European consensus-based (S2k) Guideline on the Management of Herpes Zoster

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guided by the European Dermatology Forum (EDF)
in cooperation with the
European Academy of Dermatology and Venereology (EADV)

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PART 1: Diagnosis

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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

Abstract

Background: 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.

Objective: 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 localisations. 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 PHN and other complications.

Methods: 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 organisation 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.

Results: 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.

Conclusion: 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 regards to the regulatory approval, availability and reimbursement of diagnostic and therapeutic interventions.

Keywords: Clinical practice guideline, consensus statements, European guideline, herpes zoster, immunocompromized patients, postherpetic neuralgia, pregnancy, Ramsay-Hunt-Syndrome, recommendations, shingles, zoster ophthalmicus, zoster oticus

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, contra-indications, 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.[1] 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. Decades later, when virus-specific cellular immunity wanes during aging[2] 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, ressembling a pattern of gene expression associated with blistering and vesicle formation.[3] 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[4, 5] and of 7-10/1000 person-years after the age of 50 years,[6, 7] 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[8] and the impact of the disease on the patients' quality of life may be severe[9, 10]. The incidence is strongly correlated with age[6, 7] and immunodeficiency[11]. A frequent complication of HZ, often difficult to treat, is the postherpetic neuralgia (PHN).[1] 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).[12]

The recently available vaccine for the prevention of HZ was shown to reduce the incidence of HZ by 51%[13, 14], but insufficient evidence is available to depict a reduction of the incidence of PHN beyond the reduction of the HZ incidence[15]. As life time prevalence of HZ episodes for unvaccinated 85 year-olds is estimated to be around 50%[1], 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[16] 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, ↓↓)[17]. 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.

Table 1: Strength of recommendation - wording, symbols and implications (modified from Andrews et al., 2013[17])

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.

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 outdated 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[18-20] eruption, with skin lesions evolving simultaneously from erythematous macules to papules, vesicles, pustules, and final crusting after about 5 to 7 days. Usually not the entire dermatome is involved. Clinical signs include pruritus, paresthesia, dysesthesia or anesthesia. Local lymphadenopathy may be present. Haemorrhagic lesions may occur in patients recieving 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.[19] Sometimes, adjacent or non-adjacent multisegmental, and in very rare cases bilateral, HZ is observed[21].

Zoster-associated pain (ZAP) 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 after the

onset of rash)[22]. 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[23]. In the prodromal phase of HZ, pain is present in about 70-90% of the cases and can be observed two to 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.[24, 25] 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[24] (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%.[26-29] 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.[30]

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, **we recommend** clinical diagnosis without laboratory diagnostic confirmation.	Clinical consensus	↑↑	≥ 90 %
#2	In cases of diagnostic uncertainty, **we suggest** 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 et al. 1986[26], Yamamoto et al. 1994[29], Tyring et al. 1995[28], Rubben et al. 1997[27]	↑	≥ 90 %

Molecular techniques

PCR is the most sensitive method reaching 95 to 100% sensitivity and specificity[31, 32] (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[33] and may persist positive for weeks.[34] Other clinical specimens approriate for PCR testing are biopsies, cerebro spinal

fluid (CSF), intra-ocular fluids and blood samples for the detection of VZV viremia[35]. 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.[36-38] Quantitative measurement of VZV-DNA in the CSF and blood may serve as a predictor of the outcome of the disease.[36, 38, 39] Multiplex PCR enables the simultaneous detection of VZV and other DNA viruses (e.g. HSV-1, HSV-2) in one clinical sample.[40, 41] It has to be considered that VZV can also reactivate intermittently, often sub-clinically, shedding small amounts of virus without causing symptoms.[33, 35, 42]

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% to 98 % and 76% to 94%, respectively[31, 32, 43, 44] (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.[45] 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 to 3 hours. 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.

Table 3: Health question 1, Diagnostic means, Recommendation #3

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

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.

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 - 80% in optimal conditions.[31, 41, 44, 46, 47] VZV-induced cytopathic effects usually appear after 3 to 8 days (mean: 7,5 days).[46] Shell vial cultures permit detection of specific viral antigens even before the appearance of the cytopathic effects.[48] 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.[49, 50] 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.[50, 51] 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.[52, 53]

Table 4: Health question 1, Diagnostic means, Recommendation #4

	Recommendation	Supporting literature	Strength	Consensus
#4	**We recommend** seeking for ophthalmologist advice in the event of HZ ophthalmicus in order to exclude complicated courses.	Yawn et al. 2013[50]	↑↑	≥ 90 %

HZ oticus typically presents as pain in the ear canal, possibly accompanied by an auricular vesicular rash[54]. 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[55-57]. Complications are vertigo, tinnitus, otalgia, dysgeusia, osteonecrosis and deafness.[58] No specific recommendation for enhanced diagnostic means is proposed in the case of HZ oticus, but due to the risk of severe complications[58], 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.

