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Swiss recommendations for the management of varicella zoster virus infections[1]

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Summary

Infections with varicella zoster virus (VZV) are common viral infections associated with significant morbidity. Diagnosis and management are complex, particularly in immunocompromised patients and during pregnancy. The present recommendations have been established by a multidisciplinary panel of specialists and endorsed by numerous Swiss medical societies involved in the medical care of such patients (Appendix). The aim was to improve the care of affected patients and to reduce complications.

Key words: chickenpox; shingles; herpes zoster; varicella zoster virus; acyclovir; valaciclovir; famiciclovir; brivudine

Introduction

This document is aimed at practising physicians who treat patients with varicella zoster virus (VZV) infections. The quality of the recommendations has been evaluated and codified according to the available evidence (table 1).

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Varicella zoster virus – virology and pathogenesis

VZV is a DNA virus from the family of the alpha herpes viruses [1, 2]. After replication at the portal of entry, the VZV spreads via the blood into the skin and mucosa, where further replication takes place, causing the rash typical of varicella. The endings of the sensory nerves in the epithelium are infected. From there the VZV migrates into the sensory ganglia where it establishes a latent infection. During the latency period only a few VZV genes are active. VZV can be reactivated if the immune defences are weakened. VZV has a thymidine kinase and a DNA polymerase, which account for its nucleoside analogues susceptibility. The *antivirals* aciclovir, valaciclovir, famciclovir and brivudine are available for the treatment of VZV infections, taking into account their individual indications and contra-indications (tables 3 and 5). If there is resistance to these nucleoside analogues, foscarnet is the alternative treatment.

Table 1
Evidence and recommendations.

Evidence level	Study type
I	Controlled and randomised study (or systematic review of such studies)
II	Controlled but not randomised study
III	Prospective cohort study
IV	Retrospective cohort study or case-control study
V	Case-series study, expert opinion

Recommendation level	Evidence
A	Good evidence to support the recommendation (in general based on evidence level I)
B	Fair evidence to support the recommendation (in general based on evidence level II or III)
C	Inadequate evidence to support the recommendation (in general based on evidence level IV or V) or decision of the expert group
D	Fair evidence against a recommendation (in general based on evidence level II or III)
E	Good evidence against a recommendation (in general based on evidence level I)

Table 2
Complications of varicella.

Complication	Comment
In children	
Secondary bacterial infections	*Staphylococcus aureus* and *Streptococcus pyogenes* are the most common pathogens Cellulitis, more rarely lymphadenitis or subcutaneous abscesses
	Necrotising fasciitis or toxic shock syndrome due to infection with exotoxin A-producing *S. pyogenes*
Neurological complications	Second most frequent cause of hospitalisation Cerebellitis, encephalitis, cerebellar ataxia
	Very rare: Transverse myelitis, Guillain-Barré syndrome
Other complications	Very rare: Hepatitis, thrombocytopenia, nephritis, arthritis, myocarditis, pericarditis Pancreatitis and orchitis
In adults	
Varicella pneumonia	Symptoms only in 30% of patients! Mortality rate 10%
Encephalitis	Incidence: 1–2/10,000; Mortality rate 5–10%
Myelitis	
Scar formation	
During pregnancy *Pregnant women:*	
Varicella pneumonia	Incidence 16%; mainly in the last trimester
	Mortality rate 20–40%
Foetus:	
1st- 20th week of pregnancy	
Foetal varicella syndrome	Risk 0.4% (1st–13th week of pregnancy)
	Risk 2% (14th–20th week of pregnancy)
After the 20th week of pregnancy	
Congenital varicella	Occurs in the first 5–15 days post partum
	Risk: Mortality rate 30%

Varicella

Epidemiology

VZV has a global distribution. Varicella (chickenpox), the manifestation of the primary infection with VZV, is highly contagious. 96% of susceptible subjects exposed to it develop the disease. About 90% of primary infections occur in children under the age of 10 years. Less than 5% of people develop the disease after the age of 15 years [3](II). Notably, the prevalence of primary VZV infection is lower in tropical and subtropical countries than in Europe and North America [4, 5]. Therefore, individuals from tropical and subtropical countries immigrating into Europe or North America are at increased risk of primary VZV infection in adult-

hood. VZV is shed in respiratory secretions and cutaneous lesions. *Transmission* is airborne or by direct contact of skin and mucosa with the contents of the blisters. The portal of entry is the upper respiratory mucosa and the conjunctiva.

Varicella in children

After incubation for 10–21 days, half of all children show prodromes (fever <39° C, malaise, head and stomach ache). These precede by 24–72 hours the exanthema which initially manifests itself as ex-

Table 3

Post-exposure prophylaxis and antiviral treatment of varicella.

