GUIDELINES FOR THE

MANAGEMENT OF GENITAL HERPES IN NEW ZEALAND

12TH EDITION - 2017

NEW ZEALAND
HERPES FOUNDATION

www.herpes.org.nz

Produced by the Professional Advisory Board (PAB) of the
Sexually Transmitted Infections Education Foundation

Sexually Transmitted Infections Education Foundation resources

	HERPES	HPV
Helpline	**Tollfree 0508 11 12 13**	**Tollfree 0508 11 12 13**
Website	www.herpes.org.nz	www.hpv.org.nz
Resources	**Health professionals' resources** 1. Guidelines for the Management of Genital Herpes in New Zealand – 12th Edition 2017 *Only available online at www.herpes.org.nz* 2. Sexually Transmitted Infections – Summary of Guidelines 2017 **Patient information pamphlets** 1. The Facts: A guide for people with Herpes Simplex Includes – Genital Herpes – The Facts Herpes and Relationships Herpes and Pregnancy Facial Herpes 2. Herpes: Myth vs Facts	**Health professionals' resources** 1. Guidelines for the Management of Genital, Anal and Throat HPV Infection in New Zealand – 9th Edition 2017 *Only available online at www.hpv.org.nz* 2. Sexually Transmitted Infections – Summary of Guidelines 2017 **Patient information pamphlets** 1. Some Questions and Answers about HPV and Genital Warts 2. Cervical Smears and Human Papillomavirus Infection (HPV) 3. Preventing HPV Cancers by Vaccination: What Everyone Should Know 4. HPV and Men 5. HPV and Throat Cancer: Common Questions and Answers

Website for youth with information about sexual health and sexually transmitted infections: www.justthefacts.co.nz

JUSTTHEFACTS.co.nz posters are available in A2, A3 and A4 sizes for display, in addition to wallet cards for consumers.

All the above resources are available free of charge from the Sexually Transmitted Infections Education Foundation

Phone: 09 433 6526

Email: info@stief.org.nz

New Zealand Sexual Health Society (NZSHS) resources

Comprehensive STI Management Guidelines and Patient Information handouts are available on www.nzshs.org/guidelines

ISSN 1173-6984

NEW ZEALAND HERPES FOUNDATION

GUIDELINES FOR THE MANAGEMENT OF GENITAL HERPES IN NEW ZEALAND

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The Objectives of the NZHF are:

To provide support, current educational material and management options in a caring, friendly, confidential environment for people with genital herpes.

To liaise with health professionals, providing a support network to assist in the responsible management of genital herpes.

Ultimately, to improve the social context in which people with genital herpes live their lives.

For a list of the Professional Advisory Board (PAB) members, refer to **page 38.**

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ABOUT THIS DOCUMENT

This document is a consensus opinion of the Professional Advisory Board (PAB) of the Sexually Transmitted Infections Education Foundation. The PAB has representation from medical and nursing disciplines involved in the management of people with genital herpes. The PAB works on a voluntary basis.

These guidelines have been produced by considering available literature, both local and international, and by basing the recommendations on the evidence in the literature or reasonable suppositions and opinions of experts.

The guidelines' recommendations have been rated under the following evidence-based categories:

GRADE A: **Very strong evidence**
Based on well-designed prospective randomised controlled clinical trials.

GRADE B: **Fairly strong evidence**
Based on evidence from case-control or cohort studies, or clinical trials lacking one or more of the above features.

GRADE C: **Weak evidence or firmly held opinion**
Based on published case reports, well-written reviews or consensus.

GLOSSARY OF TERMS

Primary infection: Recently acquired infection with HSV-1 or HSV-2 with an absence of antibodies to either type on serological testing.

Non-primary infection: Recently acquired infection with a virus type in the presence of antibodies to the other virus type, e.g. HSV-2 in a person with previous antibodies to HSV-1, but absence of antibodies to HSV-2 on serological testing.

First episode: First clinical episode of genital HSV-1 or HSV-2. May be a primary or non-primary or first recognised clinical expression of a previously acquired infection weeks, months or years before.

Recurrence: Previously acquired HSV-1 or HSV-2 infection with antibodies to the same type on serological testing.

WHAT'S NEW SINCE 2015

Valaciclovir

The special authority and Hospital Medicines List restriction was removed from 1 March 2016 (Pharmac).

This is recommended first line treatment.

Treatment of first episode genital herpes

- Oral valaciclovir 500mg bd for 7/7 or longer if new lesions appear during treatment or healing is incomplete.
- Immunocompromised patients consider valaciclovir 1g bd for 7–10 days.
- Alternative: oral aciclovir 400mg 3 times daily (8 hourly) for 7 days.

Treatment of recurrent genital herpes

Episodic Treatment

- Oral valaciclovir 500mg bd for 3/7.
- Alternative: oral aciclovir 800mg 3 times daily for 2 days.

Prescribe enough tablets for patients to be able to self-initiate treatment at onset of symptoms.

Suppressive therapy

Only recommended for people with HSV confirmed on testing. Given daily to prevent recurrences and reduce asymptomatic shedding. Suggest prescribing for 12 months, followed by a break of 3 months to see if recurrences are still frequent and/or bothersome.

- Oral valaciclovir 500mg daily (increase to 500mg BD on individual basis of clinical presentation and/or having breakthrough recurrences on 500mg daily).
- Alternative: oral aciclovir 400mg twice daily.

GENITAL HERPES – COMMON MISCONCEPTIONS

- **MYTH:** ***Most, if not all, genital herpes infections are due to HSV-2.***
  FACT: Genital herpes is caused by both HSV-1 and HSV-2 although HSV-1 is less likely to cause recurrent symptoms.

- **MYTH:** ***Visible genital herpes infection is very typical and does not require diagnostic testing.***
  FACT: Herpetic lesions are often atypical and other conditions may cause genital ulceration; genital lesions should be swabbed and tested for HSV.

- **MYTH:** ***Herpes simplex virus subtype determination is unnecessary.***
  FACT: As HSV-1 and -2 have different natural histories, it is important to ask for specific typing (so patients can be better informed).

- **MYTH:** ***Serological testing can be used to diagnose genital herpes in the setting of an active genital ulcer.***
  FACT: Serological testing is not recommended as an acute diagnostic or routine screening tool. It is recommended only in limited clinical scenarios (see page 9).

- **MYTH:** ***Herpes simplex virus infection can be ruled out with negative serologic testing.***
  FACT: HSV antibodies take several weeks and even months to develop after infection; false negatives and false positives are common.

- **MYTH:** ***The 72 hour zoster treatment rule applies to herpes simplex.***
  FACT: All first episodes of genital herpes should be treated regardless of timing of onset of symptoms (see page 10).

The purpose of this guideline is to dispel common misconceptions and hopefully improve current management of those with herpes infection.

GENITAL HERPES

KEY POINTS

The NZHF has a range of resources to assist patients and clinicians.
Phone: Herpes Helpline tollfree **0508 11 12 13**
Website: **www.herpes.org.nz**

A diagnosis of genital herpes can have a profound effect. Patients tell us they want –

- To be given accurate up-to-date information.
- To be provided with the best treatment available.
- To be involved in decisions about treatment and management.
- To be referred for specialist care or advice when appropriate.
- Genital herpes is a common infection caused by Herpes Simplex Virus Type One (HSV-1) and Herpes Simplex Virus Type Two (HSV-2) and as many as one in five adults in New Zealand have genital herpes due to HSV-2. Up to 50% of first episode (see Glossary of Terms on **page 3**) genital herpes is due to HSV-1.
- HSV-2 is more common in women than men, with prevalence increasing with age.
- Genital herpes is under-recognised and under-treated. Minor lesions are common; any recurring localised genital symptoms or lesions should be investigated as possible genital herpes.
- Laboratory confirmation of the diagnosis and typing, by HSV PCR is important, but should not delay treatment. HSV serology is not recommended as a routine diagnostic tool.
- Oral antiviral treatment is safe, effective and generic brands are very cheap.
- Oral antiviral treatment of the first clinical episode (without waiting for results) should always be offered, regardless of the time of symptom onset.
- The '72 hour' herpes zoster rule does NOT apply to first episode genital herpes infection and treatment should be given regardless of time of presentation.
- Antiviral therapy of recurrent genital herpes may be suppressive or episodic. Some patients prefer suppressive antiviral therapy. It is often considered for those with frequent and/or severe recurrences or associated psychosocial morbidity. For those on episodic antiviral therapy, it is more effective when patients start therapy themselves at the first signs of a recurrence; this requires anticipatory prescribing.
- Neonatal HSV infection is a rare but potentially fatal disease of babies, occurring within the first 4-6 weeks of life. Symptoms are non-specific and a high index of suspicion is required. Most neonatal HSV infections are acquired at birth, generally from mothers with an unrecognised first genital herpes infection acquired during pregnancy.
- Specialist advice on management should be sought for a woman with a history of genital herpes and active lesions at term and especially in the high-risk situation of a first episode up to 6 weeks prior to delivery.

There are no vaccines currently available for HSV infection, but the pipeline is rich with candidates in various phases of development. Vaccines are currently being developed both to prevent HSV-2 infection (preventive) and to treat HSV-2 infection (therapeutic).[1]

EPIDEMIOLOGY AND TRANSMISSION

Epidemiology

KEY POINTS

- As many as one in five adults have genital herpes due to HSV-2, most will have asymptomatic or unrecognised disease.
- Genital herpes due to HSV-1 (through oral to genital transmission) has also become common; HSV-1 is a frequent cause of primary genital herpes.
- The natural history of genital HSV-1 infection is towards significantly fewer clinically apparent recurrences and less subclinical shedding than HSV-2.

Genital herpes is an infection caused by the herpes simplex virus (HSV) and, for practical purposes, encompasses lesions on the genital area and nearby areas (i.e. buttocks, anal area and thighs). Genital herpes may be due to HSV-1 (the usual cause of orolabial herpes) or HSV-2 (more commonly associated with genital lesions). It is a very common infection that is often under-recognised, as a person may be asymptomatic or have only very minor symptoms.

HSV-2

HSV-2 prevalence varies between countries, being higher in the USA than in Europe, Australia and New Zealand. It also varies depending on the demographics of the population being tested.[2]2 Consistent findings between countries are that HSV-2 seroprevalence increases with:

Age: The incidence of new infections is highest amongst young adults, but as infection is lifelong, overall prevalence increases with increasing age.[2] Participants in the Dunedin Multidisciplinary Health and Development cohort study provided serum for HSV-2 antibody status at the ages of 21, 26, 32 and 38. By the age of 38, 26.8% of women had been positive for HSV-2 compared to 17.3% for men, confirming a higher biological susceptibility to infection for women. The infection rate for women was highest at age 21–26 compared to 26–32 for men and then declined in both genders with age, consistent with decreasing infectivity of long-term prevalent infections.[3]

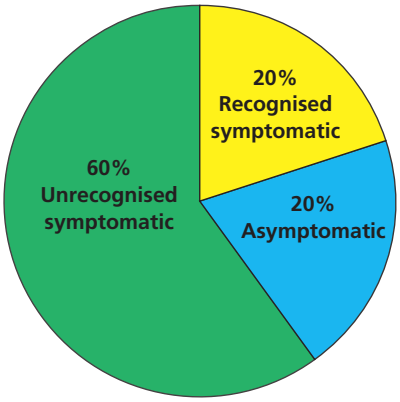


Figure 1: **Prevalence, manifestations of genital herpes**

HSV-1

HSV-1 seroprevalence studies cannot distinguish between oral and genital infection sites which makes it much more difficult to estimate the prevalence of genital HSV-1 infection. Clinical case data has limitations as well. That said, HSV-1 accounts for 35% of confirmed anogenital infections in Australia[4] and similarly a Waikato-wide study found 30–40% of anogenital isolates are due to HSV-1 each year.[5] In that study, HSV-1 accounted for 53% of positive isolates from under-25 year olds, 30% in the 25–35 year olds, and 26% from over-35 year olds. Likewise, an Auckland Sexual Health Clinic study in 2004 found most true primary (see Glossary of Terms **page 3**) episodes of genital herpes were HSV-1, whilst non-primary first episodes (see Glossary of Terms **page 3**) and recurrences were mostly HSV-2.[6]

Like HSV-2, HSV-1 seroprevalence increases with increasing age and tends to be more common in women.[7]

Note: Routine typing of isolates enhances a clinician's ability to give prognostic information and optimal clinical care. It is no longer accurate to assume that genital herpes is due to HSV-2 infection, as a substantial proportion of people will have HSV-1.[8] The natural history of genital HSV-1 infection is towards significantly fewer clinically apparent recurrences and much less subclinical shedding.[9,10] Also, prior HSV-1 infection does not alter the risk of acquisition of HSV-2, although it does lessen the symptoms; it is important for those diagnosed with HSV-1 genital herpes to understand that they remain at risk of HSV-2 infection.

Transmission

KEY POINTS

- Transmission occurs during skin-to-skin contact when virus is being shed.
- HSV-1 is commonly transmitted through oral to genital contact.
- HSV-2 is transmitted through genital to genital contact.
- Shedding of virus occurs during outbreaks and also when individuals are asymptomatic.

Most infections are acquired from someone who is unaware they are infected, who may have mild or asymptomatic infection.

Herpes simplex virus enters the body, either through a break in the skin or through mucous membranes, during direct contact with infected secretions or mucosal surfaces. For genital infections, this is usually during sexual contact, with HSV-2 commonly transmitted during vaginal or anal sex and HSV-1 commonly passed on through oral-genital sex.

Transmission is most likely to occur:

- During sexual contact.
- When the skin is broken.
- When there are lesions (e.g. vesicles or ulcers) present.
- From men to women.

