



NEW ZEALAND HERPES FOUNDATION

Guidelines for the Management of Genital Herpes in New Zealand

9th Edition - 2009

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

Viral Sexually Transmitted Infection Education Foundation Resources

Helpline

HERPES:

Tollfree 0508 11 12 13

HPV:

Tollfree 0508 11 12 13

Website

www.herpes.org.nz

www.hpv.org.nz

Resources

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 Fact

Patient Information Pamphlets

1. Some Questions and Answers about HPV and Genital Warts

2. A Patient Guide: HPV (wart virus) in perspective

3. Cervical Smears and Human Papilloma Virus Infection (HPV)

4. What every woman should know about Genital HPV (Human Papilloma Virus) Infection and the Cervical Cancer Vaccines

**These resources are available through the
Viral Sexually Transmitted Infection Education Foundation**

Phone: 09 433 6526

Fax: 09 360 2835

Email: info@herpes.org.nz

or: info@hpv.org.nz

For international resources please see inside back cover.

NEW ZEALAND HERPES FOUNDATION

Guidelines for the Management of Genital Herpes in New Zealand

9th Edition - 2009

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

Endorsed by the NZ Committee of the Royal Australian & New Zealand College of Obstetrics & Gynaecology and the Australasian Chapter of Sexual Health Medicine – RACP

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.

About This Document

These guidelines have been produced by considering available literature and by basing the recommendations on the available evidence, both local and international. The three levels of evidence used are:

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.

Table of Contents

3	Genital Herpes – Key Take Home Points
4	Epidemiology
5	Transmission
6	Reducing Risk of Transmission
7	Diagnostic Tests
9	Key Information to Discuss with a Patient Who Asks for a Blood Test
10	Clinical Episodes of Genital Herpes
10	First Clinical Episode of Genital Herpes
14	Treatment Algorithm – Management of First Episode of Genital Herpes
15	Recurrent Episodes of Genital Herpes
20	Management of Genital Herpes in Immunocompromised Individuals
20	Summary Statements Concerning the Treatment of Genital Herpes
21	Treatment Algorithm – Management of Recurrent Episodes of Genital Herpes
22	Genital Herpes in Pregnancy
24	Management of Pregnant Women with First Episode Genital Herpes
25	Treatment Algorithm – Management of First Episode Genital Herpes in Pregnancy
26	Treatment Algorithm – Management of Recurrent Genital Herpes in Pregnancy
27	Management of Pregnant Women with Recurrent Genital Herpes
27	Use of Aciclovir in Pregnancy and Breastfeeding
28	Prematurity
28	Prevention of HSV in the Neonate
29	Neonatal HSV Infection
30	Transmission to the Fetus and Newborn
30	Disease Classification
33	Management of Neonatal HSV Infection
36	Guidelines for Talking to Parents of a Baby Diagnosed with Neonatal Herpes
37	Anticipatory Management of Newborn Infant with Known Risk for Neonatal HSV
39	Genital HSV Infection in Childhood
40	Key Issues in Health Professionals' Counselling Management
42	Key Information for Health Professionals to Give Patients in Counselling
44	References
47	Members of the Professional Advisory Board
48	Index (Alphabetical)
IBC	International Resources

GENITAL HERPES – KEY TAKE HOME POINTS

- Genital herpes is a common infection. As many as one in five adults in New Zealand have genital herpes due to HSV-2. Up to 50% of genital herpes is due to HSV-1.
- Genital herpes is under-recognised and under-treated. Minor lesions are common; any recurring localised anogenital symptoms or lesions strongly suggest HSV infection.
- Laboratory confirmation of the diagnosis and typing is important, but should not delay treatment.
- Oral antiviral treatment is safe, effective and generic brands are very cheap.
- Oral antiviral treatment of the first clinical episode should always be offered regardless of the time of symptom onset. Do not confuse the treatment of first episode genital herpes with the '72 hour' herpes zoster rule.
- Antiviral therapy of recurrent genital herpes may be suppressive or episodic. Many patients prefer suppressive antiviral therapy. It is particularly recommended for those with frequent and/or severe recurrences or associated psychosocial morbidity. For those choosing episodic antiviral therapy, it is more effective when patients start therapy themselves at the first signs of a recurrence. This needs anticipatory advice on 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.
- 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

The NZHF has a range of resources to assist patients and clinicians.