Indication	Medicine	Dosage	Comments
Varicella in children (up to 12 years of age)			
Prophylaxis			
In immunocompetent children:	Not recommended		
In immunocompromised children:	VZV-immunoglobulins	12.5–25 I.U. per kg i.v.	Single dose <48 h after exposure but no later than 96 h after exposure
	IVIG	0.4 g/kg	Single dose (instead of VZV-IG)
Treatment			
In immunocompetent children:	Symptomatic topical antiseptic therapy		
	Optional systemic therapy	Aciclovir 100 mg/kg/day p.o. – 5–10 days	
In immunocompromised children:	Systemic therapy	Aciclovir 3×20 mg/kg/day i.v. – 5–10 days	
Varicella in immunocompetent adults (within the first 24 hours)			
Prophylaxis	Post exposure prophylaxis active vaccination		
Treatment	Aciclovir	5 × 800 mg per day p.o. – 5–10 days	
		3 × 10 mg/kg per day i.v – 5–10 days in severe cases	
	Valaciclovir	3×1000 mg per day p.o. – 7–10 days	
	Famciclovir	3×500 mg per day p.o. – 7–10 days	
In addition to the antivirals, the treatment of varicella includes the use of *analgesics* and *topical therapy* with disinfectants, silver sulphadiazine cream or a cream paste.			
Varicella in immunocompromised adults			
Post-exposure prophylaxis	VZV immunoglobulin	in VZV-seronegative immunocompromised patients **within the first 4 days after exposure**	
Treatment	Aciclovir	3×500 mg/m^2 or 10 mg/kg i.v. per day for 7–14 days	
	Valaciclovir	3×1000 mg per day p.o. – 7 days	
	Famciclovir	3×500 mg per day p.o. – 7 days	
Varicella during pregnancy			
Post-exposure prophylaxis in seronegative pregnant women			
	VZIG or IVIG within 72–96 hours of exposure	VZIG 0.2 ml/kg or IVIG 0.4 g/kg iv.	
Treatment			
Topical symptomatic treatment. Topical antiviral therapy not recommended.			
Antiviral treatment	Acyclovir	3×10 mg/kg per day i.v .– 7 days	if severe or complications
Varicella in neonates			
Prophylaxis			
Indications for VZIG [59]:			
Administration of VZIG immediately after birth or after postnatal exposure:			
– Neonates born to mothers in whom exanthema occurs within the period from 5 (to 7) days before to 2 days after birth (B)			
– Hospitalised premature babies and sick neonates with nosocomial VZV exposure (direct contact or at least one hour in the same room with an infectious person) with non-immune mothers (C)			
– Premature babies <28 weeks of pregnancy or with a birth weight of <1000 g with nosocomial exposure irrespective of the mother's serostatus (C)			
Disputed indication:			
– Healthy full-term babies born to non-immune mothers with postnatal varicella exposure (most likely to be justifiable in the case of exposure in the home from a sibling)			
No indication:			
– Brief exposure in the maternity clinic			
Treatment			
In the case of systemic symptoms or severe exanthema: Acyclovir i.v.		3×20 mg/kg/day	

anthema on the oral mucosa and reddish macules and papules on the scalp, face and trunk. This is rapidly followed by itching blisters and pustules. Different stages of efflorescence are present at the same time. New lesions can develop for up to 7 days. Children with varicella, after exposure in the household, can develop fever and new lesions even after 7 days [6]. Secondary as well as tertiary household contacts are at increased risk for more severe varicella and may benefit from antiviral therapy [7].

The severity of the disease increases with age. Pre-existing skin damage such as atopic dermatitis favours a rapid spread of the exanthema [8]. Pronounced scarring is extremely rare. Hypopigmentation can remain for weeks. The hospitalisation rate is 9.1/10,000 cases of varicella [9]. Serious or even fatal outcomes have been observed in the case of topical or systemic administration of steroids, especially if administered during the incubation period [10, 11]. Recurrence of varicella is extremely rare [12]. The complications of varicella in children are listed in table 2. Reye syndrome [13] is now only rarely observed since salicylates have been contra-indicated in varicella.

Immunocompetent children with varicella are treated without antivirals. Oral aciclovir shortens the course only slightly (I) [6, 14]. In immunocompromised children, intravenous aciclovir is indicated (table 3). Oral valaciclovir, a precursor of aciclovir with improved bioavailability, produces blood levels similar to those with intravenous aciclovir [15]. Due to the limited data available in children, use of valaciclovir can be considered only in those immunocompromised children who exhibit mild varicella disease (C). Children should be kept away from kindergarten or school until the lesions have crusted (C). Immunocompromised or seronegative adult contacts should be identified (C).

Table 4

Complications of Herpes zoster (frequency in %).

Cutaneous:	Bacterial superinfection (2–3%)
	Scarring formation or granulomas
	Hypopigmentation
	Cutaneous dissemination
Ocular:	Keratitis, scleritis, uveitis, chorioretinitis, iridocyclitis
	Ptosis, mydriasis
	Secondary glaucoma
	Acute retinal necrosis (very rare in immunocompetent patients)
Neurological:	Postherpetic neuralgia (up to 50% of patients, age-related)
	Motor neuropathy (mainly in HZ of the cervical segments affecting the N. accessorius)
	Hearing loss in Zoster oticus (0.2%)
	Meningitis and meningoencephalitis (0.5%)
	Acute urinary retention (in case of sacral zoster) (rare)
Visceral:	Pneumonia
	Visceral dissemination

Varicella in adults

Varicella in adults is associated with a more severe prodrome [8]. The risk of potentially fatal *complications* increases with age (table 2). The mortality rate of varicella in adulthood is 17/100,000 [16] and is mainly due to *varicella pneumonia* [17] (II). Pneumonia develops within 1–6 days after the start of the exanthema. In the event of dyspnoea a chest X-ray and hospitalisation are recommended (C). The mortality rate of varicella pneumonia is 10% [18] (II). *Encephalitis* (incidence of 1-2/10,000) is a rare complication which can manifest within 7 days of onset of the exanthema with confusion, bizarre behaviour, lethargy, meningismus and convulsions [19] and has a mortality rate of 5–10% [20] (II). In the case of varicella in adulthood, antiviral *therapy* within 24 hours of the onset of the exanthema is recommended [2, 21] (table 3) (C). In susceptible immunocompetent adults VZV disease may be prevented by post exposure active vaccination if applied within 24 hours after exposure (table 3).