Therefore, sexual contact should be avoided when active lesions are present.

Transmission may occur when a partner is shedding virus asymptomatically. Most people who acquire genital herpes get it from someone who is unaware they are infected, who may have mild or asymptomatic infection.[10]

It is important to remember that not all first episodes of HSV-1 or HSV-2 represent a new or recently acquired infection. It may be a first clinically recognised episode of a previously unrecognised or asymptomatic infection acquired weeks, months or years previously.

The virus is readily inactivated at room temperature and by drying; hence, non-contact forms of spread, for example via fomites (inanimate objects) are considered unlikely. Autoinoculation resulting in spread to different anatomical sites can occur (e.g. orolabial, whitlow), although this is believed to be uncommon. GRADE C

Asymptomatic viral shedding

Nearly everyone, both men and women, with genital HSV-2 infection sheds virus from time-to-time without symptoms, which is why sexual transmission can occur during asymptomatic periods. These intermittent episodes of asymptomatic viral shedding are more frequent:

- With genital HSV-2 than genital HSV-1 infection.
- During the first 12 months after acquiring HSV-2.
- In those with more frequent symptomatic episodes.
- Within a week before or after a symptomatic episode.
- In those with HIV infection.

The viral load threshold for transmission from an episode of asymptomatic shedding has not been established. For a given individual it is impossible to be certain when asymptomatic viral shedding occurs, but it is important not to give the impression that people are infectious all the time.

Reducing Risk of Transmission

KEY POINTS

- Consistent condom use reduces, but does not eliminate, the risk of transmission.
- Sexual contact should be avoided when oral or genital lesions are present.
- Suppressive oral antiviral treatment will significantly reduce, but not eliminate, the risk of transmission.
- Prior HSV-1 means HSV-2 infection is less likely to be symptomatic.

Barrier methods

Male and female condoms do not give absolute protection for a variety of reasons: condoms do not cover all affected areas, condom breakage or slippage may occur, close genital contact or contact with infectious secretions may occur during foreplay, etc.[11] Nonetheless, consistent condom use offers moderate protection against HSV-2 infection in both men and women.[12] GRADE B
Data on male condoms preventing transmission to men or on the efficacy of female condoms is lacking. Condom use should be discussed with the couple and tailored to the individual circumstances.

Oral-genital contact

People who do not acquire HSV-1 during childhood are at risk of HSV-1 at any site, including genital infection, during adulthood. Transmission may occur whilst receiving oral sex from someone who has oral HSV-1, even if the source partner is asymptomatic. It is estimated that up to a third of persons who are HSV-1 antibody positive do not have a clinical diagnosis of oral herpes,[13] but will still shed HSV-1 virus.[14] It is generally accepted that prior orolabial HSV-1 infection protects an individual against genital HSV-1. Possible exceptions may be those infected simultaneously at more than one site or those with very recent HSV-1 infection who have not yet seroconverted. Oral HSV-2 in isolation is uncommon.

Oral-genital contact should be avoided when oral lesions are present. GRADE C

Antivirals

Aciclovir, famciclovir and valaciclovir all suppress symptomatic and asymptomatic shedding, by up to 80–95%.[15] Also, it has been shown that suppressive once-daily valaciclovir results in reduced transmission to the discordant partner.[16] For partners, there was a 48% reduction in acquisition of HSV infection and a 75% reduction in clinical symptomatic genital herpes. Other antivirals may be similarly effective, but this has not been proven in clinical trials.

Co-infection

In most studies, pre-existing HSV-1 infection does not decrease the risk of HSV-2 infection, but prior HSV-1 means HSV-2 infection is more likely to be asymptomatic. If HSV-2 genital infection is acquired first, then a new HSV-1 genital infection does not affect the frequency of recurrences.

Diagnostic Tests

KEY POINTS

- Suspected genital herpes should be confirmed by a nucleic acid amplification test (NAAT) e.g. PCR.
- PCR is the gold standard for diagnosis of active lesions.
- A negative result does not rule out HSV infection.
- Serology is not recommended (see page 9).

Clinical diagnosis alone is insensitive and inaccurate, with a 20% false positive rate.[17] **Suspected genital herpes must be confirmed by PCR**. Recurrent lesions, which have not been previously confirmed, likewise should be tested for HSV. However, it is important not to delay appropriate therapy while awaiting confirmation.

Detection of herpes simplex virus DNA by PCR in the lesion establishes the diagnosis. Vesicles offer the best source of virus. **However, results depend on multiple factors, including the adequacy of the specimen and the time delay between onset of symptoms and presentation, therefore a negative result may not exclude infection.**

Sample collection

PCR has a low false positive rate. However, a negative test result does not necessarily exclude HSV infection since all methods are dependent on adequate collection of the specimen. Viral typing is routinely reported.

Serology

Serology is not recommended for the following reasons:

- Serological tests detect antibodies to HSV in blood and indicate **past** infection.
- Serology is not accurate enough to be offered as a 'routine' test for HSV.
- Serology does not distinguish the anatomical site of infection (see Table 1 page 9).
- Seroconversion is highly variable. Following initial infection, some people seroconvert in 2–6 weeks, but may be longer (months). Also, some people do not seroconvert and reversal from seropositive to seronegative status may occur if there is minimal antigenic stimulation.

Situations where type-specific antibody might be helpful include:

- Herpes in pregnancy (see page 18). In a woman with no previous history of herpes, serology can be helpful to ascertain if it is a primary infection (with viremia, potentially, hence higher risk of transmission) or a recurrence (much lower risk).
- Discordant couples planning pregnancy (when the male partner has a history of herpes and the female doesn't). It can be helpful to ascertain if the female partner without a previous history of herpes has got antibodies or not, as it may be appropriate to counsel abstinence in the last weeks of pregnancy and/or for the male partner to take suppressive antiviral therapy.
- Recurrent or atypical genital symptoms with negative HSV results.

For most partners of positive patients, education and not serology is recommended because of false positive/false negative serology results.

A positive HSV-2 serology result may cause significant psychological morbidity (see page 13).

KEY INFORMATION TO DISCUSS WITH A PATIENT WHO ASKS FOR A BLOOD TEST

- Explain that serology is not 'accurate' enough to be used as a 'herpes test' as there is reasonable risk of false negatives and false positives. It is not a helpful tool in assisting most patients.
- Some people take a long time to develop antibodies and some people don't develop antibodies at all.
- A blood test does not tell you the anatomical site of the infection.
- Discuss with a Sexual Health Specialist before ordering a test.

Table 1: Interpreting Blood Test Results

	HSV-2 Negative	**HSV-2 Positive**
HSV-1 Negative	No antibodies detected*; consider at risk of infection to both types.	No HSV-1 antibodies detected*; consider at risk of infection to HSV-1. HSV-2 antibodies imply prior infection. Probable genital HSV-2 infection because oral and other non-genital site infections are uncommon.
HSV-1 Positive	HSV-1 antibodies imply prior infection, but does not specify site of infection. No HSV-2 antibodies detected*; consider at risk of infection to HSV-2.	HSV-1 and HSV-2 antibodies imply prior infection with both. Probable genital HSV-2 infection, and oral HSV-1.

* May be within window period, may not have seroconverted or may have seroreverted.

MANAGEMENT OF CLINICAL EPISODES OF GENITAL HERPES

Management of First Clinical Episode

KEY POINTS

- First clinical episode may, but does not always, reflect recent infection.
- The '72 hour' herpes zoster rule does not apply to first episode herpes.

The first clinical episode of genital HSV-1 or HSV-2 may, but does not always, reflect recent acquisition of infection. It may represent a primary HSV infection or a new non-primary infection or a first recognised clinical expression of a previously acquired infection. It is not possible to reliably distinguish between these on clinical grounds alone. Nonetheless, as the first episode genital herpes is generally more severe and/or more prolonged, **treatment should always be offered regardless of time of symptom onset.**

Valaciclovir prescriptions do not require specialist authorisation and the medication is available through any pharmacy. Patients are often very unwell and **therapy should be initiated regardless of how long the lesions have been present and before virological confirmation.** This is based on evidence that the virus is shed from the infected area for a median of 11 days, with systemic and local symptoms lasting 2–3 weeks if untreated. Oral antiviral therapy substantially reduces the duration and intensity of symptoms.[18,19] GRADE A

Management for patients presenting with a first episode of genital herpes should encompass the following:

1. History.
2. Examination.
3. Tests:
   (a) Virus swab for PCR for diagnosis.
   (b) Consider screening for other STIs if appropriate, although this may be deferred to a follow-up visit, as it is often too painful.
4. Treatment involving:
   (a) Oral antiviral therapy.
   (b) Symptomatic treatment.
   (c) Provide patient information with written material or refer to **www.herpes.org.nz**
   (d) Acknowledgement of the psychosocial impact of the disease.
   (e) Referral to support systems – Herpes Helpline tollfree **0508 11 12 13**.
5. Appropriate follow-up arrangements.

It is not necessary or desirable to attempt to cover all these issues at the initial clinical assessment. However, recognition of the psychosocial impact of the diagnosis, and the provision of adequate information and/or referral to the Herpes Helpline, is important.

It may be helpful to discuss how results will be given, e.g. in person, over the phone. If giving results over the phone, check the person is in an appropriate situation to receive the call.

History of primary genital herpes

Symptoms may appear 2–20 days following exposure to infection with the virus. However, initial symptoms of genital herpes may not be recognised or may not occur until months to years later. Symptom severity differs markedly with severe cases having lesions lasting up to 3 weeks.

The prodrome (if experienced) is signalled by flu-like symptoms of fever, headache and general myalgia, accompanied by local tingling, irritation and/or pruritus or pain in the genital region. Rapidly, pruritic erythematous papules appear, followed by multiple small vesicles that contain clear to cloudy fluid. These vesicles rupture within 1–2 days to form painful, sloughy, shallow ulcers with irregular margins, which may become confluent. The area may be oedematous and can be extremely tender. Pain on urination is typical, particularly in women and spontaneous urination may be impossible. The ulcers dry to form crusts and later heal, leaving a transient red macule with minimal scarring (if any). Less commonly, lesions can pass through the blister phase quickly and blisters may not be noticed. Involvement of the cervix occurs but speculum examination may not be possible. Lesions may also appear extra-genitally, commonly on thighs and buttocks and less commonly on hands, lips, face and breasts. Local lymph nodes, i.e. inguinal nodes with genital infection, are usually enlarged and tender.

Women are more severely affected than men. Immunosuppressed people may develop very extensive disease.

Complications of primary genital herpes

- Neurological complications are more common with genital herpes than is often recognised. Acute, generally benign, lymphocytic meningitis may occur; HSV-2 is associated with aseptic meningitis in up to 36% of adult women and 13% of men with primary HSV-2 infection. Symptoms include neck stiffness, low-grade fever and severe headache. Diagnostic features include photophobia with CSF findings of positive HSV-2 PCR, increased white cell count and raised protein.[20]
- Similarly, a diagnosis of acute radiculitis (herpetic lumbosacral radiculoneuropathy or Elsberg syndrome) tends to be overlooked, yet may cause acute urinary retention, constipation and sacral neuralgia. Referred pain can affect the saddle area distribution, S3 and 4, of the sacral nerve and the bladder detrusor muscle. Erectile dysfunction, dull or severe burning pain in the anogenital region, loss of sensation and hypersensitivity can occur down the thighs and the lower legs. The condition is usually self-limiting and tends to resolve in 1–2 weeks; in the meantime, supportive cares should be offered. Symptoms may sometimes persist for weeks and rarely severe intractable pain may require opiate analgesia.
- HSV-2 myelo-radiculitis, associated with advanced immunosuppression and AIDS, may be associated with a fatal outcome.[21]
- Bells Palsy is probably caused by either VZV, HSV-1 and rarely HSV-2. Early treatment with oral steroids is effective.[22,23] A recent Cochrane review suggests that, compared with steroids alone, antiviral treatment increases the proportion of patients who recover at 3- and 12-month follow-up, albeit the quality of evidence is limited.
- Sporadic herpes simplex encephalitis is an acute necrotising viral encephalitis that is more usually caused by primary infection with HSV-1. Clinical features are often nonspecific, as is common with all forms of encephalitis, and include headache, signs of meningeal irritation, altered mental status, and seizures. Because prompt treatment of HSV encephalitis may minimise residual neurologic damage and prevent death, early consideration of this diagnosis is important.
- HSV (especially Type 1) is a common predisposing trigger for erythema multiforme, a hypersensitivity condition most often caused by infections and sometimes drugs. Many cases have no obvious precipitating cause. It develops 3–14 days following HSV infection. Mild forms of this condition are common and start and present as macules, papules and urticarial lesions which reach up to 3cm on extremities. They especially affect the hands and feet, dorsum of elbows and knees, and less often the trunk. Some lesions develop into the classical "target" lesion with three colour zones: central dusky erythema, surrounded by a paler oedematous zone and an outer erythematous ring with a well-defined border. Resolution within 7–10 days is the norm.
- Infrequently, HSV viraemia may result in infection of visceral organs. In most cases of disseminated infection, lesions are confined to the skin, but hepatitis, pneumonitis and other organ involvement may occur, with or without vesicular skin lesions.

A relevant specialist should review any patient with complications.

Examination

Examination should include inspection of the genital region; speculum examination should be considered, but may need to be delayed if discomfort is anticipated.