Phone: Herpes Helpline toll free **0508 11 12 13**

Website: **www.herpes.org.nz**

Epidemiology

Genital herpes is an infection caused by the herpes simplex virus (HSV) and, for practical purposes, encompasses lesions on the genitals 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). Although HSV-2 is the most common cause of genital infection, a significant proportion of anogenital herpes is caused by HSV-1.

The epidemiology of genital HSV-2 infection is based on studies of serological evidence of HSV-2, as the majority of HSV-2 infections are genital with comparatively few oral infections. 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.¹ The Dunedin cohort study found an increasing HSV-2 seroprevalence of 3%, 11% and 18% at ages 21, 26 and 32 years respectively.²⁻⁴

Female gender: Women are more likely than men to be HSV-2 seropositive.¹ The reasons for this are unclear; suggestions include anatomical differences that increase vulnerability to infection or sexual mixing that may expose women to a higher prevalence of infection at a younger age. In 2004-5, at age 32, women in the Dunedin cohort study had an HSV-2 seroprevalence of 22% whilst that in men was 15%.⁴

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

Geographical variation

HSV-2 prevalence varies between countries and seems to be higher in the USA than in Europe, Australia and New Zealand. It also varies depending on the demographics of the population being tested.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 Australia⁵ and similarly a Waikato-wide study found 30-40% of anogenital isolates are due to HSV-1 each year.⁶ 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 episodes of genital herpes were HSV-1, whilst non-primary first episodes and recurrences were mostly HSV-2.⁷

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 anogenital herpes is due to HSV-2 infection, as a substantial proportion of people will have HSV-1. The natural history of anogenital HSV-1 infection is towards significantly fewer clinically apparent recurrences and much less subclinical shedding.^{8,9} Also, prior HSV-1 infection does not alter the risk of acquisition of HSV-2, although it does attenuate the symptoms; it is important for those diagnosed with HSV-1 anogenital herpes to understand that they remain at risk of HSV-2 infection.

In summary:

As many as one in five adults have genital herpes due to HSV-2, but most will have asymptomatic or unrecognised disease. Genital herpes due to HSV-1 has also become common; HSV-1 is the more frequent cause of primary genital herpes.

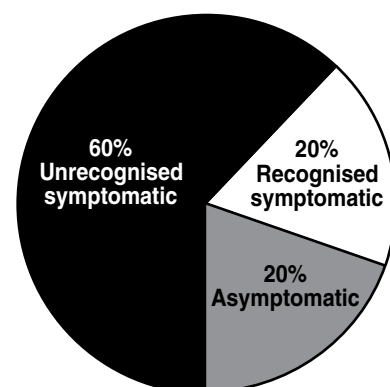


Figure 1: Prevalence, manifestations of genital herpes

Transmission

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 asymptotically. Most people who acquire genital herpes get it from someone who is unaware they are infected, who may have mild or asymptomatic infection.⁹

It is important to remember that, whilst a first clinical episode of genital HSV-1 or HSV-2 may represent a new infection, it may also be a first symptomatic recurrence of a previously asymptomatic or unrecognised infection.

The virus is readily inactivated at room temperature and by drying; hence, non-contact forms of spread, for example via fomites, 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

Barrier methods

Male and female latex condoms appear impermeable to HSV-2, but in 'real-life' 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.¹⁰ Nonetheless, consistent condom use offers moderate protection against HSV-2 infection in both men and women.¹¹ **GRADE B.** Data on male condoms preventing transmission to men or on the efficacy of female condoms is lacking. Condom use should be discussed and left to the individual couple's choice.

Oral-genital contact

It is generally believed 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. 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,¹² but will still shed HSV-1 virus.¹³

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

Oral HSV-2 isolation is uncommon. However, oral isolation of HSV-2 has been noted in those with HIV infection and in men who have sex with men, usually at the same time as genital HSV-2 symptoms.¹⁴

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 resulted 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.¹⁷ If HSV-2 genital infection is acquired first, then a new HSV-1 genital infection does not affect the frequency of recurrences.

In summary:

- Condom use needs to be assessed within the individual situation.
- Using condoms reduces, but does not eliminate, the risk of male to female transmission.
- Sexual contact should be avoided when oral or genital lesions are present.