Varicella in immunocompromised patients

Varicella is particularly severe and accompanied by complications in immunocompromised patients [22–24]. There is a high risk of internal organs involvement with high morbidity and mortality rates [23–26] (IV). Frequent complications are pneumonia, which occurs in one-third of children with leukaemia who present with varicella [25] (IV), CNS disorders (meningo-encephalitis, cerebellar ataxia, myelitis), PNS disorders (Guillain-Barré syndrome), hepatitis and bone marrow damage with thrombocytopenia [22]. The diagnosis is usually established clinically. Involvement of the internal organs can be detected by biopsies and VZV can be detected by means of culture, immunohistochemistry or PCR. In the diagnosis of VZV pneumonia, broncho-alveolar lavage can replace the lung biopsy.

Prevention of VZV infections is indicated in immunocompromised patients [22]. As varicella is highly contagious, seronegative immunocompromised patients must be protected from patients with varicella infection. Patients with varicella may already be infectious 2 days before the onset of the exanthema. If immunodeficient VZV-seronegative patients nevertheless come into contact with an infectious patient, prophylactic administration of VZV-immunoglobulins is recommended if this can be performed within 96 hours after contact [2] (C). An important objective of the antiviral therapy of VZV infections in immunocompromised subjects is the prevention of visceral dissemination [27]. It is recommended to consult specialists about the treatment. Intravenous aciclovir is the standard treatment for severely immunodeficient patients (eg after allogenic stem-cell transplantation or during treatment of a rejection reaction after solid organ transplantation) with varicella or Herpes zoster [2, 26, 27] (IA). For patients with less pronounced immunodeficiency and in the absence of

Table 5

Antiviralprophylaxis and treatment of herpes zoster.

Indication	Drug	Dosage	Comments
Indications for antiviral treatment of herpes zoster			
(1) Age: >50 years			
(2) Pain: moderately severe to severe pain before or at start of rash			
(3) Location: H. zoster in the eye area (HZ ophthalmicus); cervical HZ (motor deficits!)			
(4) Immune status: immunocompromised patients (irrespective of the reason for the immunosuppression)			
Antiviral therapy			
In immunocompetent patients:			
Prophylaxis	not recommended		
Therapy	Acyclovir	5×800 mg/day p.o. – 7 days	
	Valaciclovir	3×1 g per day p.o. – 7 days	
	Famciclovir	2–3×250 mg per day p.o. – 7 days*	* dose depending on age and location
	Brivudine	1×125 mg per day p.o. – 7 days**	** absolute contra-indication with fluoropyrimidines and 5-fluorouracil and capecitabine
In addition to the antivirals, the treatment of varicella includes the use of *analgesics* and *topical therapy* with disinfectants, silver sulphadiazine cream or a cream paste.			
In children (<12 years):	Acyclovir	500 mg/m² or 10 mg/kg every 8 h i.v. for 7–10 days i.v.	Valaciclovir and famciclovir not licensed for children <12 years
In immunocompromised patients:			
Prophylaxis	not recommended		Risk of virus resistances after long-term administration of antivirals for VZV
Treatment	Aciclovir	500 mg/m² or 10 mg/kg every 8 h i.v. for 7–10 days i.v. or 5×800 mg per day p.o.	For moderately immunocompromised patients without involvement of internal organs Treatment period 7–10 days
	Valaciclovir	3×1000 mg per day p.o.	same
	Famciclovir	3×500 mg per day p.o.	same
VZV resistance to aciclovir	Foscarnet	60 mg/kg 2–3× per day i.v. for 7–14 days or until lesions completely healed	
Treatment of Herpes zoster in pregnancy			
Topical symptomatic treatment. Topical or systemic antiviral therapy not recommended.			
Treatment of postherpetic neuralgia			
Local anaesthetics			
Lidocaine containing topical formulations Capsaicin (0.025%) cream		In the first 2 weeks must be used 5 times a day, then as required	
Systemic therapy			
(1) Paracetamol, Acetaminophen, NSAID			
(2) Antidepressants Amitriptyline (Saroten®)		Initial dose 25 mg/ day up to 100 mg / day (Check ECG from 75 mg/day)	
(3) Antiepileptics Gabapentin (Neurontin®) Pregabalin (Lyrica®) Carbamazepine (Tegretol®)		900 to 3600 mg daily 600 mg daily 400 to 1600 mg daily	Start dosage 300 mg daily Start dosage 150 mg daily Start dosage 100 to 200 mg daily
(4) Opioids Tramadol Oxycodon (Oxycontin®)		200 to 600 mg daily Initial dosage 2x10 mg daily	
(5) Steroids (controversial)		60 mg/d in the first week 40 mg/d in the second week 20 mg/d in the third week	Only in the acute phase and in combination with virostatics for the first 7 days Note contraindications
Other long-term treatments			
Pain psychotherapy, body-centred self-perception, complementary medicine (acupuncture)			

signs of visceral dissemination of VZV, high-dose oral aciclovir, valaciclovir or famciclovir are possible alternatives [2, 28] (IB) (table 3). Varicella during pregnancy carries a risk to the mother and the risk of vertical, trans-placental transmission (figure 1).