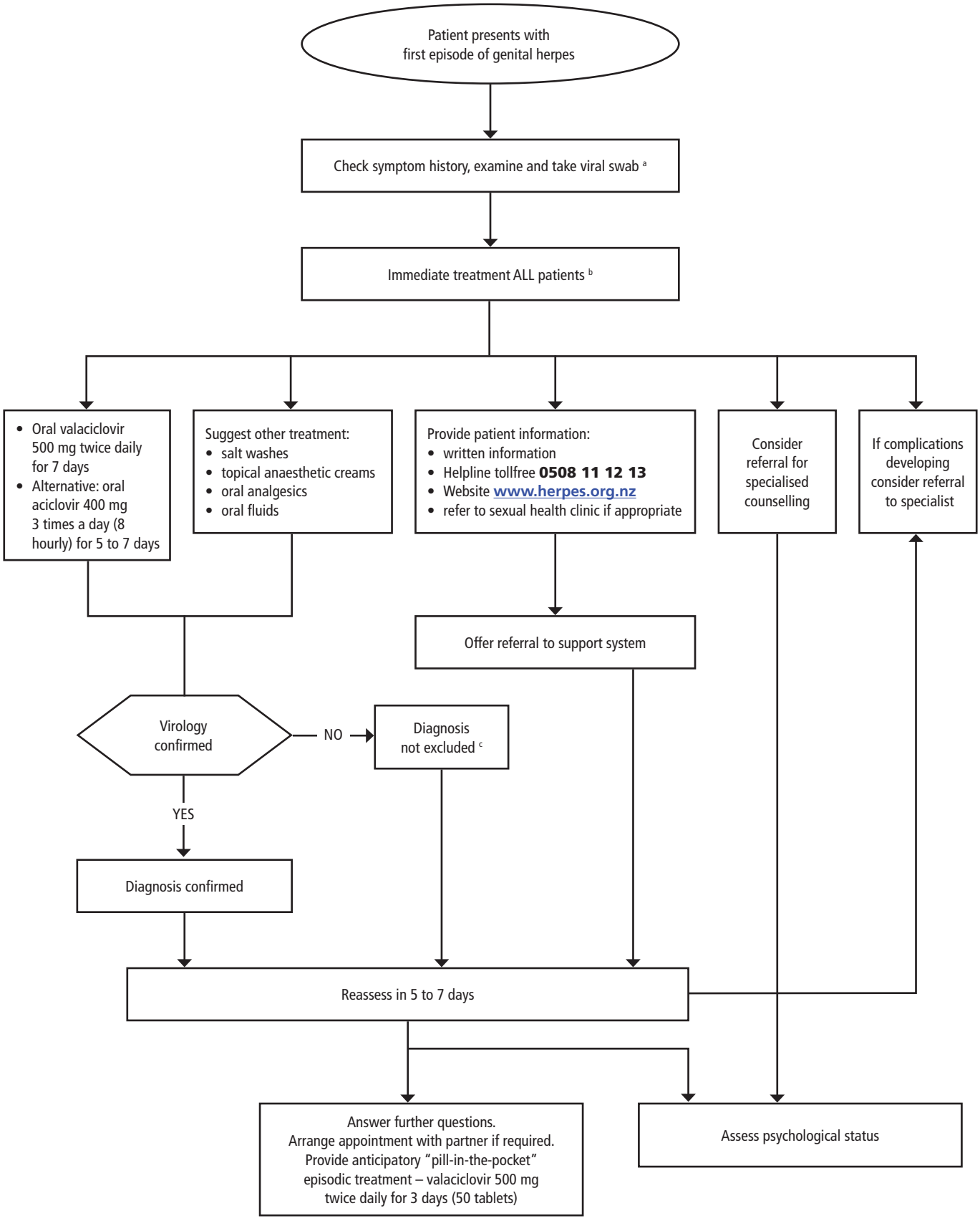
Diagnosis

Laboratory confirmation of the diagnosis is important, but should not delay the initiation of treatment. A negative result does not necessarily exclude a diagnosis of HSV (see page 8-9).

Differential diagnosis

- Aphthous ulcers. There are fewer and larger lesions with no preceding vesicles.
- Steven Johnson syndrome. This is usually but not always associated with skin lesions. (HSV infection can cause this condition.)
- Autoimmune blistering disorders such as pemphigus and cicatrical pemphigoid, which are chronic.
- Other genital infections lack the preceding vesicular stage, apart from varicella zoster infection which is unilateral.
- Candidiasis and folliculitis produce pustules, which must be differentiated from HSV infection.

Management of First Episode of Genital Herpes



a In cases of immunocompromised patients or herpes proctitis, refer to specialist.
b Specialist consultation is recommended for use of antivirals in pregnancy.
c Recommend early presentation for viral swab if recurrence.

Treatment of First Episode Genital Herpes

A. Pharmacological treatment

If there is a possibility of pregnancy, please refer to **page 18**. Refer immunocompromised patients, or those with herpetic proctitis, to an appropriate specialist, e.g. infectious diseases, sexual health.

1. Oral antiviral treatment

Recommended treatment for first episode genital herpes:

- **Valaciclovir 500mg BD for 7/7.**
- **Alternative: oral aciclovir 400mg 3 times daily (8-hourly) for 7 days.**

Lesions may not completely heal over during the course of drug treatment; similarly, mild neurological symptoms may not yet have fully resolved. Nonetheless, a further course of therapy is not usually indicated unless new lesions continue to appear.

2. Intravenous antivirals

Intravenous (IV) aciclovir therapy could be considered for patients who have severe disease or complications that necessitate hospitalisation.[24]

- For patients with severe disease requiring hospitalisation the dose for intravenous aciclovir is 5–10 mg/kg 8 hourly for 2–7 days followed by oral treatment to complete at least 10 days of antiviral therapy.

3. Topical antivirals

Topical aciclovir creams are not recommended because they offer minimal clinical benefit (see **page 16**).

B. Symptomatic treatment

In addition to oral antivirals, other measures to control symptoms should be suggested. Paracetamol 4-hourly is usually adequate, but stronger pain relief may be necessary. Drinking fluids hourly produces dilute urine that is less painful to void. Female patients can be advised to sit in a bath or bowl of warm water to pass urine. Advice about drying lesions with the lowest setting of a hair dryer may be helpful. Bathing in salt water (e.g. half a cup of household salt in the bath or 2 teaspoons per litre of warm water for topical application) may help relieve pain and promote healing. Adequate pain relief should be provided. Topical anaesthetic jelly such as lignocaine (Xylocaine) gel applied 5 minutes before micturition helps relieve the pain. As lignocaine is a potential skin sensitizer, patients should be warned to use it for the shortest possible time (usually 1 or 2 days maximum). Grade C

C. Education

It is important to ensure that patients receive accurate up-to-date information about genital herpes. A range of printed materials can be downloaded from the NZHF website, or ordered at no cost (please refer to resources listed on the **inside front cover**). Primary care practitioners should have access to these resources or be able to advise their patients on how to obtain them, e.g. **www.herpes.org.nz**. There is also a Herpes Helpline **0508 11 12 13**, a telephone service which is free to all New Zealanders.

Informing the patient of the diagnosis can be a delicate matter. **Health providers may find it helpful to review the 3 minute PowerPoint resource on the NZHF website www.herpes.org.nz which provides information on what patients tell us they want to know at this point in their management.** Although initial counselling can be provided at the first visit, it may be preferable to wait until the initial outbreak settles to discuss chronic aspects of the infection. Written materials, such as the NZHF **Myth vs Facts** leaflet and **The Facts** booklet, should be offered to patients at the first visit with discussion and further questions encouraged at the follow-up and subsequent visits.

See **Key Information for Health Professionals to Give Patients in Counselling** on page 34. Grade C

D. Follow-up

Follow-up is important for those with first episode herpes. For most patients, one visit is insufficient to properly manage the impact of genital herpes. Counselling and advice often form the major part of a follow-up appointment and time should be allowed for this. The practitioner should be alert to the possibility of further psychological problems manifesting after a diagnosis of genital herpes.

At the initial visit, a follow-up appointment should be offered for 5–7 days later, to evaluate symptoms, their psychological status, complete a full STI screen if appropriate, discuss results and answer any questions they may have. It should be noted that it might take longer than 5 days for skin lesions to heal completely. Further therapy is not usually required unless new lesions continue to appear.

Anticipatory episodic therapy is recommended. Episodic antiviral therapy is more effective when patients start therapy themselves at the first signs of a recurrence. Grade A

Suppressive antiviral therapy can be considered for those with frequent and/or severe recurrences or associated psychosocial morbidity. It is suggested that either a minimum of two recurrences or approximately 3 months without suppressive therapy is required to establish the pattern.

Management of Recurrent Episodes of Genital Herpes

KEY POINTS

- Most recurrent herpes is mild and infrequent.
- There is effective oral antiviral treatment for frequent, severe, problematic genital herpes.
- Treatment/management options should be discussed with the patient. No treatment is also a common and acceptable option.
- Individualised treatments and increased emphasis on prompt initiation of episodic treatment.
- Suppressive therapy can be considered for those with frequent and/or severe recurrences, and/or associated psychological morbidity and those associated with erythema multiforme.
- 20–25% of patients may have 'recurrences' despite being on suppression. If the patient is compliant with suppressive therapy, it is important to consider other genital conditions that mimic or coexist. A positive HSV DNA result in a patient who is compliant with suppression suggests ACV-resistant virus which is very rare.
- Withdrawal of therapy should be for a sufficient length of time to establish whether the pattern of recurrence has changed (3 months).
- Reduced dose of valaciclovir or aciclovir should be considered in the presence of severe renal failure.
- Education and counselling are an extremely important part of management (refer to **www.herpes.org.nz** or Herpes Helpline tollfree **0508 11 12 13** or from a mobile 09 433 6526).

Management of recurrent herpes depends on whether there is prior virological confirmation of infection. Management of patients presenting with recurrent herpes should encompass the following:

1. History
2. Examination
3. Tests:
   (a) Viral swab for PCR for diagnosis; confirmation of diagnosis at least once is strongly recommended.
   (b) Consider exclusion of other STIs if appropriate.
4. Treatment involving:
   (a) Either episodic therapy or suppressive therapy where appropriate.
   (b) Symptomatic treatment.
   (c) Education concerning transmission, epidemiology, etc; provide written material.
   (d) Acknowledgement of the psychosocial impact of the disease.
   (e) Referral to support systems – Herpes Helpline tollfree **0508 11 12 13** or visit **www.herpes.org.nz**.
5. Appropriate follow-up arrangements.

Sufficient time should be allowed to address all these aspects.

History, examination and diagnosis

- Only 10–25% of persons who are HSV-2 seropositive report a diagnosis of genital herpes, which suggests that most have unrecognised symptomatic or completely asymptomatic infections.[25] However, once told they are HSV-2 seropositive, more than 50% are able to identify clinically symptomatic recurrences that may have previously been thought to be due to other conditions.
- In straightforward cases with a prior laboratory-confirmed diagnosis, the clinical history is often the principal means of determining that the patient has a recurrent episode, but other genital conditions may mimic and/or coexist with recurrent herpes, and careful examination of the genitalia should always form part of the diagnostic procedure.
- Common differential diagnoses include lichen sclerosus, fissuring due to candidiasis, folliculitis, bacterial skin infections, dermatitis and any other skin conditions that cause itching and fragility of the skin.
- Uncommon conditions include erythemea multiforme, hidradenitis suppurativa, scabetic nodules, fixed drug eruption, trauma (self-inflicted or accidental) and autoimmune blistering disease (rare). Other infections may cause genital ulcers, although not necessarily recurrent, e.g. other herpes viruses such as herpes zoster virus and Epstein-Barr virus, primary syphilis and chancroid.
- All these examples serve to underpin the importance of taking a detailed history and thorough physical examination of the whole skin, including oral mucosa. Atypical presentation is not unusual and HSV should be considered in any recurrent intermittent inflammatory genital lesions regardless of appearances. **Any recurring lesion of 1–2mm in size, occurring in the same genital area, is strongly suggestive of HSV-2 infection.**

- All genital lesions not previously diagnosed should have a swab taken with an explanation to the patient why this has been done. Grade B
- It is highly desirable, but not always possible, to obtain virological confirmation. Typically, the viral load is reduced in recurrences compared with the first episode. There is a significant false-negative rate in the laboratory tests for HSV, although this is less for PCR. The best method of obtaining confirmation during a recurrence is to take a swab for PCR within 24 hours of symptoms developing. Grade B
- An option is to instruct patients how to take a swab themselves and deliver direct to the laboratory. Other causes of recurrent genital lesions should be considered, but in the event of continuing recurrent lesions and HSV PCR remaining negative, type-specific herpes serology testing may aid diagnosis.

Complications of recurrent genital herpes

- Recurrent herpes lesions can occur on the hands, arms, shoulders and other areas of the body, commonly around the buttocks; the diagnosis is often overlooked.
- Benign headaches.
- Lumbar sacral radiculopathy can recur, but usually with less severe symptoms than in primary infection. Recurrent, benign, aseptic meningitis, known as Mollaret's meningitis, may occur with HSV-2. Patients should be offered long-term suppressive antiviral management, which may need to be continued indefinitely.
- HSV is a common predisposing trigger for erythema multiforme. Mild forms of this condition are common and present with mildly itchy, pink-red blotches, starting on the extremities. Some of the skin patches take on the classical 'target lesion' appearance, with a dark centre surrounded by a pale oedematous circle and a red periphery. Resolution within 7–10 days is the norm. Recurrent episodes may be managed with continuous antiviral suppression treatment.
- Erythema multiforme major is a more severe condition with mucosal involvement affecting mouth, eyes and genital mucosae. It may become recurrent with each episode of HSV infection and requires suppressive therapy.

A specialist should review any patient with complications.

Treatment of Recurrent Genital Herpes

Episodic antiviral therapy

The aim of episodic treatment is to reduce symptoms and duration of viral shedding during recurrences, rather than reduce the frequency of recurrences. Further, early therapy may abort episodes, that is, lesions may be prevented from progressing beyond the papular stage.[26,27] In situations where patients have well recognised prodromes and/or have less frequent recurrences, some may find episodic treatment preferable to continuous suppressive therapy.

