZAP should aim at an optimal pain relief, or if not attainable, at a reduction in pain to a level acceptable for the patient. A follow-up of patients with acute ZAP is suggested, including the period after resolution of skin lesions. In case of persisting pain not acceptable for the patient, a referral to a pain specialist is recommended (Table 16).

Local therapy

General considerations

There is insufficient evidence and expert agreement to make recommendations for a specific topical treatment of acute HZ (Table 17). Clinical practices vary largely among different countries. For all topical treatment decisions, the current status of the skin needs to be assessed. Some experts from the group apply sterile saline 0.9% solution or mild antiseptics such as polyhexanide 20% solution to the affected area for 20–30 min four to six times daily. The application of local zinc oxide lotion is common practice at some centres. Some experts recommend to refrain from any topical treatment but to keep the lesions clean and dry.

The topical application of antiviral agents remains a matter of debate in case of HZ of the trunk and extremities. There are no placebo-controlled RCTs to support using these agents (Table 18).

The topical application of local anaesthetics or capsaicin cream is not advocated. A systematic review of topical lidocaine for the treatment of neuropathic pain[64] concluded that there is no evidence from high quality studies to support its use. Based on consensus, the expert panel recommends treating acute ZAP according to the above-mentioned recommendations, using systemic analgetics (Table 19).

Specific situations

The optimal topical treatment strategy for HZ ophthalmicus remains controversial since RCTs have shown conflicting results: In one RCT assessing the efficacy of topical aciclovir vs. betamethasone in zoster-associated keratouveitis, ocular symptoms resolved significantly quicker and recurrences occurred less frequently in the aciclovir-treated group.[65] In another RCT, a prolonged time to resolution of ocular inflammation was seen when compared to steroid treatment.[66] Based on consensus, the expert panel recommends the application of ocular aciclovir preparations to the affected eye five times daily (Table 20), particularly in case of VZV-associated dendriform keratitis. Topical steroids should be used with caution in staining epithelial lesions.

In disciform keratitis, endotheliitis and anterior uveitis, topical steroids are the mainstay of treatment (Table 20). Steroids

Table 16 Health question 3, Pain management, Recommendation #38

Recommendation		Supporting literature	Strength	Consensus
#38	**We recommend** referral to a pain specialist in the case of persisting pain (e.g. after 4 weeks after the resolution of skin lesions).	Clinical consensus	↑↑	≥90%

Table 17 Health question 3, Local therapy, Recommendation #39

Recommendation		Supporting literature	Strength	Consensus
#39	**We suggest** selecting a topical treatment according to the current status of the skin lesions.	Clinical consensus	↑	≥75%

Table 18 Health question 3, Local therapy, Recommendation #40

Recommendation		Supporting literature	Strength	Consensus
#40	**We cannot make a recommendation** with respect to the application of local antiviral preparations for cutaneous herpes zoster.	-	0	≥90%

Table 19 Health question 3, Local therapy, Recommendation #41

Recommendation		Supporting literature	Strength	Consensus
#41	**We suggest against** the application of local anaesthetic agents or capsaicin for acute HZ.	Clinical consensus, Derry *et al.* 2014[64]	↓	≥90%

Table 20 Health question 3, Local therapy, Recommendations #42 and #43

Recommendation		Supporting literature	Strength	Consensus
#42	In the case of HZ ophthalmicus, **we recommend** the application of local aciclovir preparations (e.g. aciclovir 3% ocular ointment) to the affected eye five times daily.	Clinical consensus	↑↑	≥90%
#43	In the case of HZ ophthalmicus with disciform keratitis, endotheliitis or anterior uveitis, **we recommend** the application of topical steroids under the management of an ophthalmologist.	Clinical consensus	↑↑	≥ 90%

need to be used with caution and under close supervision of an ophthalmologist, as the disease process may cause thinning and even perforation of the cornea, secondary glaucoma and superinfection of reactivated dendriform keratitis.[67]

For HZ oticus, evidence from trials supporting a specific topical treatment approach is not available.

Disclaimer

Guidelines are intended to assist clinicians in standardized clinical situations. The final judgement with regard to the selection and administration of therapeutic interventions lies within the responsibility of the treating physician and must be individualized in light the of all presenting circumstances. Users of the guideline must carefully check whether the recommendations are complete, correct, up-to-date and appropriate considering approval status, dosing regimes, mode of application, contraindications, adverse effects and drug interactions. European guidelines are intended to be adapted to national circumstances (e.g. regarding regulatory approval, availability, reimbursement issues).

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Data S1. Methods report. Contains detailed information on the methods of the guideline development and members of the guideline panel including declarations of interest and management of competing interests.

Data S2: Overview of recommendations. Contains an overview of recommendations of the first and second part of the guideline.