Varicella in pregnancy

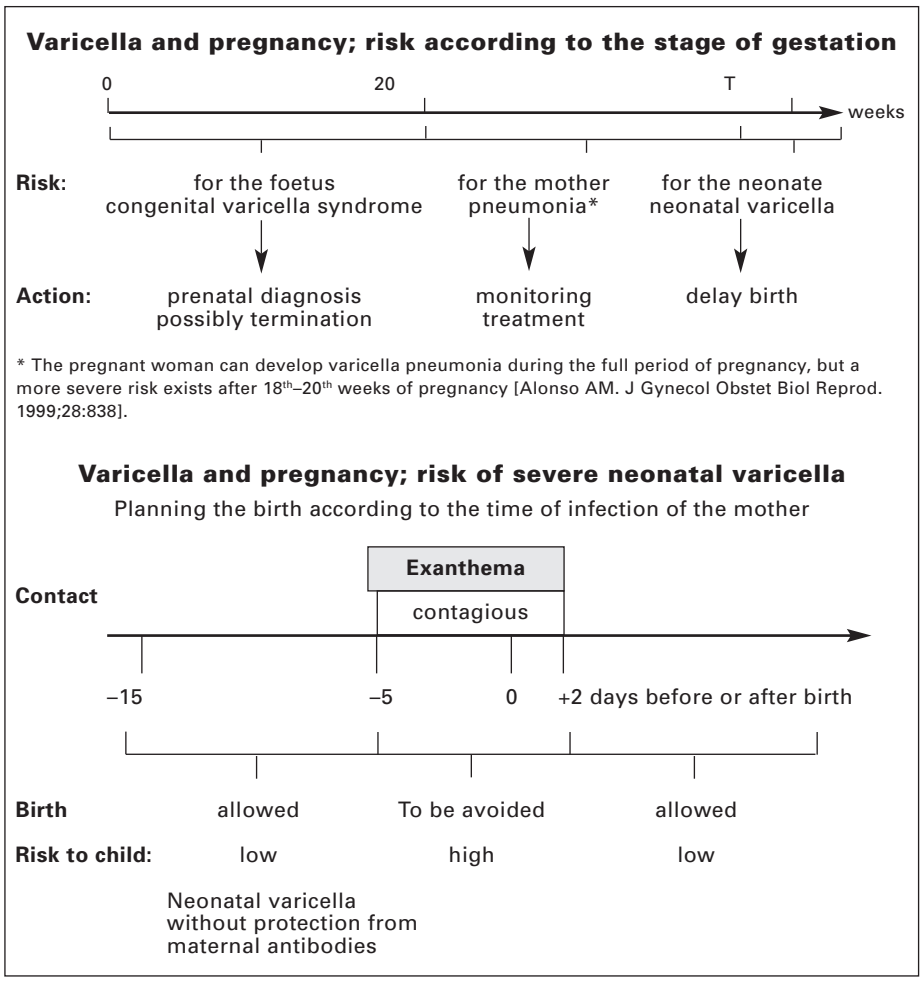
The incidence of varicella is given as one infection per 2000 pregnancies, and may likely be underestimated [29, 30] (III). The infection can be severe in pregnant women and its most common complication is varicella pneumonia [31] (III). It can cause severe, acute dyspnoea and is fatal in 20–40% if left untreated [32]. Early diagnosis and treatment of varicella pneumonia in pregnancy is therefore of great importance, especially in severe forms and in the third trimester [33, 34] (B). Antiviral therapy with aciclovir can also be given during pregnancy and is recommended in the case of pneumonia [35, 36] (table 3) (C). Specific immunoglobulins are not effective in manifest varicella disease (B).

Maternal varicella before the 20th week of pregnancy – risk to the foetus and management

In addition to an increased risk of miscarriage or intrauterine foetal death [37–39] (III) the main risk in this phase of pregnancy is varicella in the embryo or foetus (congenital varicella syndrome) which is characterised by scarring skin lesions (100%), hypoplasia or aplasia of limbs (86%), low birth weight (82%), damage to the eyes (64%), neurological disorders (30%) and retarded psychomotor development (50%) (III). The risk of congenital varicella syndrome is 0.4% when maternal varicella occurs in the first 13 weeks and 2% between the 14th and 20th weeks. It practically never occurs after the 20th week. Varicella during pregnancy does not justify termination without prior prenatal diagnosis (B). Detection of VZV in the amniotic fluid by polymerase chain reaction (PCR) is recommended for the prediction of congenital varicella syndrome in the event of varicella before the 20th week of pregnancy, although there is some controversy about its usefulness [40–42] (C). Sonography provides the best assessment of congenital varicella syndrome, and monthly checks are indicated [43] (B). If a foetal abnormality is detected, the parents should be informed of the possibility of associated brain damage [44]. Termination of the pregnancy should be discussed (B).