Effective episodic antiviral treatment of recurrent herpes requires initiation of therapy during the prodrome that precedes some outbreaks or within one day of lesion onset.[26,27] Beyond this timeframe there is no clear benefit, so it is important that a prescription is readily available. In consultation with the patient, sufficient quantities of medication may be prescribed with instructions to start treatment as soon as symptoms begin. Grade A

Recommended dosage regimen

If the patient is pregnant, specialist consultation is recommended (see page 18). In cases of immunocompromised patients, refer to appropriate specialist.

Episodic treatment

- Valaciclovir 500mg bd for 3/7.
- Alternative: oral aciclovir 800mg 3 times daily for 2 days.

Prescribe enough tablets for patients to be able to self-initiate treatment at onset of symptoms.

Note: Famciclovir is not subsidised or marketed in New Zealand.

Suppressive antiviral therapy

Suppressive therapy is an oral antiviral taken continuously over a given period of time that effectively reduces the frequency of recurrences.[28,29] Grade A

The main aims of suppressive therapy are:

- As an effective strategy for improving the quality of life of patients with recurrent genital herpes.[30,31]
- To allow the patient to have a break from experiencing recurrences of the disease.
- To reduce the risk of transmission.
- Reduced dose of valaciclovir or aciclovir should be considered in the presence of severe renal failure.

Aciclovir, famciclovir and valaciclovir all suppress symptomatic and asymptomatic shedding, by up to 80–95%.[15] Suppressive once-daily valaciclovir has been shown to reduce transmission to an uninfected partner with a 48% reduction in acquisition of HSV infection and a 75% reduction in clinical symptomatic genital herpes.[16] Other antivirals may be similarly effective, but this has not been proven in clinical trials. Patients may wish to consider this as a useful adjunct to safer sex behaviour and the use of condoms for the prevention of genital herpes transmission.

Indications for suppressive therapy

KEY POINTS
• Frequent and/or severe recurrences or associated phsychological morbidity. Consider suppressive therapy in conjunction with other management. GRADE B • For HSV-2 positive male partners of pregnant women (see **page 21**).

With long-term suppressive therapy it is strongly advisable to have virological confirmation of the diagnosis before commencing treatment. **Patients who have suggestive symptoms but do not have virological confirmation of recurrences, or who have complications or ongoing issues relating to their herpes, should see a specialist**.

Recommended dosage regimen

If the patient is pregnant, specialist consultation is recommended (see **page 18**).

In cases of immunocompromised patients, refer to appropriate specialist.

Recommended treatment regimens for suppressive therapy include:

- Valaciclovir 500mg daily. Increase to 500mg bd on individual basis of clinical presentation and/or having breakthrough recurrences on 500mg daily.
- Alternative: oral aciclovir 400mg twice daily.

Suggest prescribing for 12 months, followed by a break of 3 months to see if recurrences are still frequent. GRADE C

20–25% of patients may experience recurrent episodes whilst on suppressive therapy.[28,32] Other genital conditions may mimic and/or coexist and, even if symptoms are suggestive of breakthrough recurrences, such patients are advised to see a specialist. The usual recommended dose of valaciclovir may need to be altered if breakthrough episodes are confirmed; suppressive therapy does not alter the natural history of recurrences long term and it is common to have a recurrence soon after withdrawal of therapy. It is helpful to anticipate this and to provide sufficient medication to allow prompt self-initiated treatment of any early recurrences. It is suggested that either a minimum of two recurrences or approximately 3 months without suppressive therapy is necessary to establish the new pattern.

Some patients may need to be on suppressive therapy for years. Valaciclovir is well tolerated and safety and efficacy data are supportive of longer-term use.[33] Neurotoxicity (lethargy, confusion, hallucinations and involuntary movements) has been reported in those with renal impairment.

Topical antiviral therapy

Topical aciclovir creams are less effective than oral aciclovir.[34] Hence, use of topical treatment is not recommended. Topical antiviral creams are available over the counter, but are no longer subsidised on the pharmaceutical schedule.

Newer topical agents such as immune modulators are currently in clinical trials.

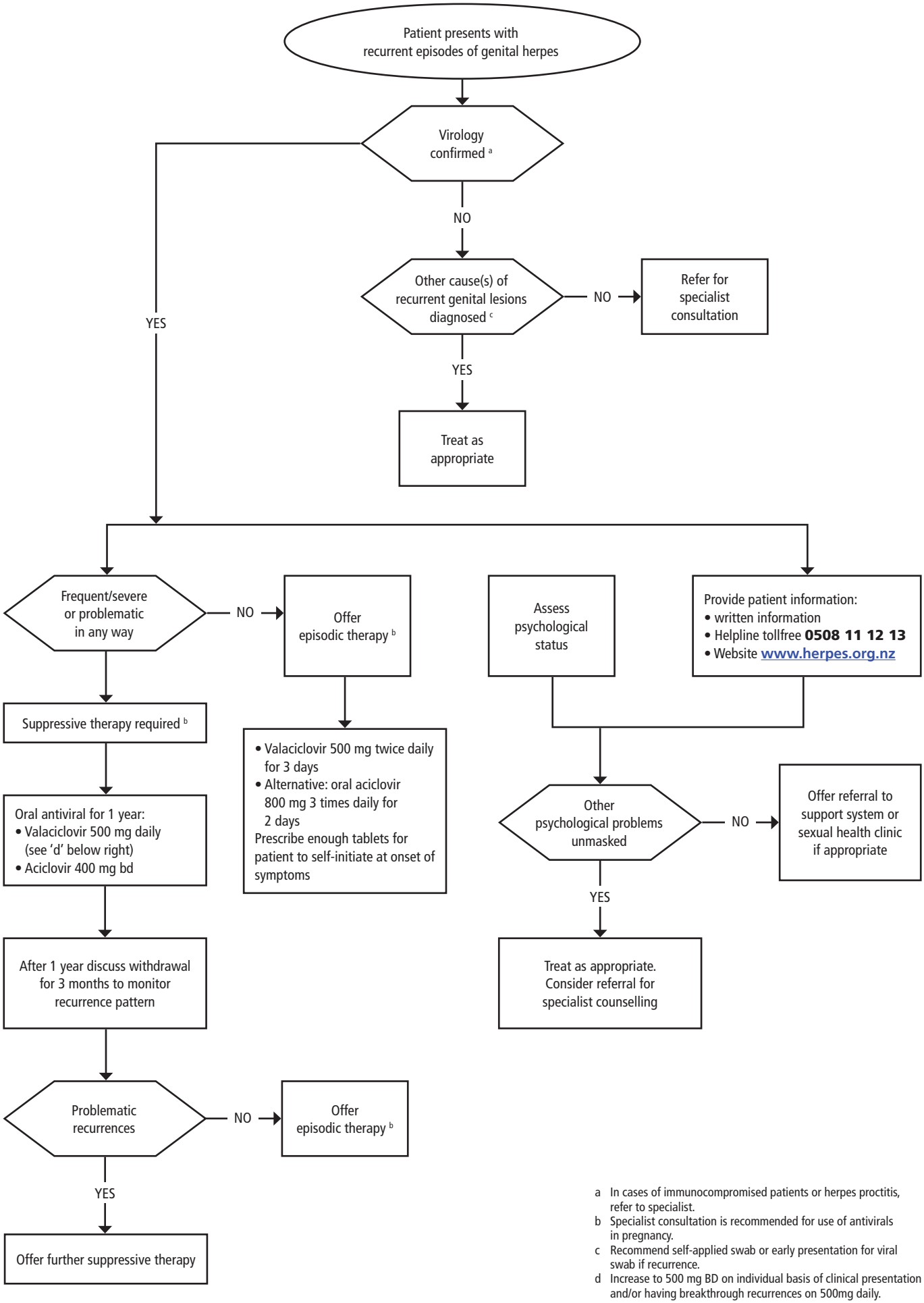
Other therapies

Evidence for other therapies (oral L-lysine, aspirin, liquorice root cream, lemon balm, aloe vera cream, etc.) is absent.

Genital Herpes in Immunocompromised Individuals

Although rare in immunocompetent individuals, clinically refractory (large, severe and sometimes atypical) lesions due to genital HSV may occur in patients with severe immunodeficiency, including late stage HIV disease. Immunocompromised individuals need referral to specialist care.

Management of Recurrent Episodes of Genital Herpes



a In cases of immunocompromised patients or herpes proctitis, refer to specialist.
b Specialist consultation is recommended for use of antivirals in pregnancy.
c Recommend self-applied swab or early presentation for viral swab if recurrence.
d Increase to 500 mg BD on individual basis of clinical presentation and/or having breakthrough recurrences on 500mg daily.

GENITAL HERPES IN PREGNANCY

KEY POINTS

- The risk of maternal-fetal transmission (MFT) is high in primary genital herpes infection if acquired at the time of labour (about 50%) or within 6 weeks prior to delivery. Delivery by caesarean section is indicated.
- Women with a past history of genital herpes and no recurrences in pregnancy can be reassured that the risk of MFT is extremely low. Maternal antibodies are protective.
- Recurrent lesions at term are a relative (not absolute) indication for caesarean section. The risk of MFT is low from recurrent lesions during labour (1–3%), although may be greater with HSV-1 than HSV-2 based on a cohort study of viral shedding at delivery. Management of this scenario should be discussed with the woman antenatally.
- There is an increased incidence of viraemia in primary herpes infection in pregnancy. Herpes simplex infection should be considered in the differential diagnosis in the management of the acutely unwell pregnant woman.
- Antiviral medications, particularly aciclovir, have been widely used in pregnancy without apparent adverse sequelae. In general, pregnant women (any trimester) should be offered treatment as for non-pregnant women following a discussion regarding the relative benefits versus possible disadvantages.
- Suppressive antivirals from 36 weeks gestation may reduce the chance of a recurrence at term and hence the need for caesarean section. An increased frequency of administration is recommended because of the increased plasma volume in pregnancy.
- If vaginal delivery occurs, scalp electrodes and instruments should not be used unless there is a clear obstetrical indication as skin trauma may increase the risk of transmission of HSV.
- The use of antiviral medications and delivery by caesarean section may not be completely protective. Women should be given the same advice on postnatal surveillance of their babies regardless of use of antiviral treatment or mode of delivery.
- Specialist obstetric and paediatric advice on management should be sought for a woman with active recurrent lesions at the time of delivery and especially in the high risk situation of a first episode within 6 weeks of delivery (see **Neonatal HSV Infection**, page 25).

Maternal Fetal Transmission

Primary infection

Neonatal herpes is a rare but potentially serious infection, which may be associated with significant morbidity and mortality. Infection may be acquired antenatally, at the time of delivery or post-partum:

- About 85–90% of neonatal herpes infections are acquired during labour through direct contact with infected genital secretions.
- In 5% of cases the infection is acquired in utero (either via ascending infection or transplacentally secondary to maternal viraemia).
- In 5–10% of cases the infection is acquired post partum.[35]

Primary maternal infection in early pregnancy may be associated with miscarriage,[36] and in the second and third trimesters may be associated with preterm delivery. Rarely, primary maternal infection may result in disseminated infection of the fetus with skin lesions, chorioretinitis or microcephaly or hydrocephalus at birth.[37] The long-term outlook for these infants is very poor. A minority with late intrauterine HSV infection will present at delivery with skin or eye lesions. The prognosis for successful anti-viral therapy in these infants is far better than that for newborns with more long-standing intrauterine infection.[38]

Recurrent infection

Antenatal recurrent disease, where HSV is not shed at delivery, is rarely associated with adverse neonatal outcomes. The risk of intrauterine fetal infection from recurrent maternal HSV infection is extremely low:[39]

- A nested case-control serology study assessing HSV-2 antibodies in stored serum samples from 283 women with a fetal loss after 20 weeks compared to 970 randomly selected women from a large source population found no association between herpes simplex infection and fetal loss.[40]
- One cohort found that untreated recurrent genital herpes infection may predispose to preterm delivery which may be prevented by the use of suppressive antiviral treatment. Further studies are required to confirm this finding.[41]

Comparison between primary and recurrent infection at delivery

Several factors influence the risk of a newborn acquiring HSV infection at the time of delivery, the most important of which is whether the mother has newly acquired vs recurrent genital disease.[42,43] **The greatest risk of perinatal transmission is when a previously seronegative woman has a primary first episode of genital herpes near or at the time of delivery.** Under such circumstances the risk of neonatal HSV infection is 50%.

Although reactivation of HSV-1 is less common than that of HSV-2, there is evidence that reactivated HSV-1 may be more readily transmitted to the neonate. The same strategies are required for prevention of both HSV-1 and HSV-2.[44]

Transmission rates are lowest for women who acquire herpes before pregnancy, with the risk being about 0.05% for such women who have no signs or symptoms of an outbreak at delivery.[42,45] Maternal antibodies cross the placenta and are protective. If lesions are present at delivery, there is a small risk of transmission of 0.25–3%.[43] Specifically, the risk for transmission of reactivated HSV-2 infection appears to be less than 1%.[46]

Women with HIV and HSV-2 co-infection have a greater risk of transmitting HSV-2, as HSV-2 shedding is increased in HIV co-infected women.[47]

Of infants with proven HSV infection, 80% have no documented history of herpes infection in either the mother or her partner. The decreasing prevalence of HSV-1 in childhood increases the susceptibility of young adults to genital HSV-1 including women of reproductive age and hence increases the risk of neonatal HSV.[48]

Use of Antivirals in Pregnancy and Breastfeeding

Aciclovir has been used widely in pregnancy. There is less experience with valaciclovir but it is expected that valaciclovir as a prodrug of aciclovir should be safe. In the majority of situations, the benefits of antiviral therapy outweigh possible risks.

