

Swiss recommendations for the management of genital herpes and herpes simplex virus infection of the neonate

*Swiss Herpes Management Forum*¹

Summary

Genital herpes is being recognised as a medical problem of increasing importance. Diagnosis and management are complex. The present recommendations have been established by a multi-disciplinary panel of specialists and endorsed by all Swiss medical societies involved in the medical care of such patients (Appendix). The aim is to

improve the care of affected patients, to reduce horizontal and vertical transmission and to diminish the psychosocial burden.

Key words: genital herpes; herpes simplex virus; neonatal herpes; aciclovir; valaciclovir; famciclovir

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Introduction

This document is aimed at practising physicians. The recommendations have been developed on the basis of directives [1, 2] recently published in Europe and the United States but take into consideration recent developments in virology, clinical practice and treatment of herpes infections as well as special features of the Swiss Pharmacopoeia. The quality of the evidence and of the recommendations has been weighted and coded in accordance with the established standards (table 1).

Genital herpes is a viral disease acquired by mucocutaneous contact. The primary infection has various clinical forms and remains asymptomatic in the majority of cases [3]. If symptomatic, primary infection manifests itself with local and frequently systemic signs [4]. Both herpes simplex

virus types (HSV-1 and HSV-2) can cause primary genital infection, whereby the proportion of HSV-1 is increasing in Europe [5, 6]. These viruses latently infect the sensory sacral ganglia, where they reactivate with or without inducing symptoms. The frequency of clinical recurrence varies between patients and diminishes with the years after primary infection [7]. In the genital area HSV-2 reactivates much more frequently than HSV-1. The prevalence of HSV-1 and HSV-2 can be determined by type-specific serological tests. About 70% of adult Swiss are infected with HSV-1, about 20% with HSV-2 [8]. Of 25 Swiss adults, one has a diagnosed, recurrent genital herpes, three have an undiagnosed genital herpes and one presents with a truly asymptomatic infection.

Table 1
Evidence and recommendations.

Evidence level	Study type
I	Controlled and randomised study (or systematic examination of such studies)
II	Controlled, but not randomised study
III	Prospective cohort study
IV	Retrospective cohort study or case control study
V	Case studies, expert's opinion
Recommendation level	Evidence
A	Good evidence to support the recommendation (generally based on Evidence Level I)
B	Faire evidence to support the recommendation (generally based on Evidence Level II or III)
C	Inadequate evidence; recommendation may be made on other grounds
D	Fair evidence against the recommendation (generally based on Evidence Level II or III)
E	Good evidence against the recommendation (generally based on Evidence Level I)

Transmission

A risk of transmission exists even in the absence of symptoms. Most horizontal (between partners) or vertical (mother-to-child) transmissions take place during asymptomatic infection [9, 10] (III). The risk of transmission from man to woman is approximately five times higher than vice versa (III). Latex condoms reduce the risk of infection (C). In one study [11] (I) the use of latex condoms in at least 25% of the sexual contacts reduced the risk of transmission from man to woman. The efficacy of condoms in preventing transmission from women to men has not been assessed. Suppressive treatment with valaciclovir

reduces transmission of HSV-2 between serodiscordant partners by 50% [12] (I). The increasing prevalence of orogenital sexual practices explains the increase in the frequency of HSV-1-related initial episodes of genital herpes in the USA [13] (III). Prior infection with HSV-1 seems not to protect against infection with HSV-2 but does diminish the probability of symptomatic herpes disease [3].

Genital herpes promotes transmission of HIV in HSV-2 seropositive persons [14] (III). Consequently, measures which prevent the transmission of HSV-2 contribute indirectly to the prevention of transmission of HIV (B).

Diagnosis

Case history and presentations

Primary infection

In more than half of patients primary infection goes unnoticed [3]. If symptoms are present, primary genital herpes occurs 3 days to 2 weeks after exposure from an infected sexual partner and manifests as a group of painful vesicles that progress to ulcers over several days. Primary disease is typically severe with large multiple ulcerations and tender inguinal lymphadenopathy. Over one-half of the patients suffer from constitutional complaints. Up to 20% of patients have dysuria, some develop frank urinary retention and a minority develop aseptic meningitis [15]. Lesions completely resolve after 3 weeks. An identical clinical syndrome is produced by both HSV-types.