If a VZV-seronegative pregnant woman is exposed to VZV, administration of specific immunoglobulins (VZIG) or polyvalent immunoglobulins is recommended to prevent a severe varicella disease (B). Passive immunisation should be given within 72 to 96 hours after exposure, but a favourable effect has also been observed up to 10 days after exposure [38, 45]. A reduction in the risk of congenital varicella syndrome could

Figure 1
Varicella in pregnancy.



not be demonstrated but the incidence of foetal infections appears to be reduced [41] (III). Various forms of treatment, including aciclovir, do not prevent vertical transmission (III).

Maternal varicella in the period around the expected birth date – risk to the foetus and management

In the case of maternal varicella around term, the clinical course of the infection in the neonate depends on the time of transmission (intrauterine or postnatal) and the presence or absence of maternal VZV-specific antibodies [46]. Transplacental transmission in the case of maternal viraemia can lead to a high inoculum, and the absence of maternal antibodies can result in the same outcome as in immunocompromised subjects. The combination of these two factors arises if the maternal exanthema occurs during the period from 5 (or possibly 7) days before to 2 days after the birth (see diagram). In this situation the rash develops in the neonate 5–15 days after birth and a severe clinical course is common with a fatality rate of up to 30% in untreated children [47] (V). However, neonatal varicella after the maternal rash appeared 5–21 days prior to birth has a good prognosis [48] (III). Therefore, in the case of maternal exposure to varicella in the period before term it is important to prevent the birth from occurring in the critical phase from 2 days before to 5 days after the development of exanthema in the mother (C).

Varicella in the neonatal period

When maternal antibodies are present, neonatal varicella is usually mild, both after intrauterine transmission (maternal exanthema more than 5–7 days before birth) and after postnatal exposure [49] (III). The risk of severe neonatal varicella in the case of postnatal transmission and absence of antibodies is not known, but there have been only a few reports of deaths in this situation [50] (V). Nosocomial transmission to premature babies in neonatal intensive care units has been reported [51] and is feared, but can be avoided if the appropriate precautions are taken [52]. Meaningful, primarily preventive, measures include ensuring the VZV immunity of the staff (as a result of earlier infection or vaccination) and a ban on visits by non-immune persons after contact with varicella in the incubation period or by people with varicella.

Administration of specific immunoglobulins to the neonate cannot prevent neonatal varicella, but no deaths and only 10–20% severe cases were observed in two prospective studies on more than 150 neonates born to mothers with exanthema between 7 days before and 2 days after delivery [49, 53] (III). However, deaths have also been reported after administration of immunoglobulins [54–57], and so prompt treatment with aciclovir is recommended [58] (C).

After administration of immunoglobulins it is important to instruct the parents on what to do if symptoms develop [58]. The antibodies administered can extend the incubation period to 28 days. In the case of varicella with systemic symptoms or severe exanthema, intravenous treatment with aciclovir is recommended (C). Starting treatment as soon as any blisters appear is a matter of dispute in view of the large number of mild forms of the disease.

It is not recommended to separate the asymptomatic neonate from its mother if she had varicella exanthema at the time of the birth or develops it subsequently. The probability that the baby has already been infected in utero or in postnatal contact during the viraemic phase before development of the exanthema is so high that the possible remaining preventive effect of such a measure cannot justify the far-reaching psychological effects of absolute separation of mother and baby. Breastfeeding is possible (C).

A common situation requiring consideration is the presence of florid varicella in a sibling at the time of discharge of the baby from hospital. If the mother has immunity to varicella, the risk is very low. If the mother is shown to be seronegative, an attempt can be made to house the sick sibling elsewhere. Administration of immunoglobulins is not recommended [59].

Herpes zoster

Epidemiology

After a latency period of years or decades, VZV can be reactivated and result in herpes zoster (HZ). The annual incidence of HZ in the general population is 1.3 to 3.4 per 1000 inhabitants [60, 61] (II). In Switzerland an annual average of 13,000 patients with HZ can be assumed. The incidence increases after the age of 50 years. Half of all 85-year-olds have suffered HZ (II). About 1 in 20 immunocompetent patients suffer a recurrence of HZ, usually in the same dermatome [61]. As HZ occurs mainly in the elderly and the immuno-compromised, an increasing number of patients with HZ is to be expected in view of the demographic trend.

Herpes zoster in adults

HZ can occur in any dermatome but is most frequently found in the thoracic or lumbar nerve segments (T3-L2) and the distribution area of the trigeminal nerve (V1-3). The preferred site is dependent on gender and age [60, 61] (II). In the majority of cases there are initially *prodromes* for 1–5 days, the quality and intensity of which vary greatly. Pain in the area of distribution of the affected spinal and cerebral nerves, pruritus, paraesthesia (including burning) or anaesthesia/hyperaesthesia can occur in addition to systemic signs. Numerous papules develop in the affected dermatome, in groups on an erythematous back-

ground, and turn into blisters in 12–24 hours and then into pustules. They are often accompanied by severe pain. Haemorrhagic lesions and more rarely necrosis can occur. In immunocompetent patients the blisters start to dry out after 7–10 days with the formation of crusts, which fall off after 2–4 weeks [62]. Shorter and milder forms without progression to blisters can occur [63]. Exanthema may be completely absent (*Zoster sine herpete*). Often there is spread to adjacent dermatomes, while multisegmental HZ of disparate dermatomes (*HZ duplex* or *multiplex*) is rare [64]. HZ with a vesicular rash in the external ear, auditive channel and/or in the homolateral half of hard palate and tongue can be accompanied by facial paresis and hypoacusia (Ramsay-Hunt syndrome) [65].