Antiviral therapy is indicated for treatment of primary and recurrent episodes as in non-pregnant women and for prophylaxis to reduce the risk of recurrence at the time of delivery. An increased frequency of dose is indicated in late pregnancy because of an increased plasma volume.

The following is a summary of the available evidence on the use of antivirals in pregnancy:

- Data collected via the Aciclovir Pregnancy Register (1984-99) on 1,234 infants exposed to aciclovir in pregnancy and in 1,804 infants exposed to aciclovir, valaciclovir or famciclovir in first trimester in a large Danish cohort demonstrated that there was not an observed increase in birth defects compared to the general population. This data is reassuring although the numbers are insufficient to assess individual defects.
- Small studies have shown that prophylactic use of aciclovir from 36 weeks decreases the number of clinical recurrences and reduces the need for caesarean section, but treatment does not eliminate viral shedding completely.[49-52] Two meta-analyses have confirmed that there is a reduction in clinical recurrences at delivery, a reduction in caesarean section for active herpes, and a reduction in viral shedding.[53,54] Grade B
- Aciclovir has been categorised as B3 in the Australian TGA Prescribing Medicines in Pregnancy database on the basis of fetal animal effects of unknown relevance to humans.
- A possible association between antiherpetic medications and gastroschisis has been reported from a case control study but numbers of affected infants were small and the association was unproven.
- There are theoretical concerns that maternal antiviral therapy may suppress rather than treat newborn infections, thus leading to a delay in presentation of neonatal disease.
- The American Academy of Pediatrics has approved use of aciclovir for treating first episode or recurrent genital herpes in breastfeeding mothers. Although concentrations are high in breast milk and the baby, toxicity is low.[55] Grade B

There are no established protocols for the use of antiviral medications in pregnancy, but the following regimens are frequently used:

First episode

Valaciclovir 1g bd for 7/7

- Alternative: Aciclovir

First episode (severe disease) or in immunosuppressed

- Aciclovir 5mg/kg IV (over 60 minutes) 8-hourly until able to switch to oral therapy, based on symptoms

Recurrent disease suppressive therapy

- Valaciclovir 500 mg **bd**
- Aciclovir 400mg orally 3 times daily (more frequent dosing indicated because of increased clearance in pregnancy)

Mode of Delivery

There are no randomised controlled trials to guide optimal delivery management for pregnant women with genital herpes.

Primary infection

Caesarean section has been demonstrated to significantly reduce vertical transmission in women with primary infection in late pregnancy or at the time of delivery.

Recurrent infection

Because the risk of vertical transmission in recurrent disease is low there has been debate about the benefit of delivery by caesarean section in women who have recurrent episodes at the time of labour. In the US delivery by caesarean section in this situation is recommended but in the Netherlands there has been a policy of offering vaginal delivery for recurrent genital herpes at the time of delivery since 1987 without an apparent increase in neonatal herpes infection.

It has been shown that the presence of symptoms at delivery correlates relatively poorly with the detection of HSV from genital sites or lesions by HSV PCR. Assessment of viral shedding is based on clinical assessment.[56]

Efficacy of caesarean section in reducing maternal fetal transmission

Caesarean section is not completely protective, as transmission of infection has occurred occasionally in the presence of intact membranes. Prolonged contact with infected secretions may further reduce the benefits of abdominal delivery.[57]

No definitive studies have been carried out on the relationship between the duration of rupture of membranes in the presence of clinical lesions and the transmission of HSV to the fetus. Previously, 4 hours has been suggested as a cut-off time beyond which caesarean section may be no longer beneficial. However, there is no evidence that there is a duration of premature rupture of membranes beyond which the fetus does not benefit from caesarean delivery.[58]

Because the risk of maternal-fetal transmission is high when primary infection is acquired within 6 weeks of delivery, maternal and neonatal aciclovir therapy should be considered if there has been membrane rupture for more than 4 hours or where a vaginal delivery is unavoidable.[59]

Observational study data

In a large prospective cohort study of women who had herpes cultures taken in labour, HSV was isolated in 202 women and, overall, neonatal transmission occurred in 10 (5%).[43] Caesarean delivery significantly reduced the HSV transmission rate in women from whom HSV was isolated (1 of 85 [1.2%] caesarean vs 9 of 117 [7.7%] vaginal). Risk factors for neonatal HSV infection included:

- First-episode infection
  - Of 26 first episode cases, transmission occurred in 8.
- HSV-1 vs HSV-2 isolation at the time of labour
  - None of the 140 women with viral shedding due to HSV-2 reactivation infected their babies.
  - HSV-1 reactivation in 2/11 women resulted in neonatal infection.
- The use of invasive monitoring.
- Premature delivery.
- Young maternal age.

There was a high caesarean section rate in those noted to have genital lesions in labour. The data from this study was pooled with two other cohorts (from the USA and Sweden) and provided further evidence that during reactivation HSV-1 may be more readily transmissible to the neonate than HSV-2. This pooled cohort study also showed that maternal HSV-1 antibody does not offer significant protection against HSV-2.[60]

Audit data

In the Netherlands since 1987 it has been the policy not to offer women caesarean section in the presence of a recurrence at term and there has not been a resultant increase in the incidence of neonatal herpes.

- There were 26 cases of neonatal herpes 1981–1986 before the change in policy compared to 19 cases 1987–1991.[48]
- A follow-up audit 1999–2005 concluded that there was again a low rate of neonatal infection in the Netherlands despite a low caesarean section.[61]
- A higher rate of neonatal infection 2006–2011 was attributed to failure of adherence to the guideline recommending caesarean section for primary infection in late pregnancy. The recommendation for vaginal delivery for recurrent episodes remain unaltered.[62]

In other countries, guidelines recommend that women who have signs or symptoms of a recurrent infection in labour should be offered caesarean section, but as a relative, rather than absolute, indication for abdominal delivery.[57]

In summary, there is a lack of robust evidence to guide management in the case of recurrent lesions at the onset of labour. Traditionally delivery by cesarean section has been offered and ideally discussion about the relative risks should occur antenatally in the event of this scenario. Because the risk of transmission is low (1–3%) some women may opt for a vaginal delivery. Factors such as prematurity, HSV-1 rather than HSV-2 and an expected long labour which may all predispose to maternal fetal transmission should be considered.

Special Situations in Pregnancy

Disseminated infection

Disseminated infection from genital or oro-labial infection is rare, but may be life-threatening. Viraemia in the mother during primary infection may result in neonatal multi-organ involvement with significant mortality. The diagnosis may be delayed if vesicular skin lesions are absent or sparse.[63,64]

Hospital admission and the use of intravenous aciclovir are required for severe disease in pregnancy. The diagnosis of disseminated disease should be considered in any woman presenting with systemic disease in pregnancy.

Premature prelabour rupture of membranes in primary infection

Little data is available on the management of preterm prelabour rupture of membranes in association with primary herpes simplex infection. Multidisciplinary discussion is required taking into consideration the gestation reached. Treatment with aciclovir 5mg/kg 8 hourly should be administered pending delivery. Caesarean section is considered to be beneficial despite prolonged rupture of membranes. Corticosteroids are not contraindicated.[58]

Premature prelabour rupture of membranes in recurrent infection

One study has shown that expectant management of 29 women with preterm premature rupture of membranes at <31 weeks gestation, complicated by active recurrent genital herpes, was not associated with neonatal transmission. It was concluded that the risks of prematurity outweighed the risks of transmission of infection in the presence of a recurrent episode.[65] The mean duration of membrane rupture was 13.2 days (range 1–35 days), 45% were delivered by caesarean section and 8% received antiviral therapy for control of symptoms.

Prevention of HSV in the Neonate

All women should be asked at the first antenatal visit if they or their partner have had genital herpes. A study of 3192 pregnant women and their partners identified that 22% of women were at risk of HSV-1 or HSV-2.[56] Of 582 women susceptible to HSV-1, 14 women or 2.5% (3.5% adjusted for length of gestation) acquired HSV-1; the only independent risk factor was a history of a partner with oral herpes. Of 125 women susceptible to HSV-2 infection, 17 or 14% (20% adjusted for length of gestation) acquired HSV-2 infection. Also, the risk of becoming infected was eight times greater in relationships of a year or less, than for those in longer duration relationships. Most newly acquired infections were subclinical.

Although there is no clear evidence to support guidelines in the situation of the partner with a history of previous herpes infection, the following are recommended on theoretical grounds: Grade C

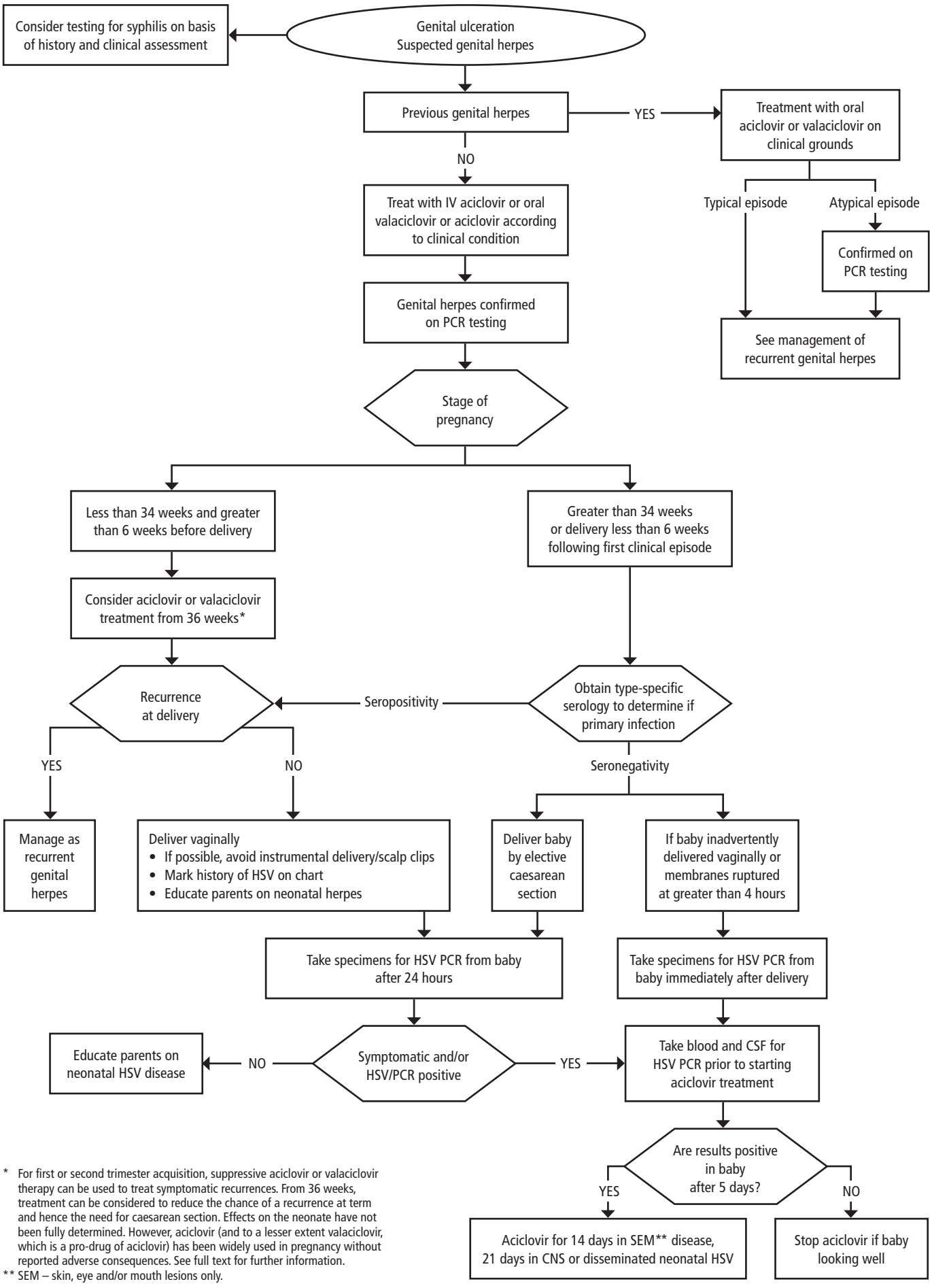
- Female partners of men with genital herpes should avoid sex when lesions are present.
- Asymptomatic female partners of men with genital herpes should have serology to check their HSV status.
- Consistent use of condoms throughout pregnancy may prevent acquisition.
- Suppressive therapy should be considered in the male partner if the couple is discordant for antibodies to HSV-2.
- Pregnant women should be advised of the risk of acquisition of HSV-1 from oral-genital contact. If partner has oral herpes and HSV status unknown, avoid oral sex.
- Parents, staff and relatives/friends with active oral lesions should be advised about the risk of post-natal transmission.

Although routine serological screening in pregnancy has been recommended by some authors, universal screening is not likely to be cost effective because of the high number needed to treat to prevent a single case of neonatal herpes.[66]

Summary of Clinical Management of First Episode Genital Herpes in Pregnancy

Note: All women with a history of genital herpes infection should be given information on postnatal neonatal surveillance. No interventions are completely protective against maternal fetal transmission.

Management of Women with Suspected Genital Herpes in Pregnancy
(in consultation with a specialist)



* For first or second trimester acquisition, suppressive aciclovir or valaciclovir therapy can be used to treat symptomatic recurrences. From 36 weeks, treatment can be considered to reduce the chance of a recurrence at term and hence the need for caesarean section. Effects on the neonate have not been fully determined. However, aciclovir (and to a lesser extent valaciclovir, which is a pro-drug of aciclovir) has been widely used in pregnancy without reported adverse consequences. See full text for further information.

