

## 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 1: Diagnosis

R.N. Werner,<sup>1,\*</sup> A.F. Nikkels,<sup>2</sup> B. Marinović,<sup>3</sup> M. Schäfer,<sup>4</sup> M. Czarnecka-Operacz,<sup>5</sup> A.M. Agius,<sup>6</sup> Z. Bata-Csörgő,<sup>7</sup> J. Breuer,<sup>8</sup> G. Girolomoni,<sup>9</sup> G.E. Gross,<sup>10</sup> S. Langan,<sup>11</sup> R. Lapid-Gortzak,<sup>12</sup> T.H. Lesser,<sup>13</sup> U. Pleyer,<sup>14</sup> J. Sellner,<sup>15</sup> G.M. Verjans,<sup>16</sup> P. Wutzler,<sup>17</sup> C. Dressler,<sup>1</sup> R. Erdmann,<sup>1</sup> S. Rossumeck,<sup>1</sup> A. Nast<sup>1</sup>

<sup>1</sup>Division of Evidence Based Medicine in Dermatology (dEBM), Department of Dermatology, Venereology and Allergy, Charité – Universitätsmedizin Berlin, Berlin, Germany

<sup>2</sup>Department of Dermatology, University Medical Center of Liège, Liège, Belgium

<sup>3</sup>Department of Dermatology and Venereology, University Hospital Center Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia

<sup>4</sup>Department of Anesthesiology, Charité – Universitätsmedizin Berlin, Berlin, Germany

<sup>5</sup>Department of Dermatology, Poznan University of Medical Sciences, Poznan, Poland

<sup>6</sup>Department of Otorhinolaryngology, The Medical School, University of Malta, Msida, Malta

<sup>7</sup>Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary

<sup>8</sup>Division of Infection and Immunity, University College London, London, UK

<sup>9</sup>Section of Dermatology and Venereology, Department of Medicine, University of Verona, Verona, Italy

<sup>10</sup>Department of Dermatology and Venereology, Universitätsklinik Rostock, Rostock, Germany

<sup>11</sup>Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

<sup>12</sup>Department of Ophthalmology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

<sup>13</sup>Department of Otolaryngology, University Hospital Aintree NHS Foundation Trust, Liverpool, UK

<sup>14</sup>Department of Ophthalmology, Charité – Universitätsmedizin Berlin, Berlin, Germany

<sup>15</sup>Department of Neurology, Christian Doppler Medical Center, Paracelsus Medical University, Salzburg, Austria

<sup>16</sup>Department of Viroscience, Erasmus MC, Rotterdam, The Netherlands

<sup>17</sup>Department of Virology and Antiviral Therapy, Jena University Hospital, Jena, Germany

\*Correspondence: R.N. Werner. E-mail: ricardo.werner@charite.de

## 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 of the incidence of postherpetic neuralgia and other complications. The guideline development followed a structured and predefined 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 first part of the guideline, diagnostic means have been evaluated. The expert panel formally consented recommendations for the management of patients with (suspected) HZ, referring to the assessment of HZ patients, considering various specific 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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### Abbreviations

AGREE II: *Appraisal of Guidelines Research and Evaluation Instrument II*

ARN: *acute retinal necrosis*

CNS: *central nervous system*

COI: *conflicts of interest*

DFA: *direct fluorescent antibody*

DRG: *dorsal root ganglia*

EADV: *European Academy of Dermatology and Venereology*

EDF: *European Dermatology Forum*

gE: *glycoproteine E*

GRADE: *Grading of Recommendations Assessment, Development and Evaluation*

HSV: *herpes simplex virus*

HZ: *herpes zoster*

IHC: *immunohistochemistry*

PCR: *polymerase chain reaction*

PHN: *postherpetic neuralgia*

TK: *thymidine kinase*

UEMS: *Union Européenne des Médecins Spécialistes (European Union of Medical Specialists)*

VZV: *varizella zoster virus*

ZAP: *zoster associated pain*

### Disclaimer

Guidelines are intended to assist clinicians in standardized clinical situations. The final judgement with regards to the selection and administration of therapeutic interventions lies within the

responsibility of the treating physician and must be individualized in light 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).

### Clinical background/Introduction

Herpes zoster (HZ, shingles) and zoster-associated pain (ZAP) result from a reactivation of varicella zoster viruses (VZV) persisting in the sensory nerve ganglia after the primary infection with VZV.<sup>1</sup> Primary infection usually occurs during childhood and leads to varicella (chickenpox), characterized by a generalized rash, during which a latent infection in sensory neurons in the dorsal root ganglia (DRG) along the entire neuroaxis is established. When virus-specific cellular immunity wanes during ageing<sup>2</sup> or as a result of immunosuppression, a reactivation of the latent infection with replication of VZV in one or more DRG causes HZ. Following reactivation, virions are carried antidromically through the axons via the microtubular system. Having arrived at the intra-epidermal nerve endings and the perifollicular neural network, viral replication is induced in the epidermal and/or infundibular keratinocytes. Classically, virus replication is associated with alterations in keratinocytic differentiation, resembling a pattern of gene expression associated with blistering and vesicle formation.<sup>3</sup> This process is associated with histological evidence of cytopathic changes, including giant cell and syncytia formation, eosinophilic nuclear inclusions and ultimately apoptosis.

With an incidence rate of 2–3/1000 person-years in the general population<sup>4,5</sup> and of 7–10/1000 person-years after the age of 50 years,<sup>6,7</sup> HZ is a frequent medical condition. The rate of hospitalization due to an episode of HZ is reported to be around 10/100 000/year in Spain<sup>8</sup> and the impact of the

disease on the patients' quality of life may be severe.<sup>9,10</sup> The incidence is strongly correlated with age<sup>6,7</sup> and immunodeficiency.<sup>11</sup> A frequent complication of HZ, often difficult to treat, is the postherpetic neuralgia (PHN).<sup>1</sup> Generally, HZ-associated mortality is low in European countries, but was shown to reach up to 19.5/100 000 in specific age groups (>95-year olds).<sup>12</sup>

The recently available vaccine for the prevention of HZ was shown to reduce the incidence of HZ by 51%,<sup>13,14</sup> but insufficient evidence is available to depict a reduction of the incidence of PHN beyond the reduction of the HZ incidence.<sup>15</sup> As life time prevalence of HZ episodes for unvaccinated 85-year olds is estimated to be around 50%,<sup>1</sup> the incidence of HZ in vaccinated populations remains considerable.

### Scope, purpose and methods

The quality criteria for guidelines development as suggested by the Appraisal of Guidelines Research and Evaluation (AGREE II) Instrument<sup>16</sup> 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, ↓↓).<sup>17</sup> 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%) for each recommendation.

To reflect the recent state of the evidence, guidelines need to be continually updated. This guideline will expire after June

2021. Should important changes in the supporting evidence or in current practice occur in the meantime due to new available interventions, new important evidence or withdrawal of drug licensing, the information contained in the guideline will be out-dated earlier.