The indications for antiviral therapy and the dosage for HZ are summarised in table 5. If BVD is used, attention must be paid to the contraindications. Recommendations for treatment of HZ are in accordance with recently published guidelines from other countries [66, 67].

Herpes zoster in the immunosuppressed

The incidence of HZ is considerably increased in the case of cellular immunodeficiency (eg HIV infection, organ transplant recipients) [22, 26]. HZ occurs in 5–32% of transplant recipients [23, 26, 68]. Necrotising forms of HZ and atypical presentations with chronic ulcerations, hyperkeratotic-verrucous or multiform skin lesions occur more frequently in immunocompromised patients [69]. Immunocompromised patients are at increased risk of disseminated mucocutaneous zoster and involvement of internal organs. The fatality rate reaches up to 28% [23, 24, 26]. Generalised HZ is defined as dissemination with more than 20 vesicles in disparate dermatomes [61, 70]. The treatment of HZ in immunocompromised patients depends mainly on the severity of the immunosuppression and the extent of the spread of the HZ [22]. In the case of severe immunosuppression and generalised HZ, intravenous antiviral therapy is indicated [26, 27] (IA).

Herpes zoster ophthalmicus

Due to the high risk of severe lasting functional impairment of the eye in the case of HZ ophthalmicus (HZO), immediate referral to the ophthalmologist is recommended even before HZO is confirmed [71](IIIB). HZO develops as a result of the spread of the reactivating VZV along the branches of the trigeminal nerve that distribute to the eye (V1 and V2; [72] [IB]). In almost all cases, the first branch of the trigeminal nerve is affected, and in 20% the second branch as well. Affection of the supraorbital branch leads to increased involvement of the upper lid. Lacrimal branch involvement results in sicca syndrome and if the nasociliary branch is affected, there is an increased risk of eye damage (Hutchinson sign [73] [IB]). Ophthalmic zoster *sine herpete* and bilateral forms have been described [74] (IVC). Eye complications are observed in more than 50% of cases, even with treatment [75] (IA).

Even in younger, immunocompetent patients, HZO is a clear indication for systemic antiviral therapy [76–78] (IB). Systemic therapy should be started as soon as possible, but can reduce the risk of intraocular involvement by more than 50% even if delayed beyond the 72-hour limit [79] (IB). For symptomatic treatment, a tear film substitute can also be considered, and careful local and systemic steroid therapy should be considered per individual case [80] (I, B). The frequently prescribed local antiviral therapy is of no additional benefit and is therefore not recommended if systemic therapy is required.

Herpes zoster in children

HZ in children is very rare with an estimated incidence of 0.74 cases/1000 children per year [81] (III). Varicella *in utero* or during the first year of life increases the risk of HZ in early childhood [82] (III). The symptoms are the same as in adults, although the skin lesions are less prominent and the symptoms of acute neuritis are mild or absent. Unlike adults, children do not suffer post-herpetic neuralgia [83] (III). If the cranial nerves are affected, conjunctivitis, dendritic keratitis, anterior uveitis, iridocyclitis, retinitis and facial paresis can occur as complications [84, 85]. Lumbosacral HZ can be complicated by neurogenous bladder dysfunction or ileus with intestinal obstruction [84, 86]. Antiviral therapy is not necessary in children with uncomplicated HZ not affecting the face (C).

Herpes zoster in pregnancy

Unlike varicella, HZ during pregnancy does not seem to pose a risk of congenital infection, irrespective of the time between HZ and birth [38, 87, 88] (III). Pregnancy has no effect on the course of HZ. The indications for antiviral therapy correspond to those for adults (C).

Post-herpetic neuralgia

Post-herpetic neuralgia (PHN) can be defined as chronic neuropathic pain that persists or develops 30 days after the skin lesions of HZ have healed [89]. PHN is often therapy refractory and may persist for several months to years [90]. PHN occurs in 10–20% of all HZ patients, and is rare in patients aged <40 years. Different incidence rates have been reported which may be in part due to different definitions of PHN. The incidence of PHN increases with age. In HZ patients >50 years the risk of PHN is 50%. Age (>50 years), pain during the prodromal and acute phase of the HZ and cranial or sacral location of HZ are regarded as risk factors for PHN (II). PHN is a neuropathic pain and develops primarily as a result of lesions to the pain-mediating nervous system itself. PHN can be of various forms and may present with sharp, deep boring, burning pain sensations or itching and can be associated with hyperaesthesia or allodynia. The sequelae include chronic fatigue, sleep disor-

ders, depression and a general reduction in quality of life.