Diagnostic Tests

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

Detection of herpes simplex virus in the lesion establishes the diagnosis unambiguously. Viral detection may involve culture, HSV DNA or direct detection of antigen. Vesicles offer the best source of virus. However, as with all laboratory tests, results depend on multiple factors including the adequacy of the specimen. A negative result therefore may not exclude infection. If direct HSV tests are repeatedly negative and the symptoms are recurring, the patient should be advised to have type-specific herpes serology. **GRADE B.**

Culture

HSV isolation in cell culture has been the diagnostic gold standard for many years. Specificity of culture is virtually 100%, but sensitivity is highly dependent on the stage of the clinical lesions, with an isolation rate of over 90% from vesicular or pustular lesions, 70% from ulcerative lesions, but only 27% at the crusting stage.¹⁸ Delayed transport of the specimen to the laboratory may further reduce yield. Positive results are usually reported within 2-5 days, but occasionally may take longer.

PCR

HSV DNA detection by polymerase chain reaction (PCR) increases HSV detection rates compared with virus culture. This is largely because it avoids problems that may affect culture results such as inadequate quantity of specimen, bacterial contamination, and inadvertent inactivation of virus by sub-optimal handling and sample transport delays. Increasingly, PCR is being implemented as the preferred diagnostic method for genital herpes, particularly since the advent of commercially available real-time assays. However, stringent quality control is necessary because of potential contamination by 'carryover' DNA from other biological samples¹⁹ and local validation is recommended.

Direct immunofluorescence

Is no longer recommended as a routine test.

Direct immunofluorescence testing for the viral antigen, present in the cells lining the base of the blister or the ulcerated lesion, shows lower sensitivity and specificity than virus culture. Rapid diagnosis is possible, but it requires operator expertise in obtaining an adequate specimen and a negative result should be interpreted with caution. It is no longer recommended as a routine test.

For patients with active lesions, direct viral detection by either culture or PCR, but not serology, is the recommended diagnostic method.

Sample collection

The following tests have 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 and, for culture in particular, on correct specimen handling and prompt transportation to the laboratory. It is important to be aware of locally available tests so that an appropriate sample is taken. **Viral typing should be requested routinely.**

Culture

- Select appropriate swab; NZ dedicated viral transport swabs (Virocult®) are available. These are usually 'green-topped' and packaged with a sleeve containing a small amount of viral transport medium.
- Swab the lesion firmly. The aim is to collect any vesicular fluid that may be present and to collect virus-infected cells from the base of the lesion.
- Insert swab into plastic tube.
- Place on a cold source, e.g. melting ice or slika pad, and send chilled to the virus laboratory. The swab should arrive the same day since the virus will decay with transport time.

PCR

- Check with local laboratory if HSV PCR is routinely available. If not, may need to specify "for herpes simplex DNA" and offer clinical explanation as to why this is the preferred test over culture, e.g. CSF sample.
- Swab as for viral culture.
- Transport time to the laboratory is less important than with culture.

Serology

Serological tests detect antibodies to HSV in blood and indicate past infection. Type specific tests, based on glycoprotein G (gG) assays, detect antibodies to the type specific proteins gG-1 and gG-2 and detect established infection with HSV-1 and HSV-2. They do not distinguish the anatomical site of infection (see Table 1). Type specific tests are used in population surveys, but their diagnostic reliability in individual patients is still debated. **False negative and false positive results are common in low prevalence populations.** Seroconversion following initial infection is usually 2-6 weeks, but may be longer (months). Also, some do not seroconvert and reversal from seropositive to seronegative status may occur if there is minimal antigenic stimulation. It is a useful test in some clinical situations, but routine screening of asymptomatic individuals is currently not recommended. **GRADE B**

Situations where measurement of type-specific antibody might be helpful include:

- Recurrent or atypical genital symptoms with negative HSV cultures and/or PCR.
- Management of herpes in pregnancy (see page 22).
- Where one partner in a relationship has symptomatic genital herpes. This may be important for discordant couples (a pregnant woman with a symptomatic male partner) 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.

The person ordering serology should be able to supply appropriate pre- and post-test counselling.
A positive HSV-2 serology result may cause significant psychological morbidity (see page 12-13).

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

- Explain whether the test is for HSV-1 and HSV-2 antibodies or just HSV-2 antibodies. If the blood test being done only tests for HSV-2 antibodies a negative test does not rule out the possibility of the person having genital herpes caused by type 1.
- The window period for antibodies developing following infection is usually 2-6 weeks, but may be longer (months).
- Caution is needed in the interpretation of results. Because false negatives and false positives occur, the results have to be weighed together with the clinical presentation and patient's history.
- Implications for the presence of only HSV-1 antibodies need to be explained. HSV-1 is a common infection, usually acquired in childhood, and may be shed from the oropharynx by asymptomatic individuals. Infection with HSV-1 does not necessarily imply sexual exposure, but genital infection with HSV-1 is increasingly common.