Non primary episodes or initial infections in the presence of prior antibodies to HSV result in milder episodes with lower frequency of constitutional symptoms. In practice, clinical distinction of primary infection from initial infection may be impossible.

Recurrent genital herpes

HSV can reactivate in the genital tract either asymptotically or symptomatically. Classical symptoms are grouped vesicles with progression to ulceration and crusting. Lesions are typically fewer in number and smaller than in primary disease. Constitutional symptoms are rare [16]. Up to 89% of patients with a symptomatic first episode due to HSV-2 experience symptomatic recurrences of variable frequency and severity [17] (III). Recurrence frequency in the genital region is much greater for HSV-2 than HSV-1 [18] (III). Recurrence is often heralded by prodromal symptoms of burning or tingling at the site of the outbreak or by neuralgic pain.

However, in many patients the lesions and their localisation are less typical and may not be identified as genital herpes unless a careful history and appropriate diagnostic tests are performed [16, 19, 20] (III). If patients who deny having genital herpes but have a serologically detectable HSV-2 infection are informed in detail about their condition, half of them will subsequently recognise herpetic lesions [20] (III).

Table 2
Different classifications of genital herpes infections.

Clinical manifestations	Type of infecting HSV	HSV antibodies	Classification of infection
Symptoms recognised as genital herpes: First episode	HSV-2	None	Primary HSV-2
	HSV-1	None	Primary HSV-1
	HSV-2	HSV-2	Non primary HSV-2
	HSV-1	HSV-1	Non primary HSV-1
	HSV-2	HSV-1	Initial HSV-2
Symptoms recognised as genital herpes: Recurrent herpes	HSV-2	HSV-2 with or without HSV-1	Recurrent HSV-2
	HSV-1	HSV-1 with or without HSV-2	Recurrent HSV-1
Absence of episode of genital herpes	HSV-2	HSV-2 with or without HSV-1 (theoretically also none)	Asymptomatic shedding of HSV-2
	HSV-1	HSV-1 with or without HSV-2 (theoretically also none)	Asymptomatic shedding of HSV-1
Symptoms not recognised as genital herpes	HSV-2	HSV-2 with or without HSV-1 (theoretically also none)	Unrecognised symptomatic genital HSV-2
	HSV-1	HSV-1 with or without HSV-2 (theoretically also none)	Unrecognised symptomatic genital HSV-1

So-called atypical localisations (buttocks, anal or thigh region) are relatively common (up to 61% in women) and sometimes accompanied by neuralgia [21] (IV). Laboratory tests to confirm herpes infection in such cases are therefore justified (C).

Atypical presentations become more common with increasing prevalence of impaired immunity, eg, after transplantation or HIV infection, where chronic and more extensive lesions are seen.

Different classifications of genital herpes are listed in table 2.

Detection of infections with herpes simplex viruses

Herpes infection may be identified directly by detection of the virus or one of its components (table 3), or indirectly by assaying for specific serum antibodies to the viruses [22-24].

Virus detection

There are many methods of detection. They are all variants of one of the three basic methods:

- virus culture
- virus antigen detection with specific antibodies (enzyme immunoassay or immunofluorescence)
- identification of the sequences of the viral genome after enzymatic amplification (polymerase chain reaction, PCR) their characteristics and use are presented in table 3.