Table 5: Health question 1, Diagnostic means, Recommendation #5

Recommendation		Supporting literature	Strength	Consensus
#5	**We recommend** 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 et al. 2015[58]	↑↑	≥ 90 %

HZ sine herpete 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 value.[59, 60] In cases of HZ sine herpete with facial palsy, VZV-DNA may be detected in oropharyngeal swabs two to four days after the onset of facial palsy using PCR[61] (Table 6).

Table 6: Health question 1, Diagnostic means, Recommendation #6

Recommendation		Supporting literature	Strength	Consensus
#6	In the case of suspected HZ sine herpete, **we suggest** searching for blood increase of anti-VZV IgG and IgM.* In the case of suspected HZ sine herpete with facial palsy, **we suggest** VZV-DNA detection on oropharyngeal swabs 2 to 4 days after the onset of facial palsy. *The identification of serum anti-VZV IgA may be helpful for the diagnosis of herpes zoster sine herpete and has been suggested by one member of the expert panel.	Ikeda et al. 1996[60], Hadar et al. 1990[59], Furuta et al. 1997[61]	↑	≥ 90 %

Atypical cutaneous presentations of HZ have been described, including verrucous,[62] lichenoid,[63] follicular,[64, 65] granulomatous HZ[66] and granulomatous angeitis.[67-71] 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).

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, **we recommend** a diagnostic biopsy for lesions without ulceration and a swab when ulceration is present.	Clinical consensus	↑↑	≥ 90 %

Childhood HZ is quite similar to adult HZ, but ZAP is absent in the majority of cases.[72-74]

Recurrent HZ is not uncommon and was observed in 6,2% over a period of 8 years rising to 30% in patients with concommittant immunosuppression.[75]

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 three 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.[76-78] Individuals affected by ophthalmic HZ with keratitis or intraocular inflammation were found to be at higher risk for PHN.[76] 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 localisation, haemorrhagic lesions, and prodromal dermatomal pain.[79] In the majority of cases, PHN progressively improves and after one year only 1-2% of the patients still experience pain.

HZ 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 multisystemic organ failure, so called visceral zoster, which is frequently fatal despite high-dose intravenous antiviral treatment.[80, 81]

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[76, 77, 82], moderate to severe prodromal or acute pain[76], immunosuppression[77, 82-84] 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 higer risk of complications. These include the presence of satellite lesions (aberrant vesicles)[85], severe rash and/or involvement of multiple dermatomes or multisegmental HZ[86], 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.

Table 8: Health question 1, Diagnostic means, Recommendations # 8 and #9

Recommendation		Supporting literature	Strength	Consensus
#8	**We recommend** 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 et al. 2015[85] ; Nagasako et al. 2002[86] ; clinical consensus	↑↑	≥ 90 %
#9	**We recommend** increased surveillance for complicated courses of HZ in patients at an age older than 50 years, concommitant immunosuppression (including cancer, haemopathies, HIV seropositivity, solid organ and bone marrow transplant recipients, and immunosuppressive therapies), concomittant severe atopic dermatitis/eczema, and in patients with HZ of the head / neck area.	Clinical consensus; Jemsek et al. 1983[82]; Forbes et al 2016[76]; Hillebrand et al. 2015[77]; DeLaBlanchardiere et al. 2000[83]; Hughes et al 1993[84]; Yawn et al. 2013[7]; Shin et al 2015[58]	↑↑	≥ 90 %