** SEM – skin, eye and/or mouth lesions only.

First Episode Genital Herpes: First and Second Trimester Acquisition

- Management of the woman should be in keeping with her clinical condition, using antivirals in standard doses as indicated (see **page 19**) for primary and recurrent episodes. GRADE C
- Provided delivery does not ensue, the pregnancy should be managed expectantly and vaginal delivery anticipated.
- Continuous antivirals in the last 4 weeks of pregnancy reduce the risk of both a clinical recurrence at term and delivery by caesarean section. However, the effects on the neonate have not been fully evaluated.

For further management advice, see **Management of Pregnant Women with Recurrent Genital Herpes**, page 23.

First Episode Genital Herpes: Third Trimester Acquisition

Note: *The first clinical episode may not be due to a primary infection, as previous infection may not have been recognised. Type PCR and serological testing in conjunction with clinical evaluation will help identify primary HSV in pregnancy. All results should be discussed with an expert knowledgeable in interpreting these results and who is aware of the sensitivity and specificity of available testing methods.*

- Offer treatment with aciclovir or valaciclovir according to clinical condition as per non-pregnant individuals (see **page 19**).
- Offer suppressive valaciclovir 500mg bd or aciclovir 400mg tds to reduce viral shedding and risk of recurrences.
- Delivery should be by caesarean section, particularly in those women infected within 6 weeks of delivery because of high rates of asymptomatic shedding of HSV and insufficient time for a complete antibody response between infection and delivery. GRADE B
- If vaginal delivery is unavoidable, consider intravenous aciclovir treatment of the mother and request an urgent referral to a paediatrician experienced in HSV infection (see **Neonatal HSV Infection**, page 25). GRADE C

Management of Pregnant Women with Recurrent Genital Herpes

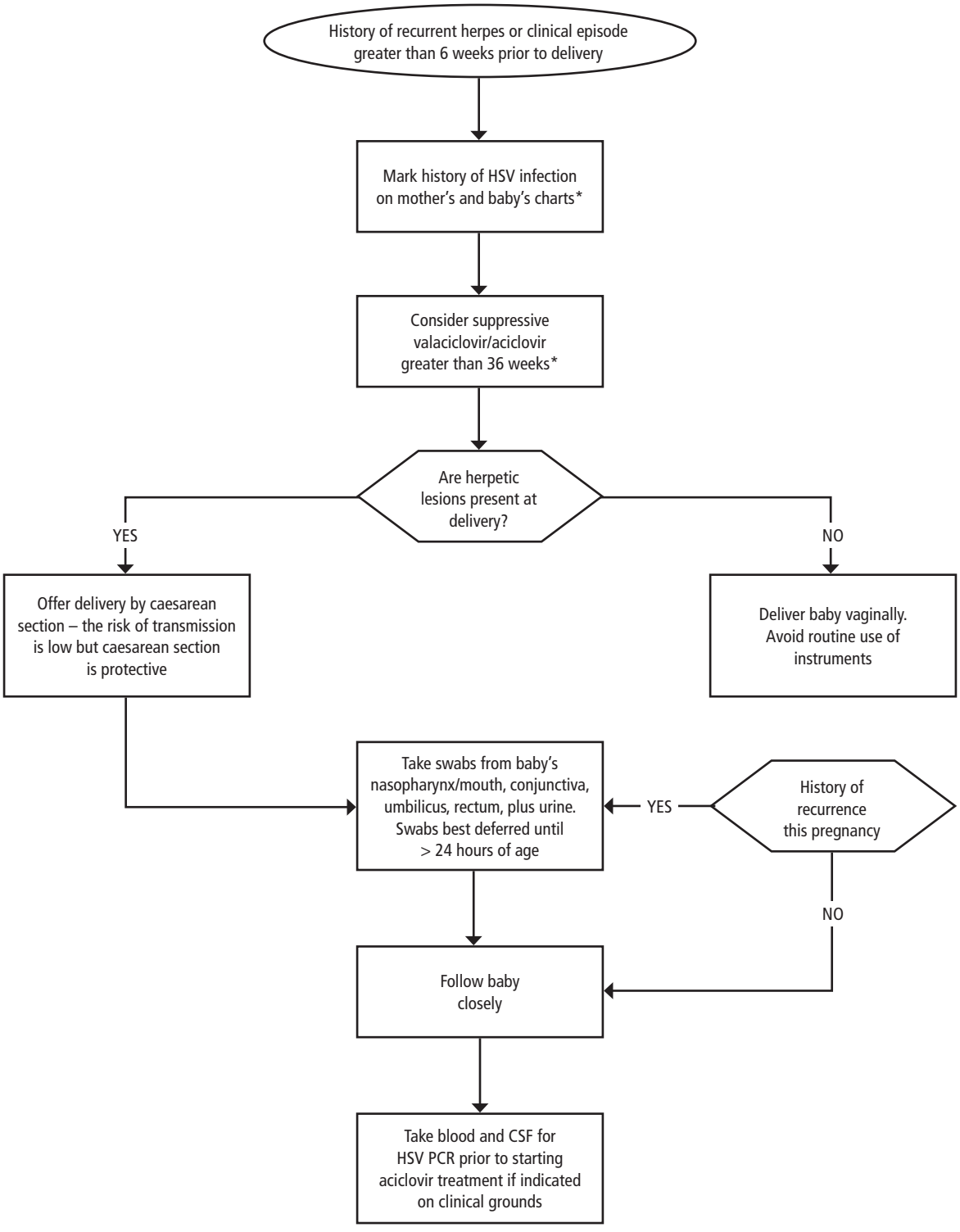
- Document the history in both mother's and infant's notes.
- Symptomatic recurrences during pregnancy are usually brief but can be treated with oral antivirals if troublesome, using the standard non-pregnancy regimens in 1st and 2nd trimesters.
- Prophylactic use of aciclovir 400mg tds or valaciclovir 500mg bd from 36 weeks decreases the number of clinical recurrences and reduces the need for caesarean section GRADE B
- Vaginal delivery is appropriate if no lesions are present at delivery.[38]
- Sequential testing in the third trimester to predict viral shedding at delivery is not indicated.[67]
- Caesarean section should not be performed in women who do not have lesions at delivery.[38] GRADE B
- In women who have recurrent genital lesions at onset of labour:
  - It is common practice to deliver by caesarean section because of the small risk of infection in the neonate.
  - However, because the fetal risk is low, this must be set against the risks to the mother of caesarean section and this is therefore regarded as a relative rather than absolute indication for caesarean section.[38] GRADE C
  - Ideally, this scenario should be discussed with the woman early in pregnancy by the primary caregiver in conjunction with specialist advice.
  - The risk of maternal fetal transmission is higher with shedding of HSV-1 than with HSV-2.
- Caesarean section does not itself provide total protection.[68]
- If vaginal delivery occurs, scalp electrodes and instruments should not be used unless there is a clear obstetrical indication as skin trauma may increase the risk of transmission of HSV.
- Intrapartum IV aciclovir may be considered based on anecdotal evidence, although there have been no trials to assess the value of such therapy.
- In a woman who presents with a recurrent episode in late pregnancy antiviral treatment will reduce the duration of symptoms and viral shedding. There are no studies documenting the duration of viral shedding in this situation, but it has been stated that vaginal delivery is safe if labour commences after 48 hours of treatment with antivirals.[69] This recommendation is consistent with the principles of episodic treatment.

Other issues in perinatal care

Investigation and surveillance in the neonate

See **Management of Neonatal HSV Infection**, page 27.

Management of Women with History of Genital Gerpes Prior to Pregnancy and Women with First Clinical Episode Greater than 6 Weeks Prior to Delivery (in consultation with a specialist)



* For women with recurrences during pregnancy, suppressive aciclovir or valaciclovir therapy can be used to treat symptomatic recurrences. From 36 weeks treatment can be considered to reduce the chance of a recurrence at term and hence the need for caesarean section. Effects on the neonate have not been fully determined. However, aciclovir (and to a lesser extent valaciclovir, which is a pro-drug of aciclovir) has been widely used in pregnancy without reported adverse consequences. See full text for further information.

NEONATAL HSV INFECTION

KEY POINTS

- Neonatal HSV infection is a rare, but potentially fatal, disease of babies, occurring within the first 4-6 weeks of life. Symptoms are non-specific and a high index of suspicion is required.
- Most neonatal HSV infections are acquired at birth, generally from mothers with an unrecognised genital herpes infection acquired during pregnancy.
- Any baby developing skin vesicles or atypical bullous, pustular skin lesions, particularly on the scalp or face (vaginal deliveries) or over the buttocks (breech presentation) must be referred immediately to a paediatrician.
- Specialist obstetric and paediatric advice on management and anticipatory guidance should be sought for a woman with a history of genital herpes and active lesions at term and especially in the high-risk situation of a first episode within 6 weeks of delivery.

Neonatal HSV infection rates vary from country to country, with national surveys reporting a wide range in annual incidence. The number of cases per 100,000 live births in Western Europe (France 1.15, United Kingdom 1.65, and the Netherlands 3.2)[70-72] is lower than reported for Scandinavia (Sweden 6.5)[73] and North America (USA 9.6 and Canada 5.9).[74,75] Marked differences in incidence can also exist within countries.[46]

The differences in reported rates is likely multifactorial, including differences in case definition and study design as well as differences in rates of HSV acquisition amongst maternal populations. Reliable New Zealand data are lacking but a prospective national active surveillance in Australia from 1997 to 2011 found an incidence of 3.7 per 100,000 live births.[76,77] This incidence was stable over this time period but noted a significant increase in the cases of HSV-1 infections compared to HSV-2 (OR, 1.10 95% CI, 1.00–1.21). This study also found a decrease in mortality in the later part of the study. Prospective longitudinal data of this nature are helpful in providing accurate incidence and epidemiological data to help guide effective education and prevention strategies.[78]

Transmission to the Fetus and Newborn

HSV-1 and HSV-2 can be transmitted to the fetus or newborn infant at one of three times: intrauterine, perinatally and postnatally.[46] However, the majority of cases of neonatal HSV result from women who acquire genital HSV-1 or HSV-2 infection at or near term.

Intrauterine infection

Intrauterine infection causes approximately 5% of neonatal HSV infection. It results from either transplacental HSV transmission or an ascending HSV infection from the cervix.

Perinatal infection

The main risk of transmission to the neonate is at delivery, where contact with HSV-infected secretions in the birth canal accounts for most neonatal HSV infection.[46] The site of entry is usually the eye, nasopharynx or an abrasion secondary to scalp electrodes or forceps. Roughly 60–80% of infants with neonatal HSV disease are born to women with unrecognised infection.[79,80]

Several factors influence the risk of the newborn acquiring HSV infection, the most important of which is whether the mother has newly acquired or recurrent genital disease.[42,43] **The risk is greatest when a previously seronegative woman acquires genital herpes (HSV-1 or HSV-2) near the time of delivery.** Under such circumstances the risk of neonatal HSV infection is 50%, while vertical transmission rates of 25% are found in those with a non-primary first episode (infection with one virus type, e.g. HSV-2, in the presence of antibodies to the other virus type e.g. HSV-1).

In contrast, the transmission rates are lowest for women who acquire herpes before pregnancy, with the risk being about 0.05% for such women who have no signs or symptoms of an outbreak at delivery.[42,45] If lesions are present at delivery, there is a small but still significant risk of transmission of 0.25–3%.[43] High maternal titres of type-specific neutralising antibody are associated with a substantially lower risk and severity of neonatal infection; risk factors include invasive obstetric procedures, such as fetal scalp electrodes, method of delivery, and prolonged rupture of membranes.[43] Recent studies report an increasing proportion of genital and neonatal herpes infection from HSV-1 strains.[74,76]

Postnatal infection

Postnatal infection accounts for approximately 10% of cases. Sources of postnatal HSV infection include maternal breast milk, skin and oral lesions, and HSV lesions on caregivers, other family members and medical staff, having close contact with the newborn.

Disease Classification

Intrauterine HSV infection

This is rare and usually occurs after primary herpes infection in pregnancy. Transplacental transmission before the 20th week of pregnancy may cause spontaneous abortion in as many as 25% of cases. In contrast to neonatal herpes infection, the signs of intrauterine HSV infection are present at delivery and may include intrauterine growth retardation, hydranencephaly, chorioretinitis and skin scarring. The long-term outlook for these infants is very poor. A minority with intrauterine HSV infection will present at delivery with skin or eye lesions. There is frequently a history of prolonged rupture of membranes, often as long as 2 weeks. The prognosis for successful anti-viral therapy in these infants is better than that for newborns with more long-standing intrauterine infection and complications such as hydranencephaly, but a small group will have severe, disseminated disease or fatal pneumonitis.[38]

Neonatal HSV infection

There is no clear pattern of signs and symptoms that identifies babies with neonatal HSV disease, meaning a high index of suspicion is required.

Presenting symptoms of neonatal HSV infection include fever, lethargy, seizures and respiratory distress. Vesicles may be present in only 40% at presentation and some infants will have no vesicles at any time during the course of their illness.[81,82] Fever may be absent initially.[79] Mortality is highest in those with an altered conscious state, seizures, disseminated intravascular coagulation, and prematurity.[38,68]

The usual age for onset of symptoms in neonatal HSV infection is between 5 and 21 days of life, but there may be a delay in presentation if the significance of the symptoms is not initially recognised. Physicians caring for sick infants in the first 6 weeks of life should always be aware that neonatal HSV infection remains a possibility, even when no parental history of herpes infection is given.[74]

Presentation is divided into three categories (Table 2), each of which has different clinical symptoms and outcomes. There is overlap within these categories and patients can progress from one category to another if not treated early.