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. Does not specify site of infection, but genital infection is more likely with HSV-2.
HSV-1 positive	No HSV-2 antibodies detected*; consider at risk of infection to HSV-2. HSV-1 antibodies imply prior infection, but does not specify site of infection. Genital HSV-1 infection is increasingly common.	HSV-1 and HSV-2 antibodies imply prior infection with both. Does not specify site of infection for HSV-1, but genital infection is more likely with HSV-2.

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

CLINICAL EPISODES OF GENITAL HERPES

Definitions

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

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

First episode: The first clinical episode of genital HSV-1 or HSV-2. This may represent a primary HSV infection or a new non-primary infection or a recurrence of a previously asymptomatic infection. It is not possible to reliably distinguish between these on clinical grounds alone.

First Clinical Episode of Genital Herpes

The first clinical episode of genital herpes may, but does not always, reflect recent infection. Nonetheless, as first episode genital herpes is generally more severe and/or more prolonged. **Treatment should always be offered regardless of time of symptom onset. Do not confuse the treatment of first episode genital herpes with the '72 hour' herpes zoster rule.**

Aciclovir 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.^{20,21} **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 culture or 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) Education concerning transmission, epidemiology, etc; provide written material
 - (d) Acknowledgement of the psychosocial impact of the disease
 - (e) Referral to support systems – NZHF Helpline toll free **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 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 plaques appear followed by a cluster of 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. Small ulcerated areas may be surrounded by oedema and be extremely tender. Pain on urination is typical, particularly in women. The ulcers then 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. Lesions may also appear extra-genitally, commonly on thighs and buttocks and less commonly on hands, lips, face and breasts. Inguinal nodes are usually enlarged and tender.

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.²²

Similarly, a diagnosis of acute radiculitis (herpetic lumbosacral radiculoneuropathy or Elsberg Syndrome) tends to be over-looked 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.²³

Bells Palsy is probably caused by HSV-1 (and HZV virus). Early treatment with oral steroids is effective;²⁴ the use of antiviral agents is less clear, but is still commonly recommended.

Sporadic herpes simplex encephalitis is an acute necrotizing 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 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 pink-red ring around a pale centre. Resolution within 7-10 days is the norm. Stevens-Johnson syndrome (erythema multiforme major) is a related, much less common, but much more serious condition. Clinically, this may be indistinguishable from toxic epidermal necrolysis and hospitalisation for supportive cares is indicated.

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.

Examination

Examination should include inspection of the genital region; speculum examination should be considered, but may need to be delayed if discomfort is anticipated. Clinical diagnosis is insensitive. For example, ulceration may be due to aphthous ulcers, Stevens Johnson syndrome, fixed drug eruption, self-inflicted (sometimes unknowingly) trauma and autoimmune blistering disease (rare). Other infections may cause genital ulcers, e.g. herpes zoster virus, Epstein-Barr virus, primary syphilis and chancroid.

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 7).

A. Pharmacological treatment

Therapy should be initiated regardless of how long the lesions have been present and before virological confirmation. **Do not confuse the treatment of first episode genital herpes with the '72 hour' herpes zoster rule.** If there is a possibility of pregnancy, please refer to page 22. Refer immunocompromised patients, or those with herpetic proctitis, to an appropriate specialist, e.g. infectious diseases, sexual health.

1. Oral antiviral treatment

The only funded oral antiviral in New Zealand for first episode herpes is aciclovir; valaciclovir and famciclovir are not subsidised, although this may change as and when generic formulations become available.

Recommended treatment regimens for first episode genital herpes (**all for 5-10 days**) include:

- Oral aciclovir 400mg three times daily (8-hourly) – recommended dose
- Oral aciclovir 200mg five times daily
- Oral famciclovir 250mg twice daily (12-hourly)
- Oral valaciclovir 500mg twice daily (12-hourly)

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 5-day course of therapy is not usually indicated unless new lesions continue to appear. Intravenous (IV) aciclovir therapy should be considered for patients who have severe disease or complications that necessitate hospitalisation.²⁵

2. Topical antivirals

Topical aciclovir creams are less effective than oral aciclovir and are not recommended (see page 19).