Antibody detection

HSV-1 or HSV-2 infection can be diagnosed in the absence of lesions in the patient or sexual partner by detection of type-specific IgG against the glycoprotein G of HSV-1 (gG-1) or the glycoprotein G of HSV-2 (gG-2). In commercially available products which can distinguish type-specific IgG, recombinant glycoproteins are predominantly used (see lists published by the Federal Office for Public Health and Swissmedic: www.bag.admin.ch/md/ivd/list_h.pdf)

Whilst significance is given to the detection of type-specific IgG in sexual partners and STD clinics it must be remembered that there are certain limits to the usefulness of type-specific serology. A primary infection cannot automatically be inferred from a negative serological result for a type (HSV-1 or HSV-2) because:

- A type-specific immune response can take weeks to months to fully develop following primary infection. The IgG response to gG-2 takes 8 weeks on average. The gG-1 response takes longer. Antiviral therapy can further delay seroconversion.
- IgG against gG-1 and gG-2 can gradually disappear. Thus antibodies may be absent in a latently infected patient who has not been re-exposed for a long time or has not undergone a reactivation of the latent virus infection [25].
- In very rare cases the detectable antibody response is not directed against the glycoprotein (gG-2) used in the tests.

Table 3
Virus detection.

Method	Tissue sampled	Sensitivity [22-24]	Specificity	Advantages	Disadvantages
Virus detection by cell culture	Skin/mucosal lesions (stage) - vesicular content - ulcers - scabs - mucosa without lesions Biopsies Conjunctival smear/corneal scrapings Neonates	>90% 80% 40% <40% 40-80% unknown	>95%	- simplicity of sampling - typing and resistance phenotype determination possible	- only available in specialised laboratories - virus transport medium necessary - transport must be rapid, cooled, protected from light - result available after 2-7 days - not suitable for cerebrospinal fluid (CSF) - arrangement with laboratory necessary
Antigen detection by ELISA*	Smears from lesions, vesicular content with base of vesicle	41-80%	80%	- simplicity of sampling - rapid (<4 h possible) - typing possible	- suitable only for fresh vesicles
Immunofluorescence (detection of infected cells)	Smears, tissue sections, smears from base of vesicle	41-70%	>95%	- rapid (<4 h possible) - typing possible	- suitable only for fresh vesicles - available only in specialised laboratories - technically demanding - not standardised
Polymerase chain reaction (PCR)	Cerebrospinal fluid Aqueous or vitreous humour Skin lesions, vesicular content or mucosa without lesions	98% **	>95% >99%	- most sensitive method - result within 24 h - no special measures needed for transport - applicable until a few days after start of therapy - typing possible - resistance genotyping possible - method of choice for CSF	- available only in specialised laboratories - not standardised - risk of contamination - not validated for all samples

* ELISA: Enzyme-Linked Immunosorbent Assay

**about 20% more sensitive than cell culture

Therapy of genital herpes

Antiviral drugs are central to the therapy of genital herpes. The physician should take into account the patient (immunocompetent, immunocompromised, pregnant, newborn), the stage of the disease (primary, recurrent), and the objective of the treatment (therapeutic-episodic, prophylactic-suppressive).

Systemic antiviral drugs diminish the signs and symptoms of an episode of primary genital herpes and also – to a lesser degree – of the recurrences. Used as suppressive therapy they lower the frequency of recurrences significantly. They do not eradicate the latent infection nor do they affect the frequency and severity of the recurrences after discontinuation of the suppressive treatment. Randomised studies indicate that three drugs have a similar clinical effect on genital herpes: aciclovir, valaciclovir and famciclovir. Valaciclovir, the L-valine ester of aciclovir, has a significantly better bioavailability than aciclovir. Famciclovir, a prodrug ester of penciclovir, also has a high bioavailability.

Topical treatment with antiviral drugs is not of demonstrable clinical benefit [26] (I) and is therefore not recommended (E).

Therapy of first episode

The usually severe symptoms warrant antiviral treatment. It should be started as early as possible without waiting for the laboratory results (A). The symptoms subside almost a week earlier if treatment is started within 5 days of the outbreak of symptoms [27–30]. The recommended therapies are listed in table 4. The valaciclovir dosage of 1000 mg twice daily used in the USA is based on the results of the study by Fife et al. [30] (A). Valaciclovir dosed at 500 mg twice daily produces a higher plasma concentration than aciclovir 200 mg five times daily [31] and the dosage of 500 mg of valaciclovir twice daily is preferred in Europe (A). The clinical efficacy of 500 mg twice daily was confirmed in a controlled study [32] (I). If the clinical picture is protracted with persistent lesions, particularly in immunodeficient patients, treatment may be maintained for at least 14 days. Aciclovir, valaciclovir and famciclovir appear to be of similar efficacy, so the choice is based on tolerance, compliance and cost. The treatment of the first episode has no influence on the recurrence rate [33–35] (I).