Table 2: Classification of Neonatal HSV Infection[46]

Type (% of Total)	Mortality		Mean Age at Presentation	Normal Outcome	
	Untreated	Treated		Untreated	Treated
SEM (45%)	< 1% (70% progress)	0%	10–11 days	62%	98%
CNS (30%)	50%	6%	16–19 days	33%	31%
DIS (25%)	90%	30%	9–11 days	50%	83%

SEM = Skin, Eyes and/or Mouth; CNS = Central Nervous System; DIS = Disseminated

Skin, eyes and/or mouth (SEM) infection[79]

Nearly half of neonates with HSV infection will present with lesions confined to the skin, eyes or mucous membranes. This is the most readily recognised form of the disease, with most babies having vesicular skin lesions at sites of trauma, such as over the presenting body part, fetal scalp electrode sites and eyelid margins. Lesions usually appear between one and two weeks of age but are sometimes evident shortly after birth when prolonged rupture of membranes has been present. Typically, vesicles overlie an erythematous base and contain clear or slightly cloudy fluid. Need to look carefully for eye involvement as this can initially be asymptomatic with early ophthalmologic review if symptoms appear.

Although rarely fatal if lesions are confined to skin and mucosal sites, without antiviral treatment many neonates progress to either the disseminated or CNS forms of the disease. In addition, more than one-third of those with untreated localised SEM lesions develop signs of major neurological impairment such as microcephaly, spastic quadriplegia or sensory loss by 12 months of age. A study of infants with presumed SEM disease reported that 24% had HSV DNA detected in their CSF by PCR testing, suggesting that HSV can infect the CNS without overt neurological symptoms.[83]

There are data to suggest that three or more recurrences of cutaneous vesicles in the first 6 months of life are predictive of poor neurological outcome.[84] Specifically the likelihood of developing normally is nearly 100% when there are fewer than three recurrences within the first 6 months of life compared with only 79% when three or more recurrences occur during this period. At the time of such episodes PCR detection of HSV-DNA in the CSF may explain the emergence of new neurological deficits.[85]

Central nervous system (CNS) disease

Almost one-third of neonates with HSV infection will have only encephalitis. Infants usually present between 10 days and 4 weeks of age with symptoms of fever or temperature instability, lethargy, poor feeding and irritability, followed by seizures, a bulging

fontanelle and focal neurological signs. Cerebrospinal fluid (CSF) findings typically include 50–100 white blood cells x 106 per litre, predominantly mononuclear cells, normal to low glucose and elevated protein concentrations, both of which increase over the first few days. At presentation many are devoid of skin lesions but overall 60–70% will have skin vesicles at some point during the disease course.[79]

Untreated, the mortality rate approaches 50% with most survivors suffering severe neurological impairment. Morbidity is higher among infants with HSV-2 infection than among those with HSV-1 infection.[46] Even with the use of high dose aciclovir, morbidity has shown little improvement. Relapses may occur.

Disseminated disease (DIS)

Disseminated disease develops in about one-quarter of neonates with HSV infection. It is more common in preterm infants and carries the worst prognosis. Symptoms generally develop in the first 14 days of life. Clinical findings include a sepsis-like presentation with respiratory distress, haemodynamic instability, jaundice, hepatomegaly, elevated liver enzymes, bleeding with associated coagulopathy, and seizures with signs of meningitis, encephalitis or respiratory failure. Vesicular skin lesions may not be present in up to 50% of cases. Mortality in untreated patients is approximately 90% and even with antiviral therapy, may still be as high as 20–30%.

Differential diagnosis for neonatal HSV

Bacterial pathogens responsible for neonatal sepsis, sometimes with skin lesions that may be mistaken for disseminated or CNS HSV infection, include group B streptococcus, Listeria monocytogenes and gram-negative bacilli. Cutaneous infections resulting in vesicular lesions similar to neonatal HSV are bullous impetigo, varicella zoster, enteroviruses and disseminated CMV infection. Other infectious agents that might be considered are toxoplasmosis, rubella and syphilis. Finally, non-infectious cutaneous disorders that could be confused with neonatal HSV infection include erythema toxicum, neonatal pustular melanosis, acropustulosis and incontinentia pigmenti.

Management of Neonatal HSV Infection

Evaluation

The poor prognosis associated with untreated neonatal HSV infection means that every effort should be made to obtain a diagnosis as early as possible. This includes prompt communication with the mother's lead maternity caregiver. Many cases present with a sepsis-like clinical picture without identifiable risk factors; many with disseminated or CNS disease will initially lack skin lesions to assist in a timely diagnosis. A high level of suspicion is required.

Management of suspected neonatal HSV infection

Successful management relies on a high index of suspicion of HSV infection and early institution of therapy. Only about 40% of affected neonates will initially have skin lesions and most lack a parental history of genital herpes.[46,81,82]

Consequently, physicians should consider neonatal HSV infection when confronted with an infant younger than 6 weeks of age who has vesicular or atypical bullous, pustular skin lesions or a progressive febrile illness without a bacterial cause. Particular alerting symptoms are a progressive febrile illness without a confirmed bacterial cause, which is unresponsive to antibiotics and associated with one or more of the following: skin vesicles, hepatomegaly, liver dysfunction, pneumonitis, thrombocytopaenia, coagulopathy, or seizures. Other factors recently suggested to be of diagnostic importance in a neonate without a rash are maternal fever, respiratory distress requiring mechanical ventilation and CSF pleocytosis.[80]

Skin and oral lesions must be carefully looked for on a daily basis, particularly on the scalp and face (vaginal deliveries) or over the buttocks (breech presentation) as these may develop later in the course of disseminated and CNS disease. The index of suspicion is heightened by progressive abnormalities of liver function, particularly during the first week of life. When neonatal HSV infection is considered likely, undertake diagnostic tests and administer aciclovir immediately, before the results of definitive investigations are available.[86] GRADE A Aciclovir should be considered for an unwell infant without clinical improvement and negative bacterial cultures at 48–72 hours.[87]

Diagnosis

In the presence of vesicular lesions, the base of the lesion should be scraped and sent for PCR; it requires operator expertise in obtaining an adequate specimen and a negative result should be interpreted with caution.

As neonatal HSV infection may occur in the absence of skin lesions, other diagnostic specimens are required. In addition to testing any cutaneous lesions, swabs of the nasopharynx/mouth, conjunctiva, umbilicus, rectum **plus** urine should be performed. Swabs are best deferred until >24 hours of age. This delay is to avoid possible contamination by maternal cervico-vaginal secretions, positive results after 24 hours should reflect viral replication.

CSF should be taken for HSV PCR testing as well as usual parameters of cell count, protein and glucose. Whole blood PCR should also be performed to assist with diagnosis of neonatal HSV infection.

PCR is a rapid, highly sensitive and specific technique, which detects minute quantities of viral DNA. It is more reliable than viral

culture for CNS infections. However, although the presence of a positive PCR is highly predictive of infection, a negative result does not eliminate the possibility of disease.[88] A negative CSF PCR should be evaluated in conjunction with the entire clinical picture including other diagnostic modalities, and should not be used on its own to exclude CNS herpes disease. Grade A

Liver function tests, including serum transaminases may indicate HSV hepatitis and a CXR may diagnose pneumonitis.[83,89] These tests are performed on **all** infants suspected of neonatal HSV infection. Grade A

Neurological imaging – CT or MRI brain scan and EEG should all be considered as an important adjunct to diagnosis. MRI and CT scan can be normal early in the disease course and do not rule out HSV CNS disease.

An ophthalmology consultation should be sought in suspected or confirmed cases of neonatal HSV infection, to help identify and monitor ocular complications that may arise during the illness. Grade C

In addition, a sexual history from the parents is taken. The mother's lead maternity caregiver is asked to obtain HSV PCR of maternal genital secretions and to perform type-specific HSV serology. This is important, even when the presentation is weeks after the delivery.

Treatment

Intravenous aciclovir (20mg/kg every 8 hours) decreases the mortality and morbidity of neonatal HSV infections (see Table 2 on page 26).[83,86,90] Early therapy improves neurological outcome. The treatment duration is 14 days for SEM disease and a minimum of 21 days for CNS and disseminated infections.[90] The recommendation for the longer course of aciclovir also includes those infants with SEM disease with abnormal CSF parameters, including HSV DNA detected by PCR. Grade A & B

For neonates with ocular involvement topical therapy may be required and an ophthalmologist should be consulted. For pre-emptive therapy in high risk asymptomatic infants without laboratory confirmation 10 days therapy with aciclovir is recommended.[91,92]

All infants with HSV CNS involvement should have a lumbar puncture at the end of aciclovir therapy to determine if the CSF is PCR negative for HSV. For those neonates when end of treatment CSF is still PCR positive the American Academy of Pediatrics recommends repeating CSF a week later and if still positive a further week later and if persistently positive discuss with an infectious disease specialist.[93] Others have suggested that neonates with PCR positive should continue receiving intravenous aciclovir until viral DNA in the CSF is no longer detected.[68,83] Grade B Aciclovir-resistant neonatal HSV remains rare.

A double-blind placebo-controlled study found that infants surviving neonatal HSV disease with CNS involvement had improved neurodevelopmental outcomes when they received suppressive therapy with oral aciclovir, 300mg/m2/dose administered 3 times daily for 6 months.[92] Use of oral aciclovir suppressive therapy also reduced skin recurrences in infants. Regular monitoring of neutrophil count needs to occur while on suppressive aciclovir therapy, with 20–25% of study patients developing neutropenia while receiving aciclovir.[94] Oral valaciclovir has not been evaluated for use as suppressive therapy. Grade A

Suppressive therapy can be considered in infants with recurrent SEM disease, but it has not been shown to alter neurological outcome.[92]

General management points

A monocytic leukocytosis in the CSF is suspicious of CNS HSV infection.[95] Treatment with aciclovir should be instituted before HSV PCR results are available. Aciclovir can be discontinued if an alternative diagnosis has been established or the clinical course is no longer compatible with HSV CNS disease, viral PCR testing is negative and a CT or MRI head scan is normal or does not suggest HSV encephalitis. Be aware, however, that a negative initial HSV PCR result does not exclude CNS disease. It is well established that neonatal HSV CNS infection may occur despite the findings of normal CSF counts and biochemistry, and that a negative CSF HSV PCR result may occur, especially if the lumbar puncture was performed early in the course of the illness.[83,96] Consequently, repeat lumbar puncture is recommended when laboratory tests are negative but clinical suspicion remains high. Grade B & C

Empirical treatment with aciclovir is recommended if, an infant remains critically ill despite antibiotic therapy and disseminated HSV cannot be excluded, if bacterial cultures are negative, or there are signs of progressive liver dysfunction with coagulopathy.[97] Grade C

In addition to the administration of aciclovir, other important aspects of the infant's management include:

- Respiratory support.
- Control of circulation.
- Management of seizures.
- Maintenance of fluid and electrolyte balance.
- Correction of coagulopathy.
- Administration of antibiotics for concomitant bacterial infections.

Infants with neonatal HSV disease should be managed by contact precautions throughout the course of their illness.[98] Grade C

Follow-up of neonatal HSV infection

Long-term follow-up in survivors is instituted to monitor for sequelae and should include assessment of hearing, vision and neurodevelopment. Grade C

When a cutaneous recurrence occurs full clinical examination should be performed. If any evidence of systemic involvement is present, e.g. fever and especially irritability, a CSF examination, including HSV DNA PCR, should be performed. A low level of suspicion should be used to initiate parenteral aciclovir therapy. Abnormal result should lead to a further course of intravenous aciclovir being administered, followed by suppressive oral aciclovir until at least 6 months of age. GRADE C

Counselling

Neonatal HSV infection causes considerable stress within the family. The experience of many is that most couples eventually separate.[99] This is because of concern over a critically ill infant, exacerbated by guilt over transmission of the virus and the demands of the long term care of an often severely impaired child. **Because of this, expert education and counselling is required.** GRADE C

GUIDELINES FOR TALKING TO PARENTS OF A BABY DIAGNOSED WITH NEONATAL HERPES

Being comfortable with discussing the diagnosis (what, why, how, etc.) is critical to the parents' ability to understand and come to terms with what has happened. The following points are additional to **Key Information for Health Professionals to Give Patients in Counselling** (see page 34).

- Parents are likely to be shocked, and feeling both grief and shame, which may be expressed as anger and/or withdrawal from staff.
- A crisis of this nature may well trigger a relationship crisis and health professionals can act most usefully by listening and not attributing blame to either parent.
- Parents need to know that healthcare providers do not blame them for the baby contracting HSV (attitudes are conveyed verbally and non-verbally).
- Although one or other parent may have had previous knowledge that they have HSV, it is most common for people not to know and be undiagnosed.
- Most neonatal herpes happens when a woman experiences a 'silent' (asymptomatic) primary episode in late pregnancy.
- Many people do not realise that cold sores are caused by HSV and may be passed through oral sex. A primary HSV-1 episode of genital herpes in late pregnancy creates a high risk for neonatal transmission.
- Given the social stigma of STIs, parents may be unable to initiate a conversation with healthcare providers or ask the questions that are worrying them. Health professionals need to take the initiative in addressing possible concerns. An opening line such as, "many parents wonder about… is this a concern for you?" is useful for normalising parental queries.
- Health professionals need to convey that they are comfortable talking about adult sexuality; that intercourse and oral sex are normal practices when a woman is pregnant and that HSV may have been transmitted during sexual activity in pregnancy.
- Health professionals may need to initiate a conversation about sexual transmission, e.g. "would it be helpful if I explained to you how the virus is passed?"
- Advise parents regarding any transmission precautions with regard to other siblings and family members, otherwise parents may initiate precautions they imagine to be necessary.