B. Symptomatic treatment

In addition to oral antivirals, other measures to control symptoms should be suggested. 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. 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. 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 stop application if increasing discomfort occurs after application. If catheterisation is unavoidable, a suprapubic catheter should be used to reduce the risk of ascending infection and is a less painful option. **GRADE C**

C. Education

It is important to ensure that patients receive accurate up-to-date information about genital herpes. NZHF resources are available to assist patients and clinicians with education and counselling. A range of printed materials can be ordered (please refer to resources listed on inside front cover). Primary care practitioners should have access to these

resources or be able to advise their patients on how to obtain them. www.herpes.org.nz. There is also a Herpes Helpline **0508 11 12 13**, a telephone service that is free to all New Zealanders.

Informing the patient of the diagnosis can be a delicate matter. A diagnosis of genital herpes can have a profound effect on patients.²⁶ They may become upset and distressed; guilt, depression, lowered self-esteem and fear of rejection are common reactions.²⁷ For some, extra-genital (including facial) herpes lesions may also have a considerable psychological impact. 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 Fact** leaflet and **The Facts** book, should be offered to patients at the first visit with discussion and further questions encouraged at the follow-up and subsequent visits.

D. Counselling

Social and psychological issues should be addressed both at the first appointment and at follow-up. There are three main aspects or levels of counselling:

- Basic health counselling (which involves information concerning the disease process).
- Psychological impact of the disease on the patient and their relationships (particularly important in the long term).
- Support offered in the community (e.g. Helpline, support groups).

It may be appropriate to offer the opportunity for their partner to have questions answered as well.

Practice nurses or nurses who have training in this area may also be a good source of counselling support. Useful resources include the NZHF website www.herpes.org.nz, the Herpes Helpline toll free **0508 11 12 13**, or local sexual health clinic, for both management advice and/or more information. Discussing the role of support groups is often helpful; the patient should understand the reassurance that can be gained through discussions with people who have a similar condition; such discussions can be facilitated by the NZHF. The practitioner may also choose to refer patients on to professional counselling, if this is available. Confidentiality and sensitivity are paramount; patients need to agree to a third party becoming involved.

See **Key Information for Health Professionals to Give Patients in Counselling** on page 42. **GRADE C**

E. 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.

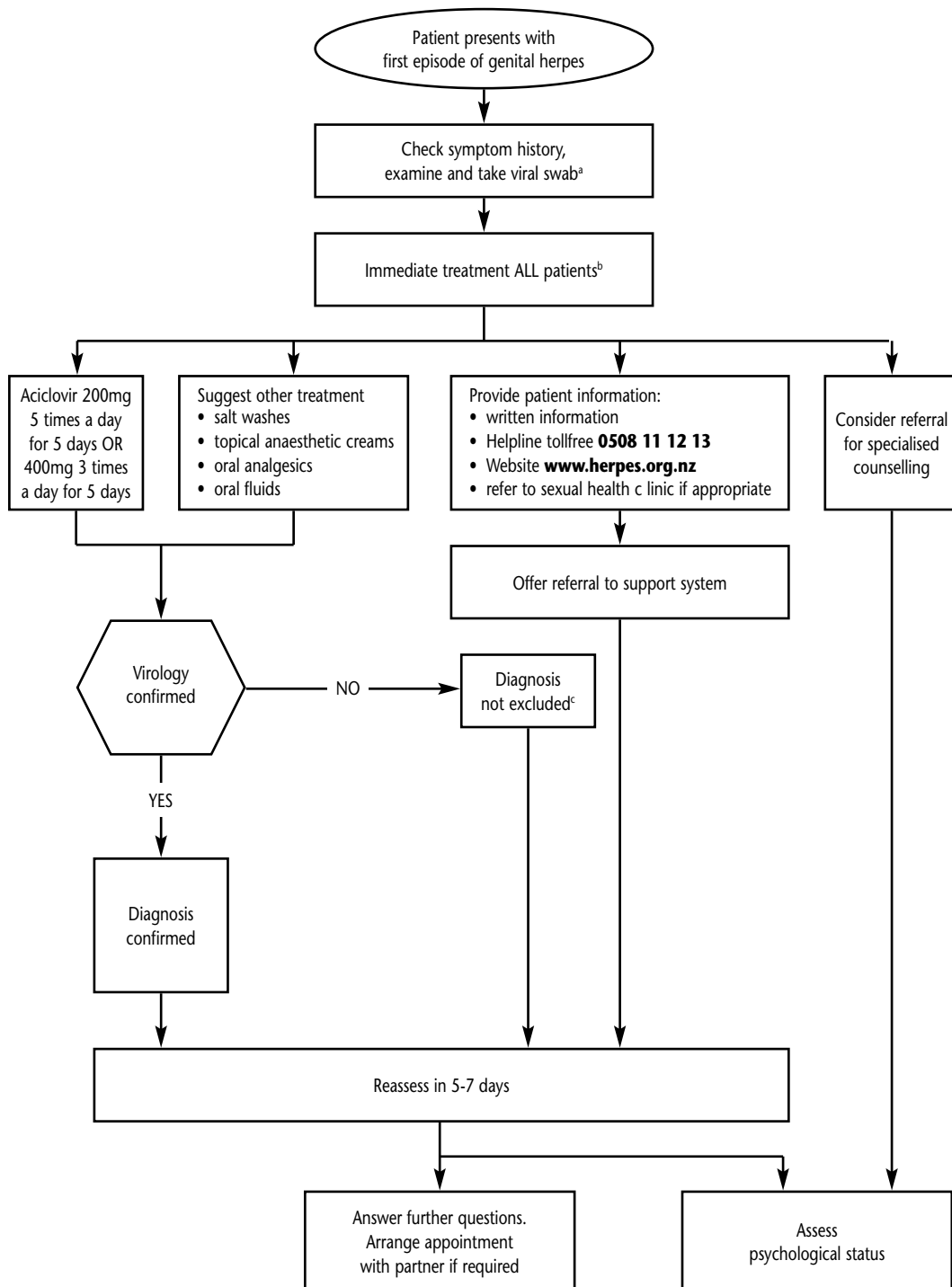
At the initial visit, a follow-up appointment should be offered for 5-7 days later so as to evaluate symptoms, their psychological status, complete a full STI screen if appropriate, discuss results and answer any questions they may have. It should be noted that it might take longer than 5 days for skin lesions to heal completely. Further therapy is not usually required unless new lesions continue to appear. It is also helpful to give anticipatory advice over future management options including oral antiviral therapy; recurrent HSV episodes are usually milder than the initial episode and can be treated with either intermittent therapy (treating each episode) or suppressive therapy (treating continuously over a period of months to prevent episodes).