The following complications require hospitalisation: sphincter disorders with urine retention, meningitis, severe general symptoms, and inability to take oral medicines. In the case of urine retention a catheter may be left *in situ* for a few days, a suprapubic drainage being preferred (C).

Analgesics are recommended. Local anaesthetics should be used reluctantly to avoid sensitisation. Topical antiseptic and anti-inflammatory treatment with iodine-containing or astringent solutions (tannins) applied by bathing or with gauze pads is recommended (C).

Therapy of recurrences

Depending on the severity of the recurrences, episodic or suppressive oral antiviral therapy or symptomatic local therapy will be indicated. The type of treatment is chosen after discussing each option with the patient. An episodic treatment for 2–5 days (table 4), which is started by the patient within 24 hours of symptom onset, can shorten the duration of an episode by 1 or 2 days [29, 36–42]. Suppressive treatment can prevent about 80% of the recurrences and has a much greater effect on the morbidity associated with genital herpes than episodic treatment [43] (I).

Episodic treatment

Because the medication needs to be started without delay when symptoms occur, the patient must be given an antiviral starter pack or a prescription with appropriate directions (table 4) [37–42] (C).

Suppressive treatment

In patients with frequent recurrences (>6 per year) suppressive treatment reduces the frequency of recurrence by 70 to 80% [44] (I). The safety and efficacy of suppressive treatment have been observed for a period of more than 10 years for aciclovir [45] and for a period of more than one year for valaciclovir and famciclovir [29, 44, 46–48]. Valaciclovir 250 mg twice daily is slightly more effective than 500 mg once daily and is therefore recommended for patients with more than 10 recurrences per year [44] (A). The suppressive treatment improves the quality of life [49] (I). The frequency of recurrences decreases with the number of years since the first attack [7]. This suggests that suppressive treatment should be discontinued for a while after 6–12 months (ie, wait for at least two recurrences) so as to estimate the residual recurrence frequency [50] (B). Suppressive treatment can be resumed if frequent or stressful recurrences continue to occur. It causes neither appreciable side effects nor selection of resistant strains [51] (IV).

The suppressive treatment with valaciclovir taken by persons with recurrences had another major impact: the reduction of genital HSV-2 transmission in serodiscordant monogamous couples. Once daily 500 mg valaciclovir reduced by 50% the transmission of HSV-2 and by 75% clinically symptomatic HSV-2 infections [12] (I).

Treatment in immunocompromised patients

Chronic or severe lesions are observed in the immunocompromised and, in particular, in advanced HIV infection. Episodic or suppressive treatment is generally recommended for these patients [29] (B). Intravenous administration may be needed in severe cases (eg, visceral dissemination)

or in case of inability to take oral drugs (table 4). The risk of selection of resistant strains increases with the degree of immunosuppression and the number of antiviral courses. If the lesions no longer respond to the standard treatment an experienced specialist should be consulted (C).

Information and advice for the patient

Information and counselling are integral to the treatment of genital herpes and have two objectives: to help the patient to cope with the disease and to prevent sexual and perinatal transmission [59]. In general, comprehensive information and advice cannot be given within a single consultation. Many patients use additional sources of information such as leaflets and internet sites (eg, www.herpessalliance.org, www.herpessnet.ch).

The psychosocial burden of genital herpes

should not be underestimated. It is often perceived as a stigmatising disease and diminishes the quality of life. Counselling helps the patient to better understand the negative feelings related to recurrent herpes [60] (B). The patient should also be informed that HSV-2 does not play a causative role in the pathogenesis of cervix carcinoma (A).