This first part of the guideline is devoted to diagnostic means in situations that occur in the management of patients who present with (suspected) HZ. This section of the guideline (background texts and recommendations) was drafted by A. F. Nikkels (Lead author), J. Breuer, G. E. Gross, R. Lapid-Gortzak, U. Pleyer, G. M. Verjans, P. Wutzler, A. M. Agius, T. M. Lesser, and J. Sellner. The final recommendations were formally consented within the expert panel of the guideline.

### General considerations

Classically, HZ is a unilateral, dermatomal<sup>18–20</sup> eruption, with skin lesions evolving simultaneously from erythematous macules to papules, vesicles, pustules, and final crusting after about 5–7 days. Usually not the entire dermatome is involved. Clinical signs include pruritus, paresthesia, dysesthesia or anaesthesia. Local lymphadenopathy may be present. Haemorrhagic lesions may occur in patients receiving anticoagulants, antiaggregants and long-term corticosteroids. Most frequently, thoracic dermatomes are affected (55%), followed by regions supplied by the trigeminal nerve (20%), cervical (11%), lumbar (13%) and sacral (2%) dermatomes.<sup>19</sup> Sometimes, adjacent or non-adjacent multisegmental, and in very rare cases bilateral, HZ is observed.<sup>21</sup>

Zoster-associated pain includes the entire pain spectrum of HZ with three distinguishable phases: acute pain phase (up to 30 days), subacute pain phase (30–90 days after rash healing) and post herpetic neuralgia (PHN, pain for more than 90 days

**Table 1** Strength of recommendation – wording, symbols and implications (modified from Andrews *et al.*, 2013<sup>17</sup>)

Strength	Wording	Symbols	Implications
<b>Strong</b> 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
<b>Weak</b> 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.)
<b>Weak</b> recommendation <b>against</b> 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
<b>Strong</b> recommendation <b>against</b> 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

after the onset of rash).<sup>22</sup> A prodromal phase as part of acute ZAP, with an onset of pain or dysaesthesia prior to visible symptoms of HZ, may additionally be distinguished.<sup>23</sup> In the prodromal phase of HZ, pain is present in about 70–90% of the cases and can be observed 2–18 days before the appearance of skin lesions, often leading to a wide array of erroneous diagnoses, according to the anatomical site of VZV reactivation, including myocardial infarction, cholecystitis, etc.<sup>24,25</sup> Pain quality is often described as a ‘burning’, ‘sharp’, ‘stabbing’, ‘pulsating’ localized pain and at times accompanied by an unpleasantness to stroke or light touch.

The clinical diagnosis of HZ is easy in the presence of an asymmetrical (unilateral), unidermatomal rash of grouped vesicles on an erythematous background, associated with prodromal and ZAP<sup>24</sup> (Table 2). However, polymerase chain reaction (PCR) studies demonstrated that the differential diagnosis with zosteriform herpes simplex virus (HSV) infections is erroneous in up to 4–20%.<sup>26–29</sup> Therefore, laboratory testing is suggested in the event of diagnostic uncertainty, particularly in case of HZ of the face and genital areas, as these areas are the natural sites for recurrent labial and genital herpes respectively (Table 2). Atypical mucocutaneous forms are clinically difficult to diagnose, especially when the typical zosteriform distribution is lacking. Other zosteriform dermatoses are to be excluded.<sup>30</sup>

### Molecular techniques

PCR is the most sensitive method reaching 95–100% sensitivity and specificity<sup>31,32</sup> (Table 3). A vesicle fluid swab can be performed on an ulcerated or oozing lesion or after deroofing a vesicular lesion. VZV can also be recovered by PCR from lesion crusts or by swabbing the dried lesion with a moistened swab. Salivary fluid or buccal swabs taken during the acute rash are tested positive for VZV-DNA in up to 100% of cases<sup>33</sup> and may persist positive for weeks.<sup>34</sup> Other clinical specimens appropriate for PCR testing are biopsies, cerebro spinal fluid (CSF), intra-

ocular fluids and blood samples for the detection of VZV viremia.<sup>35</sup> Real-time PCR, ideally in combination with serology on paired serum and CSF/intra-ocular fluid in patients sampled at >2–3 weeks after onset of disease, is the method of choice for diagnosis of HZ with cerebral and ocular complications or other organ involvements.<sup>36–38</sup> Quantitative measurement of VZV-DNA in the CSF and blood may serve as a predictor of the outcome of the disease.<sup>36,38,39</sup> Multiplex PCR enables the simultaneous detection of VZV and other DNA viruses (e.g. HSV-1, HSV-2) in one clinical sample.<sup>40,41</sup> It has to be considered that VZV can also reactivate intermittently, often sub-clinically, shedding small amounts of virus without causing symptoms.<sup>33,35,42</sup>

### Antigen detection

Using monoclonal antibodies directed against different VZV proteins renders direct fluorescent antibody (DFA) or immunohistochemistry (IHC) testing type-specific. The sensitivity and specificity of DFA were reported to be 82–98% and 76–94% respectively<sup>31,32,43,44</sup> (Table 3). When IHC was applied to Tzanck smears of HZ patients, the diagnostic accuracy reached 92.3% [immediate early protein 63 (IE63)] and 94.9% [glycoprotein E (gE)] with a 100% specificity.<sup>45</sup> This study also revealed that the anti-gE antibody seems to be the ideal diagnostic tool. In fact, gE is the major glycoprotein of the VZV envelope. The DFA and IHC on Tzanck smears are easy to perform within 1–3 h. Limitations are the need for experienced staff for the microscopic evaluation and that the scrapings and swabs on the slide must contain sufficient numbers of cells.

### Antibody detection

Serology for detecting VZV-specific IgM, IgG and IgA responses by ELISA, EIA, electron and immunogoldelectron microscopy as well as histochemical staining without IHC on smears are only recommended for HZ diagnosis in specific situations.

**Table 2** Health question 1, diagnostic means, Recommendations #1 and #2

Recommendation	Supporting literature	Strength	Consensus
#1 In the case of classical unilateral HZ of the thoracic or lumbar dermatomes, <b>we recommend</b> clinical diagnosis without laboratory diagnostic confirmation	Clinical consensus	↑↑	≥90%
#2 In cases of diagnostic uncertainty, <b>we suggest</b> using viral antigen detection or molecular based techniques (PCR), particularly in order to distinguish HZ of the face and genital areas from zosteriform HSV-infection	Clinical consensus, Kalman <i>et al.</i> 1986, <sup>26</sup> Yamamoto <i>et al.</i> 1994, <sup>29</sup> Tyring <i>et al.</i> 1995, <sup>28</sup> Rubben <i>et al.</i> 1997 <sup>27</sup>	↑	≥90%

HZ, Herpes zoster.

**Table 3** Health question 1, diagnostic means, Recommendation #3

Recommendation	Supporting literature	Strength	Consensus
#3 <b>We recommend</b> using PCR as technique to identify VZV in sampled material, or antigen detection based methods as valuable alternatives	Sauerbrei <i>et al.</i> 1999 <sup>31</sup> Wilson <i>et al.</i> 2012 <sup>32</sup>	↑↑	≥90%

VZV, varicella zoster viruses.