Table 9: Risk factors for complicated courses of Herpes zoster

Risk factor		**Increased risk of…**
HZ of the head and / or neck area	HZ ophthalmicus	Intraocular involvement and complications[49-51] PHN[76, 79] Neurological involvement / sequelae[87]
	HZ oticus	Vestibulo-cochlear sequalae[58] Neurological involvement / sequelae[87]
	HZ in other facial or cervical dermatomes	Neurological involvement / sequelae[87]
HZ with moderate to severe prodromal or acute zoster-associated pain		PHN[76, 79]
HZ with severe rash and / or signs of cutaneous dissemination	Aberrant vesicles	PHN[76, 79] Cutaneous dissemination[85] Neurological involvement / sequelae[82] Visceral dissemination
	Hemorrhagic and / or necrotizing lesions	
	Involvement of the mucuous membranes	
	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[76, 77, 79] Cutaneous dissemination[77] Neurological involvement / sequelae[77, 82]
HZ in immunocompromised patients (including cancer, haemopathies, HIV infected, solid organ and bone marrow transplant recipients, and other patients receiving immunosuppressive therapies)		Recurrent HZ[75] Atypical manifestation Cutaneous, neurological and / or visceral dissemination[77, 82-85] Persisting HZ / aciclovir resistant HZ[88, 89]
HZ in patients with severe predisposing skin diseases (e.g. atopic dermatitis)		Cutaneous dissemination

Asymptomatic involvement of the central nervous system (CNS) is frequently reproducible in patients with HZ of the head/neck area.[87] Among others, encephalitis, meningoencephalitis, myelitis, cerebellitis, cerebrovascular disease, radiculitis and Guillan-Barré syndrome have been reported as CNS manifestations associated with HZ, predominantly in immunocompromised patients.[70, 82-84] 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.[90] Since treatment may improve the outcome at least for the second eye, it is relevant for clinicians to be aware of this association.

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, **we recommend** 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 was shown to be an independent risk factor for vascular disease, particularly for stroke, transient ischaemic attack, stroke and myocardial infarction[91-93]. We therefore suggest to be particularly attent towards acute symptoms of cardio- and cerebrovascular events (Table 11).

Table 11: Health question 1, Diagnostic means, Recommendation #11

Recommendation		Supporting literature	Strength	Consensus
#11	**We suggest** paying particular attention towards symptoms of acute cardio- and cerebrovascular events in patients who present with HZ.	Breuer et al. 2014[91] ; Minassian et al. 2015[93] ; Langan et al. 2014[92]	↑	≥ 90 %

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).

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, **we recommend** searching for associated complications such as pneumonitis, hepatitis, disseminated intravascular coagulation, or involvement of the central nervous system.	Clinical consensus	↑↑	≥ 90 %

Searching for (occult) risk factors

HZ 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 seropositivity[94-96]. In younger patients (possible cut-off 50 years of age) exhibiting HZ, particularly in case of widespread multidermatomal 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).

Table 13: Health question 1, Diagnostic means, Recommendation #13

Recommendation		Supporting literature	Strength	Consensus
#13	**We recommend** 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 et al. 2013[96]; Naveen et al. 2011[94]; Sharvadze et al. 2006[95]	↑↑	≥ 90 %

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.[97] 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).[98] 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).

Table 14: Health question 1, Diagnostic means, Recommendation #14

Recommendation	Supporting literature	Strength	Consensus

#14	**We suggest against** investigations for cancer only based on the occurrence of HZ.	Clinical consensus; Cotton et al. 2013[98]; Wang et al. 2012[97]	↓	≥ 90 %

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 to 21 days[88, 89], and particularly observed in patients presenting verrucous VZV infections[62] (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,[99] the natural and aciclovir resistance associated polymorphisms of VZV TK and DNA Pol are incomplete and not yet applicable for diagnostic purposes.[89, 100-102] VZV genotyping is restricted to specialized laboratories (Table 15).

Table 15: Health question 1, Diagnostic means, Recommendations #15 and #16

Recommendation		Supporting literature	Strength	Consensus
#15	**We recommend** suspecting clinical resistance of VZV infections in case of drug therapy failure after 10 to 21 days, particularly in patients presenting with verrucous VZV infections.	Safrin et al 1991[88], Saint-Léger et al. 2001[89], Wauters et al. 2012[62]	↑↑	≥ 90 %
#16	**We suggest** that VZV genotyping could be used as technique to provide information on the appearance of aciclovir or other antiviral resistant variants.	Boivin et al. 1994[102], Saint-Léger et al. 2001[89], Sauerbrei et al. 2011[101], Brunnemann et al. 2015[100]	↑	≥ 90 %

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

Table 16: Health question 1, Diagnostic means, Recommendation #17

Recommendation		Supporting literature	Strength	Consensus
#17	Where available, **we suggest** to confirm whether HZ in	Depledge et al.	↑	≥ 90 %

	vaccinated patients is due to the vaccine strain by sequencing.	2014[105], Costa et al. 2016[104]		

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