The points to be discussed with patients are presented in table 5 (Patient counselling checklist).

Management of the partner

Sexual partners should also be given advice. Symptomatic partners should be managed in the same way as the index patient. Asymptomatic part-

ners should be questioned regarding genital lesions and be educated to recognise herpes lesions. Type-specific serological testing should be offered (C).

Table 4
Treatment of genital herpes.

	First episode	Recurrent episodes
Immunocompetent persons		
Episodic treatment	Regimens licensed in Switzerland: Aciclovir oral 200 mg five times daily for 5–10 d [27, 34] (A) Valaciclovir 500 mg twice daily for 5–10 d (A) Famciclovir 250 mg thrice daily for 5–10 d (C*) Aciclovir iv 5 mg/kg thrice daily for 5 d [28, 35] (A) Other regimens: Aciclovir oral 400 mg thrice daily for 7–10 d (C) Valaciclovir 1000 mg twice daily for 7–10 d [30] (A)	Regimens licensed in Switzerland: Aciclovir oral 200 mg five times daily for 5 d [38, 39] (A) Valaciclovir 500 mg twice daily for 3–5 d [37, 42] (A) Famciclovir 125 mg twice daily for 5 d [40] (A) Other regimens: Aciclovir oral 400 mg thrice daily for 5 d (C) Aciclovir oral 800 mg thrice daily for 2 d [41] (A)
Suppressive treatment (Recommended if >6 recurrences/year or serious effect on quality of life)	–	Aciclovir oral 400 mg twice daily [52, 53] (A) Valaciclovir 250 mg twice daily (>10 recurrences/year) or 500 mg once daily (<10 recurrences/year) [37] (A) Famciclovir 250 mg twice daily [47, 48] (A)
Immunocompromised persons		
Episodic treatment	Consultation with specialist(s) (C)	Aciclovir iv 5 mg/kg thrice daily [54] (A) Aciclovir 400 mg five times daily [55] (A) Valaciclovir 1000 mg twice daily [56] (C) Famciclovir 500 mg twice daily [57] (A, AIDS-patients)
Suppressive treatment	–	Aciclovir 400–800 mg twice or thrice daily [54] Valaciclovir 500 mg twice daily (A*) Famciclovir 500 mg twice daily [58] (A)
Symptomatic treatment	Analgesics, antiseptic and local anti-inflammatory treatment (C)	Analgesics, antiseptic and local anti-inflammatory treatment (C)
Pregnancy		
Episodic treatment	Aciclovir oral 200 mg five times daily for 10 d Valaciclovir 500 mg twice daily for 10 d**	Aciclovir oral 200 mg five times daily for 5 d Valaciclovir 500 mg twice daily for 5 d
Suppressive treatment (from week 36 until delivery)	Aciclovir oral 400 mg thrice daily Valaciclovir 250 mg twice daily**	Aciclovir oral 400 mg thrice daily Valaciclovir 250 mg twice daily**

* published as Abstract, cited in [29]

** Aciclovir pregnancy registry and valaciclovir pregnancy registry, 1 June 1984 – 30 April 1999

Genital herpes during pregnancy

Vertical transmission

Both HSV-2 and HSV-1 can be transmitted from the mother to the neonate during parturition and cause severe infections. In Switzerland the incidence of neonatal herpes infection is apparently low according to an ongoing nation-wide surveillance study [61].

The risk of transmission depends on the character of the current episode (primary infection carries a much greater risk than recurrence) and the virus type (HSV-1 > HSV-2). Thus in cases where viruses are positively identified at delivery it may vary between 30% in primary infections and <1% in recurrent infections [62, 63]. The risk of transmission is reduced following caesarean delivery (OR 0.14 95%-CI 0.02–1.08) [62] (III).