### Viral culture

Viral culture on human diploid lung fibroblast (W-38 or MRC-5) or on human retinal pigment epithelial (RPE) cells permits isolation of the virus and has long been considered the gold standard. However, due to the instability of this highly cell-associated herpesvirus, sensitivity ranges from 20 to 80% in optimal conditions.<sup>31,41,44,46,47</sup> VZV-induced cytopathic effects usually appear after 3–8 days (mean: 7.5 days).<sup>46</sup> Shell vial cultures permit detection of specific viral antigens even before the appearance of the cytopathic effects.<sup>48</sup> Viral culture remains a useful approach when a viable virus isolate is needed for testing drug sensitivity or molecular characterization.

### Specific situations

**Ophthalmic HZ** is associated with a high rate of complications, especially when the nasociliary division of the ophthalmic nerve is involved, as evidenced by Hutchinson's sign, namely papulovesicular lesions on the side and top of the nose. Significant complications include acute or delayed keratitis, uveitis, conjunctivitis, scleritis, eyelid retraction, oculomotor palsies, paralytic ptosis, secondary glaucoma, optic neuritis or even acute retinal necrosis (ARN) with the risk of bilateral blindness.<sup>49,50</sup> Ocular involvement may occur with delayed onset of more than 4 weeks. Keratitis and uveitis recur in approximately 10% of HZ ophthalmicus patients and increase the risk of visual impairment.<sup>50,51</sup> Since (intra)ocular involvement is common and may not be noted by general inspection, the panel

recommends to ask for ophthalmologist advice in the event of facial HZ with ocular involvement (Table 4), in order to determine the treatment strategy and necessity for ophthalmologist reassessment. The most accurate method to confirm the diagnosis of intraocular involvement is to demonstrate the presence of VZV DNA or intraocular production of anti-VZV antibodies.<sup>52,53</sup>

**Herpes zoster oticus** typically presents as pain in the ear canal, possibly accompanied by an auricular vesicular rash.<sup>54</sup> Ramsey Hunt syndrome is defined as involvement of the facial or auditory nerves, with ipsilateral facial palsy, HZ lesions of the external ear, tympanic membrane and/or the anterior two-thirds of the tongue.<sup>55–57</sup> Complications are vertigo, tinnitus, otalgia, dysgeusia, osteonecrosis and deafness.<sup>58</sup> No specific recommendation for enhanced diagnostic means is proposed in the case of HZ oticus, but due to the risk of severe complications,<sup>58</sup> it is recommended to seek advice of an otorhinolaryngologist, especially in the case of involvement of the facial or auditory nerves (Table 5), in order to determine the treatment strategy and necessity for otorhinolaryngologist reassessment.

**Herpes zoster sine herpette** is defined as the presence of unilateral dermatomal pain without cutaneous lesions in patients with virologic and/or serologic evidence of VZV infection. The most accurate method to confirm the diagnosis is to demonstrate an increase in the blood of anti-VZV IgG and IgM. The identification of specific serum IgA may be of additional

**Table 4** Health question 1, diagnostic means, Recommendation #4

Recommendation	Supporting literature	Strength	Consensus
#4 <b>We recommend</b> seeking for ophthalmologist advice in the event of HZ ophthalmicus in order to exclude complicated courses	Yawn <i>et al.</i> 2013 <sup>50</sup>	↑↑	≥90%

HZ, Herpes zoster.

**Table 5** Health question 1, diagnostic means, Recommendation #5

Recommendation	Supporting literature	Strength	Consensus
#5 <b>We recommend</b> seeking advice of an otorhinolaryngologist in the event of HZ oticus, especially in the case of involvement of the facial and/or auditory nerves	Clinical consensus, Shin <i>et al.</i> 2015 <sup>58</sup>	↑↑	≥90%

HZ, Herpes zoster.

**Table 6** Health question 1, diagnostic means, Recommendation #6

Recommendation	Supporting literature	Strength	Consensus
#6 In the case of suspected HZ sine herpette, <b>we suggest</b> searching for blood increase of anti-VZV IgG and IgM.* In the case of suspected HZ sine herpette with facial palsy, <b>we suggest</b> VZV-DNA detection on oropharyngeal swabs 2–4 days after the onset of facial palsy	Ikeda <i>et al.</i> 1996, <sup>60</sup> Hadar <i>et al.</i> 1990, <sup>59</sup> Furuta <i>et al.</i> 1997 <sup>61</sup>	↑	≥90%

\*The identification of serum anti-VZV IgA may be helpful for the diagnosis of herpes zoster sine herpette and has been suggested by one member of the expert panel. HZ, Herpes zoster; VZV, varicella zoster viruses.

**Table 7** Health question 1, diagnostic means, Recommendation #7

Recommendation	Supporting literature	Strength	Consensus
#7 For atypical mucocutaneous manifestations including lichenoid, verrucous, granulomatous and follicular lesions, <b>we recommend a</b> diagnostic biopsy for lesions without ulceration and a swab when ulceration is present	Clinical consensus	↑↑	≥90%

value.<sup>59,60</sup> In cases of HZ sine herpette with facial palsy, VZV-DNA may be detected in oropharyngeal swabs 2–4 days after the onset of facial palsy using PCR<sup>61</sup> (Table 6).

**Atypical cutaneous presentations** of HZ have been described, including verrucous,<sup>62</sup> lichenoid,<sup>63</sup> follicular,<sup>64,65</sup> granulomatous HZ<sup>66</sup> and granulomatous aneitis.<sup>67–71</sup> In the event of atypical cutaneous manifestations, a diagnostic skin biopsy is advocated to detect the virus using immunohistochemistry, *in situ* hybridization or PCR. If atypical cutaneous manifestations are ulcerated or oozing, a swab may be performed for antigen detection/PCR testing (Table 7).

**Childhood HZ** is quite similar to adult HZ, but ZAP is absent in the majority of cases.<sup>72–74</sup>

**Recurrent HZ** is not uncommon and was observed in 6.2% over a period of 8 years rising to 30% in patients with concomitant immunosuppression.<sup>75</sup>

### Complicated courses of HZ

Cutaneous complications of HZ include hypo- or hyperpigmentation, scarring, keloid formation and bacterial superinfection, clearly related to the severity of the skin lesions.

The most frequent sequela of acute HZ is PHN, usually defined as pain persisting 3 months or more after resolution of the cutaneous HZ lesions. The incidence and severity of PHN increase with age, particularly affecting those aged 50 years or more.<sup>76–78</sup> Individuals affected by ophthalmic HZ with keratitis or intraocular inflammation were found to be at higher risk for PHN.<sup>76</sup> A scoring system for the calculation of the individual PHN risk, including the following risk factors has been proposed: female gender, age >50 years, number of lesions >50, cranial/sacral localization, haemorrhagic lesions, and prodromal

dermatomal pain.<sup>79</sup> In the majority of cases, PHN progressively improves and after 1 year only 1–2% of the patients still experience pain.