Moderately severe and severe pain during the prodromal and acute phase is an indication for early antiviral therapy. The risk of PHN is reduced by the antivirals licensed for the treatment of HZ (A). Antiviral treatment for more than 7 days is not indicated [78]. Immediate and lasting analgesia right from the early phase may have a preventive effect on the development of PHN [91]. Treatment of established PHN is symptomatic and corresponds in general to the treatment of neuropathic pain. Centrally acting modulators have the most effect (table 5). The evidence supports the oral use of tricyclic antidepressants, certain opioids, and gabapentinoids in PHN. Topical therapy with lidocaine patches and capsaicin is similarly supported [92, 93]. Systemic steroids improve the quality of life in the acute phase of zoster-associated pain but do not reduce the risk of PHN [80]. The choice of the long-term treatment should consider side-effects such as sedation or mood enhancement.

Investigation of underlying diseases

Unisegmental HZ in immunocompetent elderly patients is not an indication for a screening investigation for malignancies [94,95] (IIIB). Nor could any such connection be found in children [96] (IIIB). In hospitalised patients with HZ, a 1.2-fold increase in the risk of malignancies, especially lymphoproliferative diseases, has been detected [97] (IIIC). Screening is not recommended because the detection rate is low. HZ in children does not require any further investigation. HZ in young adults (under 40 years of age) is 10–20 times more frequent in conjunction with HIV infection than in subjects with a healthy immune system. The cumulative incidence in HIV patients over ten years is 41% [98, 99] (II). In the case of corresponding risk behaviour, an HIV test should be carried out (IIB).

Varicella zoster virus infections in hospital

Patients with VZV infections are mainly hospitalised in three situations: (1) in the case of respiratory complications of varicella, which occur mostly in adults, (2) if the extent of the HZ is severely impairing the patient's general condition or if there is a risk of complications (eg Herpes zoster ophthalmicus) or if such complications are present, and (3) in immunocompromised subjects with multisegmental or disseminated HZ.

From the standpoint of hospital hygiene, the infectivity of patients with VZV infections is relevant for hospitalisation or outpatient care. Varicella is highly contagious as the VZV is excreted in respiratory secretions and transmitted by aerosol. In patients with HZ of limited extent there is no or extremely little aerosol infectivity, as VZV is not released into the air in sufficient concentrations from the skin lesions. Transmission by direct contact with non-crusted lesions is possible (IV). In patients with limited HZ, topical covering of skin lesions but not isolation measures is recommended.

Hospital hygiene measures include isolation of patients with varicella during inpatient care, in order to protect other patients and non-immune staff from infection. Isolation is done in single rooms which can only be entered by immune people. No particular protective measures are required to protect immune individuals. These protective measures also apply for patients with disseminated, reactivated VZV infection or with multi-segmental HZ, as these patients may be slightly more contagious, although conclusive data in this respect are missing.

Medical institutions should take precautions to prevent transmission of VZV infections from infected staff. As 80–95% of adults are immune to VZV in the industrialised countries, the proportion of medical staff who is potential carriers of VZV infection is relatively low. Regarding non-immune medical staff (including medical students), there are two possible procedures which are based on the medical history relating to varicella. Individuals with a positive history for varicella can be assumed to be immune. When the history is not conclusive the immune status can be tested by serology. When the immune status is negative the person should be vaccinated against VZV. On the other hand, vaccination of all those with a negative history can be carried out automatically as a pragmatic measure. Complete immunity of the medical staff is particularly important in paediatric, neonatal and obstetric departments. Many hospitals follow the strategy that all medical staff must demonstrate immunity to VZV. A recent cost-effectiveness analysis compared the cost per avoided case of varicella among a theoretical cohort of 63,353 physician and nurses aged less than 45 years in Israel. Screening and vaccination of susceptible workers using anamnestic selection was expected to reduce future cases, within 20 years since vaccination, from 58.3 to 33.0 with an incremental cost of US $ 23,713 per avoided case. Using only serological tests to detect susceptible workers would prevent an additional 5.7 cases with an incremental cost of US $ 206,692 per avoided case [100].

Diagnosis

Detection of the virus

The virus or its components (eg an envelope protein or the virus genome) can be detected using various techniques (table 6), if a diagnosis cannot be made clinically. The following possibilities for detecting VZV are available:

– virus detection by culture
– detection of virus antigen by means of specific antibodies
– detection of sequences of the virus genome after enzymatic amplification (polymerase chain reaction = PCR)

The most widely employed methods are summarised in table 6. Due to their differing sensitivity and specificity, application of these techniques depends on the stage of the disease. Detection of VZV by virus culture is a relatively time-consuming detection technique, which requires a special virus transport medium and is less sensitive than direct detection by immunofluorescence or electron microscopy. By combining culture ("shell vial" technique) and immunofluorescence, the detection can be considerably accelerated and the sensitivity increased. Detection of the virus genome by polymerase chain reaction (PCR) has now become the method of choice for various sample materials such CSF or aqueous humour. Compared with culture, the sensitivity of the VZV-specific PCR with swabs is 95% with a specificity of 100% [101, 102]. Pre-analysis or laboratory-associated contaminations must be avoided in order to avoid false positive results [102].