See page 34 for Key Information for Health Professionals to Give Patients in Counselling and consider referring to the Herpes Helpline tollfree 0508 11 12 13.

Anticipatory Management of Newborn Infant with Known Risk for Neonatal HSV[91,100]

High risk

This category involves a subgroup of infants born to mothers with their first episode of genital herpes during late pregnancy, that is, those women infected near or at term. A paediatrician experienced in identifying the signs of neonatal HSV infection should examine these newborn infants. GRADE C

Women with first episode genital HSV infection associated with either genital lesions or subclinical shedding at delivery have a 25–57% chance of transmitting HSV to their babies if they deliver by the vaginal route.[42] Although not completely protective against neonatal HSV disease, elective caesarean section significantly reduces the risk of transmission and is recommended for pregnant women who have a known or presumed first episode of genital herpes within 6 weeks of delivery, even if receiving suppressive anti-viral therapy.[42] GRADE B

Because of the high risk of infection, an asymptomatic infant inadvertently delivered vaginally from a woman with active first episode genital lesions should be managed as for suspected neonatal HSV infection. This means the immediate collection of specimens, including CSF, for cell count, chemistry and PCR testing, HSV blood PCR, full blood count, liver function tests and surface HSV PCR swabs, ideally at 24 hours but earlier if clinically indicated. Anticipatory aciclovir therapy should be initiated. Duration of aciclovir will depend on surface HSV PCR and CSF results. Also check the mother's total and type-specific HSV serological status, to confirm that this is a first episode of genital herpes and not a recurrence. GRADE C

Similarly, when the woman has active first episode genital lesions and is febrile, or has ruptured membranes for more than 4 hours, or when fetal scalp electrodes or forceps have been used, irrespective of the mode of delivery, the infant should be managed as for suspected neonatal HSV infection. GRADE C

Anticipatory aciclovir therapy can be discontinued if the neonate remains well, HSV PCR and molecular diagnostic testing have not identified HSV, and the CSF studies including PCR results are normal. If the HSV PCR of surface swabs only is positive and the neonate remains clinically well aciclovir treatment should continue for 10 days.[100] Treatment is continued for 14 days when HSV is identified but CSF results are normal, and for 21 days if there is an abnormal CSF finding.[101] GRADE B & C

Low risk

Within this category are most infants born to mothers with their first episode of genital herpes during pregnancy and those with recurrent genital lesions at the time of delivery. A paediatrician experienced in identifying the signs of neonatal HSV infection should examine these newborn infants. GRADE C

Anticipatory guidance including surveillance HSV PCR testing, but no empiric aciclovir, is reserved for well appearing infants without skin or mucosal lesions at birth and born to mothers within the following categories: GRADE B & C

1. First episode genital herpes more than 6 weeks before delivery.
2. First episode genital herpes within 6 weeks of delivery where the mother has delivered by elective caesarean section.
3. Active recurrent genital herpes at delivery.
4. History of recurrent genital herpes during this pregnancy.

The examining paediatrician should undertake the following:

Anticipatory guidance

- Document risk of neonatal HSV infection on infant's chart.
  Notify the infant's lead maternity caregiver and general practitioner of risk.
- Educate parents on risks of HSV and instruct them to report signs of fever, respiratory distress, jaundice, lethargy or irritability, poor feeding, skin, eye or oral mucosal lesions.
- If clinical symptoms, skin, eye or mucosal lesions appear, manage as for suspected neonatal HSV infection.

Surveillance HSV PCR testing

- HSV PCR swabs should be taken at 24–48 hours of age (not at birth or within the first 24 hours of life, because of possible contamination by maternal cervico-vaginal secretions).
- HSV PCR swabs should be obtained from eyes (conjunctiva), mouth, nasopharynx, umbilicus, urine and rectum.
- Further clinical and laboratory evaluation, as for suspected neonatal HSV infection, followed immediately by aciclovir therapy is mandated, if HSV PCR testing is positive.[86] GRADE A

For caregivers who develop lesions after delivery

Advise caregivers about hand washing. For mothers with vesicular breast lesions, caution those not to breastfeed while vesicles are present. Particular care when handling the baby must be taken by those with recently acquired or reactivated oral or other skin lesions. In addition to hand washing, this includes covering skin sites and, for herpes labialis or stomatitis, wearing a surgical mask and not kissing the baby until the lesions have crusted and dried.

Breastfeeding and Use of Oral Aciclovir/Valaciclovir

The American Academy of Pediatrics has approved use of aciclovir for treating first episode or recurrent genital herpes in breastfeeding mothers. Although concentrations are high in breast milk and the baby, toxicity is low.[55] GRADE B

GENITAL HSV INFECTION IN CHILDHOOD

KEY POINTS

- All children with suspected genital herpes infection should be referred for specialist assessment and management.
- Genital herpes is less common in childhood than in adulthood, but can occur.
- When assessing a child or young person with genital ulcers the diagnosis of herpes simplex should be considered, but not presumed.
- Ulcers can occur as a manifestation of aphthosis in response to acute illness.[102] The appearance of aphthous genital ulcers is also usually preceded by a history of fever, malaise and headache, but PCR testing, including HSV PCR, is negative.
- Epstein-Barr virus and cytomegalovirus infections have also been reported to cause genital ulceration.
- Any genital ulcers should therefore be swabbed before decisions are made about management.

Pre-adolescent children

Genital herpes infection may present in pre-adolescent children. When it does it is important to explore carefully in the history the aetiology of the herpes infection. Possible sources of transmission include an orolabial lesion or a herpetic whitlow in another family member and autoinoculation. For example, genital herpes in a child under one year of age may result from kissing 'all over' by a pre-school aged sibling with orolabial herpes.

If an obvious source of the infection cannot be identified, then sexual transmission should be considered. The diagnosis must be confirmed by HSV PCR testing with typing of the herpes virus. The presence of HSV-1 does not rule out sexual transmission, but a non-sexual route of transmission should be carefully sought, especially if there are no other pointers to suggest sexual abuse. The presence of HSV-2 in the genital area does not automatically imply sexual contact, but does mean that sexual abuse, as a cause of the infection, must be seriously considered. In a recent local review of 2,162 children who had an examination in the context of allegations of sexual abuse, eight of the 1,909 children who underwent laboratory screening for sexually transmitted infections were positive for HSV and a sexual transmission was thought likely for six of these children.[103]

Because of these very difficult issues in diagnosis, all children with suspected genital herpes infection should be referred to a paediatrician for assessment and treatment. The paediatrician may in turn seek advice from a local Sexual Abuse Assessment and Treatment Service (SAATS) with special training in the area of recognition of child sexual abuse.

Adolescents

For the purposes of these guidelines, sexually active adolescents should be managed as adults. Adolescents who have never been sexually active should be managed as per the pre-adolescent children section above.

The above is based upon on internationally accepted standards of practice. GRADE C

ISSUES IN COUNSELLING

KEY POINTS

- Providing accurate up-to-date information in a non-judgmental way is key to assisting a person to understand and come to terms with herpes.
- The pyschological morbidity of a diagnosis often far outweighs physical symptoms.
- Recommended resource for patients **www.herpes.org.nz** or the Herpes Helpline tollfree **0508 11 12 13**.

Genital herpes is a common and, medically speaking, usually a relatively minor condition in people who are sexually active. However, conditioning and social values contribute to individuals having a range of emotional responses when given a diagnosis of genital herpes.[104-107]

EMOTIONS RELATED TO THE DIAGNOSIS OF GENITAL HERPES

- Some people cope well without any problems, however for others a diagnosis of genital herpes may be the most challenging health disruption they have experienced, given the stigma and societal conditioning associated with it.
- The diagnosis of genital herpes can provoke confusion and a grief reaction causing feelings such as guilt, anger, fear, shock, denial and a sense of injustice.
- Common concerns of patients relate to social stigma, transmission, fear of rejection upon telling potential sexual partners, and how herpes will affect their sex life and social activities.[106,108]
- Patients with genital herpes are usually very concerned about the diagnosis, and its potential impact on their relationships.[109,110]
- The diagnosing clinician should address patient concerns at the first presentation, even if the patient is referred elsewhere for counselling.[111]
- Herpes Helpline tollfree **0508 11 12 13** provides counselling and education in both acute and non-acute situations.
- Not all patients will take up the offer of initial counselling and support. It is very important to advise all patients of resources as these are often accessed at a later date, for example, when establishing a new relationship or wanting to conceive. **www.herpes.org.nz**

Successful psychosocial management of genital herpes is time-intensive. The impact of the diagnosis is influenced by the person's coping strategies, level of social support and underlying beliefs about sexuality and sexual health. A diagnosis of herpes can also trigger worries about:

- Acquisition of HIV or other STIs.
- They are seen as promiscuous and that the doctor has a low opinion of them.[112]
- In all cases (whether primary, non-primary or first symptomatic reactivation), the emotional consequences and perceived social stigma of the infection should be addressed. No matter the time since diagnosis, do not assume that another clinician has spoken with the person about genital herpes.[109,113]

PATIENTS' CONCERNS ARE PREDOMINANTLY ABOUT RELATIONAL ISSUES

- Fear of discovery – when and how to tell a partner
- Intimate relationships and sex life affected
- Social activities and lifestyle altered
- Social stigma of STI
- Condition is 'incurable'
- Fear of transmission or contagion
- Fear of disclosure and subsequent rejection
- Inaccurate online material may exacerbate above points

Reassure patients that they are not alone in having genital herpes. The NZ Herpes Foundation **www.herpes.org.nz** or Helpline tollfree **0508 11 12 13** provide specialist support, education and counselling, or refer for specialist counselling at the local sexual health clinic. Advise about reputable internet resources and stress that the online 'cure' claims are not scientifically supported.

The above section on counselling is based on internationally accepted standards of practice. GRADE C

KEY INFORMATION FOR HEALTH PROFESSIONALS TO GIVE PATIENTS IN COUNSELLING

The following information contributes significantly to people being able to normalise the meaning of a viral STI. The challenge for health professionals is to convey that they understand that a relatively innocuous infection in medical terms may, however, be experienced as life changing for the person. The following points are most likely to be effective when they are incorporated into the acknowledgement of the above psychosocial points:

Herpes is common, manageable and treatable.

- Herpes simplex virus (HSV) causes cold sores on the mouth and cold sores (herpes) on the genitals. It is two strains of the same virus. HSV-1 causes most oral cold sores and causes 50% of genital herpes (through oral to genital transmission). HSV-2 mostly causes genital herpes.
- It is a very common, relatively medically insignificant infection, but can cause significant psychosocial morbidity when it causes genital symptoms.
- Up to one in three people have genital herpes, but only 20% of them experience symptoms (this includes genital herpes caused by both HSV-1 and HSV-2).
- Most people (80%) who become infected with genital herpes will not have any symptoms, or have such mild symptoms that they will not be recognised or diagnosed as genital herpes. 75% of herpes is acquired from partners unaware they have it.
- For most people who experience symptoms, genital herpes is a sometimes-recurring cold sore on the genitals. It does not affect your overall health or longevity of life.
- A small percentage of people who get genital herpes may experience problematic recurrences.
- There is effective oral anti-viral treatment available.
- People who experience a first episode of genital herpes will get better, lesions will heal and there will be no evidence of the initial lesions left.
- Most people who experience a first episode of HSV-2 will have recurrences, but they are generally milder than the first episode. HSV-1 tends to cause fewer recurrences than HSV-2.
- Getting genital herpes in a long-term relationship does not mean that the other partner has been unfaithful. However, a full sexual health screen may be reassuring.
- Where both partners in a long-term relationship have the virus, use of condoms is not necessary as they cannot reinfect each other.
- It is advisable to avoid sexual contact when lesions are present, as friction may delay healing.
- Oral to genital transmission of HSV-1 is very common through oral sex. This can happen when cold sores are not causing symptoms.
- Genital herpes does not affect your fertility or stop you having children. Vaginal delivery is usual for most women with a history of genital herpes.
- Genital herpes does not stop you having sex.
- Anybody with genital herpes, whether they get symptoms or have never had symptoms, may shed the virus from time to time with no symptoms present.
- There is no evidence that genital herpes causes cancer of the cervix.
- Condoms reduce the risk of transmission. The use of condoms in a long-term relationship should be a matter of discussion between the individuals. It is advisable to avoid genital-to-genital contact, even with a condom, until any lesions are completely healed.
- Even if the virus is passed on, the most likely outcome is that the person will never experience symptoms.
- Ensure patients have access to the NZHF patient pamphlets and/or the Helpline tollfree **0508 11 12 13**, or **www.herpes.org.nz**.

Herpes in pregnancy

- Neonatal herpes is serious but extremely rare; one in 10,000 live births.
- The commonest cause of neonatal herpes is a woman experiencing a first episode (often asymptomatic) in the last trimester. Early medical management will minimise the risk.
- Recurrent herpes in pregnancy has a much lower risk of transmission. Maternal antibodies contribute to protecting the baby and viral shedding in recurrences is low. It is important to notify the health professional(s) managing the pregnancy of the previous history.
- Vaginal delivery is usual for most women with a history of genital herpes.
- While neonatal herpes is rare, it is important that parents are instructed on which symptoms to look out for if there is any possibility of transmission. Knowledge of the early symptoms of neonatal herpes will enable such infants to present early and will increase the likelihood of a good outcome for the infant.

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The Ministry of Health supports the use of these clinical guidelines, developed by clinical experts and professional associations to guide clinical care.

Supported by an educational grant from New Zealand District Health Boards

12th Edtion: Version 1 – September 2017