Herpes zoster can be more severe and extensive, with disseminated and/or confluent involvement of the skin. Furthermore, VZV can spread from the skin or through VZV viremia to other organs, with a spectrum of single organ VZV involvement, and can be associated with anything from a good prognosis to multi-systemic organ failure, so-called visceral zoster, which is frequently fatal despite high-dose intravenous antiviral treatment.<sup>80,81</sup>

Patients at risk of severe HZ and hence at increased risk for cutaneous and/or systemic dissemination as well as more severe PHN can be identified by a series of risk factors, such as age older than 50 years,<sup>76,77,82</sup> moderate to severe prodromal or acute pain,<sup>76</sup> immunosuppression<sup>77,82–84</sup> including cancer, haemopathies, HIV infected, solid organ and bone marrow transplant recipients, and other patients receiving immunosuppressive therapies. Certain clinical findings at an early stage of HZ identify patients at higher risk of complications. These include the presence of satellite lesions (aberrant vesicles),<sup>85</sup> severe rash and/or involvement of multiple dermatomes or multisegmental HZ,<sup>86</sup> simultaneous presence of lesions in different developmental stages, altered general status, and meningeal or other neurological signs and symptoms. The panel recommends to search for these signs in patients presenting with HZ (Table 8). Table 9 gives an overview of risk factors for complicated courses of HZ.

Asymptomatic involvement of the central nervous system (CNS) is frequently reproducible in patients with HZ of the head/neck area.<sup>87</sup> Among others, encephalitis,

**Table 8** Health question 1, diagnostic means, Recommendations # 8 and #9

Recommendation	Supporting literature	Strength	Consensus
#8 <b>We recommend</b> searching for haemorrhagic/necrotizing lesions, satellite lesions (aberrant vesicles), multisegmental or generalized cutaneous involvement, simultaneous presence of lesions in different developmental stages, altered general status and meningeal signs in every patient who presents with HZ	El Hayderi <i>et al.</i> 2015 <sup>85</sup> ; Nagasako <i>et al.</i> 2002 <sup>86</sup> ; clinical consensus	↑↑	≥90%
#9 <b>We recommend</b> increased surveillance for complicated courses of HZ in patients at an age older than 50 years, concomitant immunosuppression (including cancer, haemopathies, HIV seropositivity, solid organ and bone marrow transplant recipients, and immunosuppressive therapies), concomitant severe atopic dermatitis/eczema, and in patients with HZ of the head/neck area	Clinical consensus; Jemsek <i>et al.</i> 1983 <sup>82</sup> ; Forbes <i>et al.</i> 2016 <sup>76</sup> ; Hillebrand <i>et al.</i> 2015 <sup>77</sup> ; De La Blanchardiere <i>et al.</i> 2000 <sup>83</sup> ; Hughes <i>et al.</i> 1993 <sup>84</sup> ; Yawn <i>et al.</i> 2013 <sup>7</sup> ; Shin <i>et al.</i> 2015 <sup>58</sup>	↑↑	≥90%

HZ, Herpes zoster.

**Table 9** Risk factors for complicated courses of Herpes zoster (HZ)

Risk factor		Increased risk of . . .	
HZ of the head and/or neck area	HZ ophthalmicus	Intraocular involvement and complications <sup>49-51</sup> PHN <sup>76,79</sup> Neurological involvement/sequelae <sup>87</sup>	
	HZ oticus	Vestibulo-cochlear sequelae <sup>58</sup> Neurological involvement/sequelae <sup>87</sup>	
	HZ in other facial or cervical dermatomes	Neurological involvement/sequelae <sup>87</sup>	
HZ with moderate to severe prodromal or acute zoster-associated pain		PHN <sup>76,79</sup>	
HZ with severe rash and/or signs of cutaneous dissemination	Aberrant vesicles	PHN <sup>76,79</sup>	
	Hemorrhagic and/or necrotizing lesions	Cutaneous dissemination <sup>85</sup> Neurological involvement/sequelae <sup>82</sup>	
	Involvement of the mucuous membranes	Visceral dissemination	
	Multisegmental HZ		
	Generalized HZ		
HZ with signs of involvement of the central nervous system		Neurological sequelae Complicated, fatal course	
HZ with signs of visceral involvement		Complicated, fatal course	
HZ in advanced age		PHN <sup>76,77,79</sup> Cutaneous dissemination <sup>77</sup> Neurological involvement/sequelae <sup>77,82</sup>	
	HZ in immunocompromised patients (including cancer, haemopathies, HIV infected, solid organ and bone marrow transplant recipients, and other patients receiving immunosuppressive therapies)		Recurrent HZ <sup>75</sup> Atypical manifestation Cutaneous, neurological and/or visceral dissemination <sup>77,82-85</sup> Persisting HZ/aciclovir-resistant HZ <sup>97,98</sup>
HZ in patients with severe predisposing skin diseases (e.g. atopic dermatitis)		Cutaneous dissemination	

**Table 10** Health question 1, diagnostic means, Recommendation #10

Recommendation	Supporting literature	Strength	Consensus
#10 In case of neurological symptoms and/or signs in the event of HZ, <b>we recommend</b> seeking for neurologist advice and performing a lumbar puncture. An acute MRI is recommended if there are any neurological signs outside the VII and VIII the nerves (e.g. a VI palsy) or if there is any change in the level of consciousness. A CT Scan is suggested when there is a loss of more than 2 points on the Glasgow Coma Scale score	Clinical consensus	↑↑	≥90%

HZ, Herpes zoster.

**Table 11** Health question 1, diagnostic means, Recommendation #11

Recommendation	Supporting literature	Strength	Consensus
#11 <b>We suggest</b> paying particular attention towards symptoms of acute cardio- and cerebrovascular events in patients who present with HZ	Breuer <i>et al.</i> 2014 <sup>89</sup> ; Minassian <i>et al.</i> 2015 <sup>91</sup> ; Langan <i>et al.</i> 2014 <sup>90</sup>	↑	≥90%

HZ, Herpes zoster.

meningoencephalitis, myelitis, cerebellitis, cerebrovascular disease, radiculitis and Guillan–Barré syndrome have been reported as CNS manifestations associated with HZ, predominantly in immunocompromised patients.<sup>70,82–84</sup> Symptomatic motor nerve paralysis is not a frequent complication of HZ, and is usually transitory; it may lead to paralysis of diaphragm paralysis, shoulder, bladder, limb paresis etc., depending on the anatomical site affected by HZ.

Neurological complications of HZ are rare, but nevertheless it is recommended to check for meningeal signs (Table 8). In the case of acute focal neurological dysfunction or other neurological signs and symptoms in HZ patients, further workup involving a neurologist is recommended (Table 10). In any event, an MRI should be performed if there are any long-term sequelae. Furthermore, herpetic encephalitis and meningitis (both HSV- and VZV-induced) appear a risk factor for the sight-threatening

ARN.<sup>88</sup> Since treatment may improve the outcome at least for the second eye, it is relevant for clinicians to be aware of this association.