Detection of antibodies

The most important indication for VZV serology is ascertainment of immune status, ie detection of VZV-specific IgG in the case of potentially increased risk of disease or transmission, such as exposure to varicella in pregnancy or immune dysfunction before transplantation or chemotherapy. However there is no international standard which makes it possible to determine the minimal protective titre value. The diagnostic value of detection of VZV-specific IgM is limited, on the one hand, by the commonly straightforward clinical diagnosis of the primary infection as varicella, and on the other hand, by low sensitivity and specificity in other manifestations such as herpes zoster. Immunofluorescence or the ELISA technique is mainly used for the detection of VZV-specific antibodies. With the most sensitive methods antibodies can be measured just 3–4 days after the development of the exanthema. The detection of VZV-specific intrathecal antibody production is a rare special indication when VZV-infection of the CNS is suspected, which can only be detected in later phases of the disease. In general virus detection should be the preferred mode of detection.

Varicella zoster virus vaccination

Attenuated VZV live vaccines based on the Oka strain have been available since the eighties and have been recommended in the USA as routine vaccination for children after 12 months of age and as a booster for older children without a history of varicella since 1996 [103]. One dose is administered at the age of 1 to 10 years, and two doses 4 weeks apart after the age of 11 years. The vaccination is well tolerated. Undesirable effects are observed in 5–35%. About 20% experience local reactions at the injection site. 3–5% develop a localised or generalised varicella-like rash (I) [103]. The vaccination produces seroconversion in 90–100% (I) and gives >80% of vaccinees com-

Table 6
Diagnosis of VZV infection.

Method	Properties	Sample	Sensitivity	Specificity
Immunofluorescence (detection of infected cells) Price: 25 Tax points	Rapid (result in <4 h possible) Only for florid lesions Only in specialised labs	Swabs from lesions with blister base on slide	80%	90%
Polymerase chain reaction (PCR) Price: 170 Tax points	Most sensitive method Result in 24–48 h Simple transport Any material Only in specialised labs	Samples without additives (native) Cerebrospinal fluid Aqueous humour Skin lesions Blister content EDTA-blood, tissue	>95% not known	>95%
Virus detection by cell culture Price: 80 Tax points	Only for florid lesions Virus transport medium, Transport must be rapid, cooled, protected from light Result in 5–14 days Not adequate for CSF Only in specialised labs	Skin/mucosa lesions (Stage) Blister content Ulcers Crusts Tissue	16–29% decreasing according to stage not known	>95%

All the prices for analysis re-reimbursed by the insurance for social security are calculated in tax points.
All the analyses executed by medical laboratories are billed in tax points. Currently one tax point corresponds to 0.90 CHF.

Table 7
Varicella vaccination in Switzerland [113].

Indications	• 11–15-year-old adolescents without history of varicella. • People who are not immune (serum IgG negative) and have an increased risk of varicella complications: – People with leukaemia or malignant tumours (vaccination during clinical remission), before immunosuppressant treatment or organ transplant, children with HIV infection (if CD4-lymphocytes >500/µl age 1–5 years, >200/µl age >6 years) – Children with severe neurodermatitis – People in close contact with the above (siblings, parents) – Medical and care staff (especially in gynaecology/obstetrics, paediatrics, oncology, intensive care, care of immunosuppressed patients). • Booster vaccination in older adolescents and young adults (<40 years), who have not had varicella, especially women of childbearing age.
Administration	• Age 12 months to 11 years: 1 dose subcutaneously. • >11 years: 2 doses subcutaneously 4 weeks apart
Vaccine	Varilrix®
Contra-indications	• Age <12 months. • Anaphylactic reaction to previous vaccination or a vaccine component. • Cellular immune deficiency. • Advanced HIV infection and AIDS. • Steroid treatment (prednisone: ≥2 mg/kg/d or ≥20 mg/d for >14 days). • Treatment with immunoglobulins or blood products (waiting period of at least 5 months). • Pregnancy (after vaccination contraceptive measures should be taken until one month after the second dose). • Severe acute disease

plete protection, >90% protection against moderately severe and severe courses (I) [104]. In a more recent case-control study the protective effect in the overall observation period was 87% [105], but fell as the time since vaccination increased (97% in the first year, 84% after 2–8 years) (IV) [106]. The protective effect also decreased if the vaccination had been given before the age of 15 months [107]. Breakthrough infections with the wild type virus can be as contagious as varicella in unvaccinated subjects [108]. The question is whether a second vaccine dose is necessary for children. A follow-up of vaccinees for 10 years showed that children who have had two doses of vaccine have a lower risk of varicella than children who have had only one dose (2.2% versus 7.3%) (III) [106]. On the other hand, new data from the USA show that the one-dose regimen demonstrably leads to a considerable reduction in varicella complications [109]. Vaccination reduces the risk of HZ in VZV-seropositive patients with leukaemia and kidney transplant recipients (III) [110–112].

Recently, a vaccine with a considerably higher virus concentration was studied in a randomised, double-blind, placebo-controlled trial with 38,546 patients 60 years of age or older [89]. The use of this life-attenuated vaccine (Oka/Merck VZV vaccine) reduced the incidence and burden of illness of herpes zoster by 51.3% and 61.1%, respectively (I). In addition, it reduced the incidence of postherpetic neuralgia by 66.5% in vaccinees (I). This vaccine has not yet been licensed. In Switzerland varicella vaccination is recommended for adolescents and young adults with a negative varicella history and for people with specific risks. The recommendations of the Federal Office of Health (BAG) which have been published in 2005 and the method of administration and contra-indications are given in table 7 [113].

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