Estimation of the risk for the neonate

The clinical distinction between primary infection, initial infection with the other HSV type and reactivation during pregnancy is not possible. However, it would be of utmost importance for the assessment of the risk to the neonate (III). A first manifestation of genital herpes during pregnancy is in most cases not a primary infection [64]. Conversely, most primary infections are not symptomatic [63]. An episode that appears clinically to be a recurrence may well be an initial infection with the other serotype and thus present a considerably higher neonatal risk [62]. On the basis of these data it would not appear logical to manage first presentation and recurrent episodes of genital herpes differently during pregnancy. This changes if the type

Table 5
Patient counselling
checklist.

Topic to discuss	Approach
Natural course and epidemiology	
Course and forms of the disease	Explain recurrence potential, asymptomatic virus secretion, and risk of transmission
	Mention that genital herpes can be caused by HSV-2 or by HSV-1
	Point out that one in six people is affected worldwide
	Emphasise that about 80% of the infections are not recognised because the symptoms are minimal or absent
Information to sex partners	Motivate the patient to tell present and future sexual partners about his/her infection status
	Sexual partners of infected persons should be told that they may be infected even in the absence of symptoms
	A type-specific serological investigation can be helpful for guidance as to the necessary precautions
Asymptomatic virus secretion	Explain that asymptomatic secretion is responsible for transmission in most cases
	It occurs more frequently in the first year after the primary infection, in immunocompromised patients and in patients with frequent recurrences (>12/year)
	Mention that HSV-2 is shed asymptotically from the genitalia much more frequently than HSV-1
Contact transmission	Explain that transmission occurs genitally by skin contact (even in the absence of penetration, eg, during “petting”)
	Transmission also occurs orogenitally and all body regions can be affected as a result of inadvertent (auto)inoculation
	Emphasise that virus shedding is practically certain if prodromi or lesions occur so sexual contact with uninfected partners should be forgone at these times
Condom use	Explain that latex condoms can reduce the risk of infection from man to woman
Neonatal herpes	Explain that herpes neonatorum is the most serious, albeit rare, complication
	Pregnant women or women of childbearing age who are infected with HSV-2 must inform the obstetrician/midwife and paediatrician
	Pregnant women not infected with HSV-2 must be made aware of the danger of sexual contacts (genital and orogenital) with an infected partner during pregnancy (especially in the last trimester)
Atypical symptoms	Asymptomatic persons diagnosed by type-specific serology as having an HSV-2 infection must be counselled and the possible skin manifestations (including atypical forms) be explained
Therapeutic options	
Options	Explain the options (episodic antiviral therapy, suppressive therapy, symptomatic local therapy)
Breakthrough infections	Explain that recurrences may occur despite suppressive therapy and that they usually last only a few days
	When breakthrough occurs the drug dose is temporarily increased to that given for episodic treatment (Table 4)
Suppressive treatment	Emphasise that suppressive therapy does not alter the natural course of the infection and that recurrences are to be expected after it has been discontinued
	Although the frequency of recurrences usually decreases over time at a rate that varies from patient to patient, some patients will experience frequent recurrences after stopping suppressive treatment, in which case the suppressive treatment can be resumed
Effect on virus shedding	Point out that suppressive treatment diminishes the shedding of virus significantly [12] (I) and reduces the risk of virus transmission by 50% [12] (I)
Tolerance	Reassure the patient that adverse effects of suppressive treatment are extremely rare and that no problems of resistance have been observed in immunocompetent patients

of infection can be characterised by virus typing and determination of the type-specific antibodies.

Neither serological nor virological (culture or PCR) screening of the mother before delivery permit reliable identification of neonates at risk of neonatal herpes infection [62] (III). Therefore such investigation cannot routinely be recommended (D). The value of serological screening early in pregnancy to identify women at risk for primary infection is under investigation.

Management of pregnant women with a first or recurrent episode of genital herpes

Treatment of clinical episodes

Pregnant women with a first clinical episode or a recurrence may be treated with aciclovir or valaciclovir at the recommended dosages (table 4). An excess risk for the foetus has not been associated with these treatments [65, 66].

Suppressive treatment

Randomised studies have shown that suppressive treatment from the 36th week of pregnancy until delivery reduces the frequency of clinical manifestation and virus shedding at the time of delivery and, in many cases, caesarean section can be avoided [67-70] (I) (A).