Herpes zoster was shown to be an independent risk factor for vascular disease, particularly for stroke, transient ischaemic attack, stroke and myocardial infarction.<sup>89–91</sup> We therefore suggest to be particularly attent towards acute symptoms of cardio- and cerebrovascular events (Table 11).

Systemic VZV dissemination in immunocompromised patients with HZ is the most severe, but fortunately rare, acute complication. It is recommended that clinicians exclude

potential associated complications such as pneumonitis, hepatitis, disseminated intravascular coagulation, CNS signs in patients with HZ and acute severely altered general status (Table 12).

### Searching for (occult) risk factors

Herpes zoster is considered an indicator condition for HIV infection, and in various settings, an increased prevalence of HIV seropositivity could be demonstrated for HZ patients, particularly in the presence of multidermatomal or recurrent HZ and in the presence of other risk factors for HIV

**Table 12** Health question 1, diagnostic means, Recommendation #12

Recommendation	Supporting literature	Strength	Consensus
#12 In patients who present with HZ and severely altered general status, <b>we recommend</b> searching for associated complications such as pneumonitis, hepatitis, disseminated intravascular coagulation, or involvement of the central nervous system	Clinical consensus	↑↑	≥90%

HZ, Herpes zoster.

**Table 13** Health question 1, diagnostic means, Recommendation #13

Recommendation	Supporting literature	Strength	Consensus
#13 <b>We recommend</b> testing for HIV infection in younger patients (possible cut-off 50 years of age or younger) exhibiting widespread multidermatomal or recurrent HZ, particularly when lesions are simultaneously present in different disease stages and/or when other risk factors for HIV seropositivity are present	Sullivan <i>et al.</i> 2013 <sup>94</sup> ; Naveen <i>et al.</i> 2011 <sup>92</sup> ; Sharvadze <i>et al.</i> 2006 <sup>93</sup>	↑↑	≥90%

HZ, Herpes zoster.

**Table 14** Health question 1, diagnostic means, Recommendation #14

Recommendation	Supporting literature	Strength	Consensus
#14 <b>We suggest against</b> investigations for cancer only based on the occurrence of HZ	Clinical consensus; Cotton <i>et al.</i> 2013 <sup>96</sup> ; Wang <i>et al.</i> 2012 <sup>95</sup>	↓	≥90%

HZ, Herpes zoster.

**Table 15** Health question 1, diagnostic means, Recommendations #15 and #16

Recommendation	Supporting literature	Strength	Consensus
#15 <b>We recommend</b> suspecting clinical resistance of VZV infections in case of drug therapy failure after 10–21 days, particularly in patients presenting with verrucous VZV infections	Safrin <i>et al.</i> 1991, <sup>97</sup> Saint-Léger <i>et al.</i> 2001, <sup>98</sup> Wauters <i>et al.</i> 2012 <sup>62</sup>	↑↑	≥90%
#16 <b>We suggest</b> that VZV genotyping could be used as technique to provide information on the appearance of aciclovir or other antiviral resistant variants	Boivin <i>et al.</i> 1994, <sup>102</sup> Saint-Léger <i>et al.</i> 2001, <sup>98</sup> Sauerbrei <i>et al.</i> 2011, <sup>101</sup> Brunnemann <i>et al.</i> 2015 <sup>100</sup>	↑	≥90%

VZV, varicella zoster viruses.

**Table 16** Health question 1, diagnostic means, Recommendation #17

Recommendation	Supporting literature	Strength	Consensus
#17 Where available, <b>we suggest</b> to confirm whether HZ in vaccinated patients is due to the vaccine strain by sequencing	Depledge <i>et al.</i> 2014, <sup>105</sup> Costa <i>et al.</i> 2016 <sup>104</sup>	↑	≥90%

HZ, Herpes zoster.

seropositivity.<sup>92–94</sup> In younger patients (possible cut-off 50 years of age) exhibiting HZ, particularly in case of widespread multi-dermatomal or recurrent HZ, simultaneous lesions in different disease stages, or presence of other risk factors for HIV seropositivity, it is recommended to test for HIV infection (Table 13).

Searching for occult cancer in patients with HZ remains debated. In a large cohort of HZ patients, subsequent incidence rates of various types of cancer were analysed. Standardized incidence rates were not increased in this sample.<sup>95</sup> In contrast, a retrospective controlled cohort study found a hazard ratio for the risk of cancer following HZ of 2.42 (95% confidence interval 2.21–2.66).<sup>96</sup> Based on these controversial findings and on clinical consensus, the panel does not recommend investigations for occult cancer solely based on the occurrence of HZ (Table 14).

### Other specific situations

Clinical resistance of VZV infections to aciclovir has been defined as a treatment failure after antiviral drug therapy for at least 10–21 days,<sup>97,98</sup> and particularly observed in patients presenting verrucous VZV infections<sup>62</sup> (Table 15). Phenotypical assessment of aciclovir resistance *in vitro* has been considered the gold standard for resistance testing of VZV, but it is not always feasible and VZV isolation in cell culture has low sensitivity. VZV genotyping is faster and may also provide information on the emergence of aciclovir resistant variants during long-term aciclovir treatment. However, in contrast to HSV,<sup>99</sup> the natural and aciclovir resistance-associated polymorphisms of VZV TK and DNA Pol are incomplete and not yet applicable for diagnostic purposes.<sup>98,100–102</sup> VZV genotyping is restricted to specialized laboratories (Table 15).

It is suggested to confirm whether HZ and any eventual complications occurring in vaccinated patients are due to the vaccine strain<sup>103,104</sup> by PCR or sequencing if this is available (Table 16). Sequencing the viral genome can also exclude recombination.<sup>105</sup>

### References

- Cohen JL. Herpes zoster. *N Engl J Med* 2013; **369**: 255–263.
- Hayward AR, Herberger M. Lymphocyte responses to varicella zoster virus in the elderly. *J Clin Immunol* 1987; **7**: 174–178.
- Jones M, Dry IR, Frampton D, et al. RNA-seq analysis of host and viral gene expression highlights interaction between varicella zoster virus and keratinocyte differentiation. *PLoS Pathog* 2014; **10**: e1003896.
- Insinga RP, Itzler RF, Pellissier JM, Saddier P, Nikas AA. The incidence of herpes zoster in a United States administrative database. *J Gen Intern Med* 2005; **20**: 748–753.
- Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. *Arch Intern Med* 1995; **155**: 1605–1609.
- Pinchinat S, Cebrian-Cuenca AM, Bricout H, Johnson RW. Similar herpes zoster incidence across Europe: results from a systematic literature review. *BMC Infect Dis* 2013; **13**: 170.
- Yawn BP, Gilden D. The global epidemiology of herpes zoster. *Neurology* 2013; **81**: 928–930.
- Gil-Prieto R, Walter S, Gonzalez-Escalada A, Garcia-Garcia L, Marin-Garcia P, Gil-de-Miguel A. Different vaccination strategies in Spain and its impact on severe varicella and zoster. *Vaccine* 2014; **32**: 277–283.
- Lydick E, Epstein RS, Himmelberger D, White CJ. Herpes zoster and quality of life: a self-limited disease with severe impact. *Neurology* 1995; **45**: S52–S53.
- Lukas K, Edte A, Bertrand I. The impact of herpes zoster and post-herpetic neuralgia on quality of life: patient-reported outcomes in six European countries. *Z Gesundh Wiss* 2012; **20**: 441–451.
- Moanna A, Rimland D. Decreasing incidence of herpes zoster in the highly active antiretroviral therapy era. *Clin Infect Dis* 2013; **57**: 122–125.
- Bricout H, Haugh M, Olatunde O, Prieto RG. Herpes zoster-associated mortality in Europe: a systematic review. *BMC Public Health* 2015; **15**: 466.
- Gagliardi AMZ, Silva BNG, Torloni MR, Soares BGO. Vaccines for preventing herpes zoster in older adults. *Cochrane Database Syst Rev* 2012; **10**: CD008858.
- Gagliardi AM, Andriolo BN, Torloni MR, Soares BG. Vaccines for preventing herpes zoster in older adults. *Cochrane Database Syst Rev* 2016; **3**: CD008858.
- Chen N, Li Q, Zhang Y, Zhou M, Zhou D, He L. Vaccination for preventing postherpetic neuralgia. *Cochrane Database Syst Rev* 2011; **3**: CD007795.
- AGREE Next Steps Consortium. The AGREE II Instrument [WWW document] 2009. URL <http://www.agreertrust.org> (Last accessed on 03 June 2016).
- Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol* 2013; **66**: 719–725.
- Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. *Proc R Soc Med* 1965; **58**: 9–20.
- Meister W, Neiss A, Gross G, et al. Demography, symptomatology, and course of disease in ambulatory zoster patients. A physician-based survey in Germany. *Intervirology* 1998; **41**: 272–277.
- Ragozzino MW, Melton LJ 3rd, Kurland LT, Chu CP, Perry HO. Population-based study of herpes zoster and its sequelae. *Medicine (Baltimore)* 1982; **61**: 310–316.
- Pedrosa A, Cruz MJ, Mota A, Baudrier T, Azevedo F. Herpes zoster multiplex and bilateral in an immunocompetent child. *Pediatr Infect Dis J* 2015; **34**: 225–226.
- Johnson RW, Alvarez-Pasquin MJ, Bijl M, et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. *Ther Adv Vaccines* 2015; **3**: 109–120.
- Volpi A, Gross G, Hercogova J, Johnson RW. Current management of herpes zoster: the European view. *Am J Clin Dermatol* 2005; **6**: 317–325.
- Gross G, Schofer H, Wassilew S, et al. Herpes zoster guideline of the German Dermatology Society (DDG). *J Clin Virol* 2003; **26**: 277–289; discussion 91–3.
- Zerngast WW, Paauf DS, O'Connor KM. Varicella zoster with extended prodrome: a case series. *Am J Med* 2013; **126**: 359–361.
- Kalman CM, Laskin OL. Herpes zoster and zosteriform herpes simplex virus infections in immunocompetent adults. *Am J Med* 1986; **81**: 775–778.
- Rubben A, Baron JM, Grussendorf-Conen EI. Routine detection of herpes simplex virus and varicella zoster virus by polymerase chain reaction reveals that initial herpes zoster is frequently misdiagnosed as herpes simplex. *Br J Dermatol* 1997; **137**: 259–261.
- Tyring S, Barbarash RA, Nahlik JE, et al. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. A randomized, double-blind, placebo-controlled trial. Collaborative Famciclovir Herpes Zoster Study Group. *Ann Intern Med* 1995; **123**: 89–96.
- Yamamoto S, Shimomura Y, Kinoshita S, Tano Y. Differentiating zosteriform herpes simplex from ophthalmic zoster. *Arch Ophthalmol* 1994; **112**: 1515–1516.