Route of delivery

A history of genital herpes in the absence of genital symptoms (active lesions or prodromal pain or burning) at the beginning of delivery should not be taken as an indication for an elective caesarean section [70] (E). If clinical herpes lesions, positive virus detection tests, or both are present at the time of delivery, then a caesarean section is an effective preventive measure [62] (III) and therefore indicated (B). At membrane rupture, if it may be assumed that the foetal lungs are mature, a caesarean

section should be performed as quickly as possible and no more than 4-6 hours later [69] (B).

In case of immature lungs there is no established basis for the decision. Continuing the pregnancy carries a small residual risk of a manifest foetal/neonatal herpes infection despite maternal antiviral therapy (with or without induction of lung maturation with corticosteroids). This must be weighed against the risk (which depends primarily on the gestational age) of immediate delivery by caesarean section [69]. The risk of expectant management of pregnant women with recurrent genital herpes and preterm premature rupture of membranes appears to be small [70] (IV) (B). In these complex cases the immediate transfer to a specialist centre is recommended (C).

As long as the membranes are intact and contractions have not started an episode of recurrent genital herpes in the weeks before the expected delivery date should not be taken as an indication for an elective caesarean section [70] (D). It must be remembered that even in the 37th and 38th weeks of pregnancy there is still a substantial risk of neonatal respiratory distress syndrome which is sharply increased by delivery by elective caesarean section [71] (III).

After a clinical recurrence during pregnancy, vaginal delivery is possible as soon and as long as no clinical lesions are present. However, if in the third trimester a primary or an initial genital infection has been established or seems highly probable, the optimal way of proceeding is not well defined. Most guidelines propose caesarean section for all women developing a primary clinical infection within 4-6 weeks of delivery [1, 72-76] (IV) (C). But some experts think that the foetus may be at risk from vaginal delivery until the appearance of type-specific IgG which may take 8-12 weeks [77] (C).

Neonatal herpes simplex infection

Clinical manifestations

Neonatal herpes infections appear in three clinical forms. The most common (50% of cases) and mildest form remains localised to the skin and/or eyes and mouth. The form predominantly involving the CNS, neonatal encephalitis (33%), manifests as lethargy and seizures and, in many cases, leads to late sequelae. The disseminated form (17%) has high lethality and is associated with hepatitis, pneumonia, disseminated intravascular coagulation and shock [78].

At diagnosis symptoms are found with the following frequencies: skin vesicles 68%, fever 39%, lethargy 38%, seizures 27%, conjunctivitis 19%, pneumonia 13%, disseminated intravascular coagulation 11%.

Symptoms may occasionally be present at birth, but occur in 60% later than 5 days after birth, and sometimes even present after 4-6 weeks of life [79] (III).

Diagnostic procedures

Procedures in cases with known perinatal HSV exposure

In case of manifest genital herpes or known maternal virus shedding at the time of delivery it is advisable to cultivate swabs from the neonate's conjunctiva, oropharynx and rectum. In order to demonstrate transmission (and not merely contamination) the swabs should be taken when the neonate is 24-48 hours old [69] (C).

The neonate must be observed carefully and long enough (to age 4-6 weeks) for the possible onset of symptoms of a neonatal herpes infection. The parents must be instructed accordingly when the baby is discharged from hospital (B).

Procedures in cases with suspected symptoms of herpes

Since most neonatal herpes infections occur where the mother has no history of genital herpes [63], an HSV infection must be suspected imme-

diately if the neonate exhibits suspicious symptoms (B). However, one third of neonates with herpes infection show no characteristic skin lesions and thus present a particular diagnostic challenge [79].

The possibility of neonatal herpes infection must be especially considered in case of:

- characteristic skin or mucosal lesions
- conjunctivitis, particularly if there is injection of the conjunctiva, bulbi, or keratitis
- seizures and/or lethargy without any other explanation
- fever or other systemic symptoms without any other explanation.