- 30 El Hayderi L, Libon F, Nikkels-Tassoudji N, Ruebben A, Dezfoulian B, Nikkels AF. Zosteriform dermatoses-A review. *Global Dermatol* 2015; **2**: 163–173.
- 31 Sauerbrei A, Eichhorn U, Schacke M, Wutzler P. Laboratory diagnosis of herpes zoster. *J Clin Virol* 1999; **14**: 31–36.
- 32 Wilson DA, Yen-Lieberman B, Schindler S, Asamoto K, Schold JD, Procop GW. Should varicella-zoster virus culture be eliminated? A comparison of direct immunofluorescence antigen detection, culture, and PCR, with a historical review. *J Clin Microbiol* 2012; **50**: 4120–4122.
- 33 Levin MJ. Varicella-zoster virus and virus DNA in the blood and oropharynx of people with latent or active varicella-zoster virus infections. *J Clin Virol* 2014; **61**: 487–495.
- 34 Nagel MA, Choe A, Cohrs RJ, et al. Persistence of varicella zoster virus DNA in saliva after herpes zoster. *J Infect Dis* 2011; **204**: 820–824.
- 35 Quinlivan ML, Ayres KL, Kelly PJ, et al. Persistence of varicella-zoster virus viraemia in patients with herpes zoster. *J Clin Virol* 2011; **50**: 130–135.
- 36 Aberle SW, Aberle JH, Steininger C, Puchhammer-Stockl E. Quantitative real time PCR detection of Varicella-zoster virus DNA in cerebrospinal fluid in patients with neurological disease. *Med Microbiol Immunol* 2005; **194**: 7–12.
- 37 Knox CM, Chandler D, Short GA, Margolis TP. Polymerase chain reaction-based assays of vitreous samples for the diagnosis of viral retinitis – Use in diagnostic dilemmas. *Ophthalmology* 1998; **105**: 37–44.
- 38 Persson A, Bergstrom T, Lindh M, Namvar L, Studahl M. Varicella-zoster virus CNS disease-viral load, clinical manifestations and sequels. *J Clin Virol* 2009; **46**: 249–253.
- 39 Rottenstreich A, Oz ZK, Oren I. Association between viral load of varicella zoster virus in cerebrospinal fluid and the clinical course of central nervous system infection. *Diagn Microbiol Infect Dis* 2014; **79**: 174–177.
- 40 Engelmann I, Petzold DR, Kosinska A, Hepkema BG, Schulz TF, Heim A. Rapid quantitative PCR assay for the simultaneous detection of herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6 DNA in blood and other clinical specimens. *J Med Virol* 2008; **80**: 467–477.
- 41 Tan TY, Zou H, Ong DCT, et al. Development and clinical validation of a multiplex real-time PCR assay for herpes simplex and varicella zoster virus. *Diagn Mol Pathol* 2013; **22**: 245–248.
- 42 van Velzen M, Ouwendijk WJ, Selke S, et al. Longitudinal study on oral shedding of herpes simplex virus 1 and varicella-zoster virus in individuals infected with HIV. *J Med Virol* 2013; **85**: 1669–1677.
- 43 Coffin SE, Hodinka RL. Utility of direct immunofluorescence and virus culture for detection of varicella-zoster virus in skin-lesions. *J Clin Microbiol* 1995; **33**: 2792–2795.
- 44 Dahl H, Marcocchia J, Linde A. Antigen detection: the method of choice in comparison with virus isolation and serology for laboratory diagnosis of herpes zoster in human immunodeficiency virus-infected patients. *J Clin Microbiol* 1997; **35**: 347–349.
- 45 Nikkels AF, Delvenne P, Debrus S, et al. Distribution of varicella-zoster virus gpI and gpII and corresponding genome sequences in the skin. *J Med Virol* 1995; **46**: 91–96.
- 46 Folkers E, Vreeswijk J, Oranje AP, Duivenvoorden JN. Rapid diagnosis in varicella and herpes-zoster – re-evaluation of direct smear (Tzanck Test) and electron-microscopy including colloidal gold immunoelectron microscopy in comparison with virus isolation. *Br J Dermatol* 1989; **121**: 287–296.
- 47 Nahass GT, Goldstein BA, Zhu WY, Serfling U, Penneys NS, Leonardi CL. Comparison of Tzanck smear, viral culture, and DNA diagnostic methods in detection of herpes simplex and varicella-zoster infection. *JAMA* 1992; **268**: 2541–2544.
- 48 Schirm J, Meulenbergh JJM, Pastoor GW, Vader PCV, Schroder FP. Rapid detection of varicella-zoster virus in clinical specimens using monoclonal-antibodies on shell vials and smears. *J Med Virol* 1989; **28**: 1–6.
- 49 Pleyer U, Metzner S, Hofmann J. Diagnostics and differential diagnosis of acute retinal necrosis. *Ophthalmologie* 2009; **106**: 1074–1082.
- 50 Yawn BP, Wollan PC, St Sauver JL, Butterfield LC. Herpes zoster eye complications: rates and trends. *Mayo Clin Proc* 2013; **88**: 562–570.
- 51 Johnson JL, Amzat R, Martin N. Herpes zoster ophthalmicus. *Prim Care* 2015; **42**: 285–303.
- 52 Kido S, Sugita S, Horie S, et al. Association of varicella zoster virus load in the aqueous humor with clinical manifestations of anterior uveitis in herpes zoster ophthalmicus and zoster sine herpette. *Br J Ophthalmol* 2008; **92**: 505–508.
- 53 Robert PY, Liekfeld A, Metzner S, et al. Specific antibody production in herpes keratitis: intraocular inflammation and corneal neovascularisation as predicting factors. *Graefes Arch Clin Exp Ophthalmol* 2006; **244**: 210–215.
- 54 Dickins JR, Smith JT, Graham SS. Herpes zoster ophthalmicus: treatment with intravenous acyclovir. *Laryngoscope* 1988; **98**: 776–779.
- 55 Chodkiewicz HM, Cohen PR, Robinson FW, Rae ML. Ramsay Hunt syndrome revisited. *Cutis* 2013; **91**: 181–184.
- 56 Sweeney CJ, Gildea DH. Ramsay Hunt syndrome. *J Neurol Neurosurg Psychiatry* 2001; **71**: 149–154.
- 57 Wagner G, Klinge H, Sachse MM. Ramsay Hunt syndrome. *J Dtsch Dermatol Ges* 2012; **10**: 238–244.
- 58 Shin DH, Kim BR, Shin JE, Kim CH. Clinical manifestations in patients with herpes zoster ophthalmicus. *Eur Arch Otorhinolaryngol* 2015; **273**: 1739–1743.
- 59 Hadar T, Tovi F, Sarov B, Sidi J, Sarov I. Detection of specific iga antibodies to varicella zoster virus in serum of patients with Ramsay Hunt syndrome. *Ann Otol Rhinol Laryngol* 1990; **99**: 461–465.
- 60 Ikeda M, Hiroshige K, Abiko Y, Onoda K. Impaired specific cellular immunity to the varicella-zoster virus in patients with herpes zoster ophthalmicus. *J Laryngol Otol* 1996; **110**: 918–921.
- 61 Furuta Y, Fukuda S, Suzuki S, Takasu T, Inuyama Y, Nagashima K. Detection of varicella-zoster virus DNA in patients with acute peripheral facial palsy by the polymerase chain reaction, and its use for early diagnosis of zoster sine herpette. *J Med Virol* 1997; **52**: 316–319.
- 62 Wauters O, Lebas E, Nikkels AF. Chronic mucocutaneous herpes simplex virus and varicella zoster virus infections. *J Am Acad Dermatol* 2012; **66**: e217–e227.
- 63 Nikkels AF, Sadzot-Delvaux C, Rentier B, Pierard-Franchimont C, Pierard GE. Low-productive alpha-herpesviridae infection in chronic lichenoid dermatoses. *Dermatology* 1998; **196**: 442–446.
- 64 Muraki R, Iwasaki T, Sata T, Sato Y, Kurata T. Hair follicle involvement in herpes zoster: pathway of viral spread from ganglia to skin. *Virchows Arch* 1996; **428**: 275–280.
- 65 Nikkels AF, Pierard GE. Necrotizing varicella zoster virus folliculitis. *Eur J Dermatol* 2003; **13**: 587–589.
- 66 Nikkels AF, Pierard GE. Are granulomatous reactions in old zoster lesions due to an immune response to varicella zoster virus envelope glycoproteins? *Clin Exp Dermatol* 1998; **23**: 237–238.
- 67 Chiang F, Panyaping T, Tedesqui G, Sossa D, Costa Leite C, Castillo M. Varicella zoster CNS vascular complications. A report of four cases and literature review. *Neuroradiol J* 2014; **27**: 327–333.
- 68 Gildea DH, Nagel M. Varicella zoster virus in temporal arteries of patients with giant cell arteritis. *J Infect Dis* 2015; **212**(Suppl 1): S37–S39.
- 69 Gildea DH, Mahalingam R, Cohrs RJ, Kleinschmidt-DeMasters BK, Forghani B. The protean manifestations of varicella-zoster virus vasculopathy. *J Neurovirol* 2002; **8**(Suppl 2): 75–79.
- 70 Grahm A, Studahl M. Varicella-zoster virus infections of the central nervous system – prognosis, diagnostics and treatment. *J Infect* 2015; **71**: 281–293.
- 71 Nagel MA, Forghani B, Mahalingam R, et al. The value of detecting anti-VZV IgG antibody in CSF to diagnose VZV vasculopathy. *Neurology* 2007; **68**: 1069–1073.