In suspected cases of neonatal HSV infection the following examinations must be performed [62] (C):

- cultures of vesicular, conjunctival, oropharyngeal, stool/rectal swabs, urine and blood
- lumbar puncture with HSV-PCR (CSF cultures are less sensitive)
- routine laboratory tests including transaminases and coagulation tests
- cerebral imaging and/or ophthalmological examination if indicated.

Therapy and prognosis

Although high-dose therapy with intravenous aciclovir for a sufficient length of time has been proven to be effective [78] (II) neonatal herpes infection is still associated with high residual lethality and morbidity. Whilst the localised form almost always heals without sequelae, the CNS form has a lethality of 6% and permanent late sequelae are seen in 69% of cases. The disseminated infection takes a lethal course in 31% and has late sequelae in 17% of cases [78]. The point in time at which treatment is started is crucial for prognosis (III).

In order to achieve the best possible treatment outcomes the diagnostic specimens described in

the preceding chapter must be taken, and intravenous therapy with aciclovir 60 mg/kg/d in three doses started, as soon as there is a clinical suspicion of neonatal herpes infection (A). If the virological test results are negative treatment may be discontinued. Localised HSV infections are treated for 14 days and CNS forms or disseminated infection for 21 days [78] (B). If the eyes are involved additional topical antiviral therapy must be administered.

Cutaneous recurrences may occur for some time after a neonatal herpes infection. The role of suppressive therapy for such cases has yet to be elucidated. In cases of herpes infections of the eyes an ophthalmological examination should be carried out 2–3 weeks after discontinuing therapy in order to rule out keratitis.

Since there is no proven basis for pre-emptive aciclovir therapy for asymptomatic neonates of mothers with genital herpes it cannot be recommended [69] (D).

Preventive measures

Neonates with a confirmed or suspected HSV infection should be isolated and care be taken to avoid direct contact with skin and mucosal lesions as well as excretions and body fluids.

Herpes lesions on the lips, fingers or nipples of the mother or other individuals who have direct contact with neonates may present a risk, albeit low, of nosocomial transmission to other neonates. The mother, the father, visitors and medical staff on the rooming-in ward must be informed and take the necessary precautionary measures (sealed cover of the lesions to prevent direct contact with the skin or mucosa of the neonate). Medical staff with oral herpes simplex who observe these precautions need not be suspended from caring for neonates [69] (B).

Ophthalmology

All patients with eye infections should be referred for ophthalmological examination on account of the high risk of complications of even “simple” epithelial herpes infections of the cornea and of an extremely high risk of serious permanent impairments of vision if the deeper layers of tissue are implicated.

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The Swiss recommendations for the management of genital herpes and herpes simplex virus infections of the neonate have been endorsed by the following Swiss medical societies:

- Swiss Society for Dermatology and Venerology
- Swiss Society for Urology
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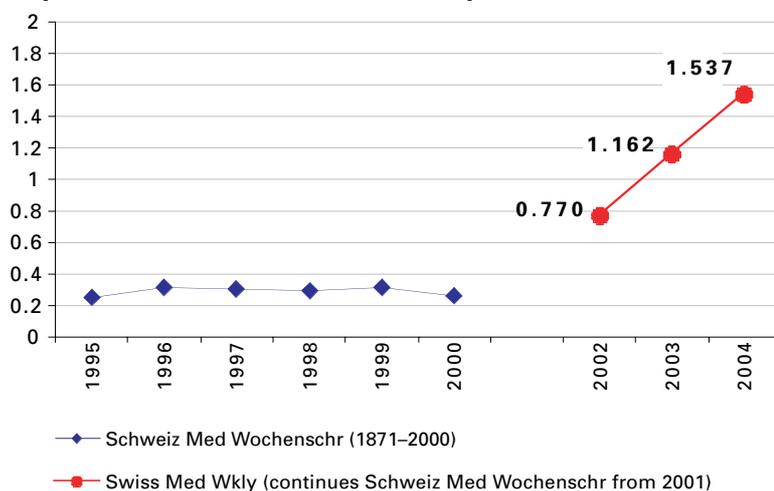
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