- 72 Guess HA, Broughton DD, Melton LJ 3rd, Kurland LT. Epidemiology of herpes zoster in children and adolescents: a population-based study. *Pediatrics* 1985; **76**: 512–517.
- 73 Petrusson G, Helgason S, Gudmundsson S, Sigurdsson JA. Herpes zoster in children and adolescents. *Pediatr Infect Dis J* 1998; **17**: 905–908.
- 74 Nikkels AF, Nikkels-Tassoudji N, Pierard GE. Revisiting childhood herpes zoster. *Pediatr Dermatol* 2004; **21**: 18–23.
- 75 Yawn BP, Wollan PC, Kurland MJ, Sauver JLS, Saddier P. Herpes zoster recurrences more frequent than previously reported. *Mayo Clin Proc* 2011; **86**: 88–93.
- 76 Forbes HJ, Thomas SL, Smeeth L, et al. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. *Pain* 2016; **157**: 30–54.
- 77 Hillebrand K, Bricout H, Schulze-Rath R, Schink T, Garbe E. Incidence of herpes zoster and its complications in Germany, 2005–2009. *J Infect* 2015; **70**: 178–186.
- 78 Ghaznawi N, Virdi A, Dayan A, et al. Herpes zoster ophthalmicus: comparison of disease in patients 60 years and older versus younger than 60 years. *Ophthalmology* 2011; **118**: 2242–2250.
- 79 Meister W, Neiss A, Gross G, et al. A prognostic score for postherpetic neuralgia in ambulatory patients. *Infection* 1998; **26**: 359–363.
- 80 Nikkels AF, Delvenne P, Sadzot-Delvaux C, et al. Distribution of varicella zoster virus and herpes simplex virus in disseminated fatal infections. *J Clin Pathol* 1996; **49**: 243–248.
- 81 Volpi A. Severe complications of herpes zoster. *Herpes* 2007; **14**(Suppl 2): 35–39.
- 82 Jemsek J, Greenberg SB, Taber L, Harvey D, Gershon A, Couch RB. Herpes zoster-associated encephalitis: clinicopathologic report of 12 cases and review of the literature. *Medicine (Baltimore)* 1983; **62**: 81–97.
- 83 De La Blanchardiere A, Rozenberg F, Caumes E, et al. Neurological complications of varicella-zoster virus infection in adults with human immunodeficiency virus infection. *Scand J Infect Dis* 2000; **32**: 263–269.
- 84 Hughes BA, Kimmel DW, Aksamit AJ. Herpes zoster-associated meningoencephalitis in patients with systemic cancer. *Mayo Clin Proc* 1993; **68**: 652–655.
- 85 el Hayderi L, Bontems S, Nikkels-Tassoudji N, et al. Satellite lesions accompanying herpes zoster: a new prognostic sign for high-risk zoster. *Br J Dermatol* 2015; **172**: 1530–1534.
- 86 Nagasako EM, Johnson RW, Griffin DR, Dworkin RH. Rash severity in herpes zoster: correlates and relationship to postherpetic neuralgia. *J Am Acad Dermatol* 2002; **46**: 834–839.
- 87 Haanpaa M, Dastidar P, Weinberg A, et al. CSF and MRI findings in patients with acute herpes zoster. *Neurology* 1998; **51**: 1405–1411.
- 88 Ludlow M, Kortekaas J, Herden C, et al. Neurotropic virus infections as the cause of immediate and delayed neuropathology. *Acta Neuropathol* 2016; **131**: 159–184.
- 89 Breuer J, Pacou M, Gauthier A, Brown MM. Herpes zoster as a risk factor for stroke and TIA: a retrospective cohort study in the UK. *Neurology* 2014; **82**: 206–212.
- 90 Langan SM, Minassian C, Smeeth L, Thomas SL. Risk of stroke following herpes zoster: a self-controlled case-series study. *Clin Infect Dis* 2014; **58**: 1497–1503.
- 91 Minassian C, Thomas SL, Smeeth L, Douglas I, Brauer R, Langan SM. Acute cardiovascular events after herpes zoster: a self-controlled case series analysis in vaccinated and unvaccinated older residents of the United States. *PLoS Med* 2015; **12**: e1001919.
- 92 Naveen KN, Tophakane RS, Hanumanthayya K, Pv B, Pai VV. A study of HIV seropositivity with various clinical manifestation of herpes zoster among patients from Karnataka, India. *Dermatol Online J* 2011; **17**: 3.
- 93 Sharvadze L, Tsertsvadze T, Gochitashvili N, Stvilia K, Dolmazashvili E. HIV prevalence among high risk behavior group persons with herpes zoster infection. *Georgian Med News* 2006; **132**: 60–64.
- 94 Sullivan AK, Raben D, Reekie J, et al. Feasibility and effectiveness of indicator condition-guided testing for HIV: results from HIDES I (HIV indicator diseases across Europe study). *PLoS ONE* 2013; **8**: e52845.
- 95 Wang YP, Liu CJ, Hu YW, Chen TJ, Lin YT, Fung CP. Risk of cancer among patients with herpes zoster infection: a population-based study. *Can Med Assoc J* 2012; **184**: E804–E809.
- 96 Cotton SJ, Belcher J, Rose P, Jagadeesan SK, Neal RD. The risk of a subsequent cancer diagnosis after herpes zoster infection: primary care database study. *Br J Cancer* 2013; **108**: 721–726.
- 97 Safrin S, Berger TG, Gilson I, et al. Foscarnet therapy in five patients with AIDS and acyclovir-resistant varicella-zoster virus infection. *Ann Intern Med* 1991; **115**: 19–21.
- 98 Saint-Léger E, Caumes E, Breton G, et al. Clinical and virologic characterization of acyclovir-resistant varicella-zoster viruses isolated from 11 patients with acquired immunodeficiency syndrome. *Clin Infect Dis* 2001; **33**: 2061–2067.
- 99 Sauerbrei A, Bohn-Wippert K, Kaspar M, Krumbholz A, Karrasch M, Zell R. Database on natural polymorphisms and resistance-related non-synonymous mutations in thymidine kinase and DNA polymerase genes of herpes simplex virus types 1 and 2. *J Antimicrob Chemother* 2016; **71**: 6–16.
- 100 Brunnemann AK, Bohn-Wippert K, Zell R, et al. Drug resistance of clinical varicella-zoster virus strains confirmed by recombinant thymidine kinase expression and by targeted resistance mutagenesis of a cloned wild-type isolate. *Antimicrob Agents Chemother* 2015; **59**: 2726–2734.
- 101 Sauerbrei A, Taut J, Zell R, Wutzler P. Resistance testing of clinical varicella-zoster virus strains. *Antiviral Res* 2011; **90**: 242–247.
- 102 Boivin G, Edelman CK, Pedneault L, Talarico CL, Biron KK, Balfour HH Jr. Phenotypic and genotypic characterization of acyclovir-resistant varicella-zoster viruses isolated from persons with AIDS. *J Infect Dis* 1994; **170**: 68–75.
- 103 Bhalla P, Forrest GN, Gershon M, et al. Disseminated, persistent, and fatal infection due to the vaccine strain of varicella-zoster virus in an adult following stem cell transplantation. *Clin Infect Dis* 2015; **60**: 1068–1074.
- 104 Costa E, Buxton J, Brown J, Templeton KE, Breuer J, Johannessen I. Fatal disseminated varicella zoster infection following zoster vaccination in an immunocompromised patient. *BMJ Case Rep* 2016; **2016**: 1–3.
- 105 Depledge DP, Kundu S, Jensen NJ, et al. Deep sequencing of viral genomes provides insight into the evolution and pathogenesis of varicella zoster virus and its vaccine in humans. *Mol Biol Evol* 2014; **31**: 397–409.

## 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.