Suppressive antiviral therapy is recommended 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. At all times this process should be one of negotiation with the patient, as the pattern and severity of recurrent episodes is unpredictable.

For those choosing episodic antiviral therapy, this is more effective when patients start therapy themselves at the first signs of a recurrence. This needs anticipatory advice and prescribing. **GRADE A**

Recommendations on counselling and follow-up are based on internationally accepted standards of practice. **GRADE C**

Management of First Episode of Genital Herpes



a In cases of immunocompromised patients or herpes proctitis, refer to specialist.

b Use in pregnancy requires specialist consultation.

c Recommend early presentation for viral swab if recurrence.

Recurrent Episodes of Genital Herpes

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) Virus swab for culture or PCR for diagnosis; confirmation of diagnosis at least once is strongly recommended
 - (b) Consider exclusion of other STIs if appropriate
4. Treatment involving:
 - (a) Consideration of oral antiviral therapy – either intermittent 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 toll free **0508 11 12 13**
5. Appropriate follow-up arrangements

Sufficient time should be allowed to address all these aspects. Shared management is important for the patient to feel a measure of control; the clinician should aim to be the facilitator of education and treatment options.

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.²⁸ 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 straight-forward 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, e.g. candida (thrush), may mimic and/or coexist with recurrent herpes, and careful examination of the genitalia should always form part of the diagnostic procedure. For example, recurrent ulceration may be due to aphthous ulcers, erythema multiforme, fixed drug eruption, self-inflicted (sometimes unknowingly) trauma 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.

The atypical or non-ulcerative presentations of genital herpes can mimic most genital diseases, hence the need to consider more than one diagnosis at any given time. For example, lichen sclerosus results in increased skin fragility; because this condition is usually itchy, secondary scratching may cause superficial erosions and haemorrhagic bullae are not uncommon. Eczema and less commonly psoriasis complicated by scratching may cause superficial erosions. Herpes lesions may become secondarily infected with *Staphylococcus aureus* and will give the appearance of a folliculitis, similar to mild forms of hydradenitis suppurativa, primary folliculitis, or scabetic nodules. In most cases extra-genital lesions provide a useful clue to other pathology.

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 viral swab taken with an explanation to the patient why this has been done. **GRADE B**

It is 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 culture or 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 viral culture swabs remaining negative, PCR testing of lesions or type-specific herpes serology testing may aid diagnosis.

Complications of recurrent genital herpes

Herpes recurrent lesions can occur on the hands, arms, shoulders and other areas of the body, commonly around the buttocks; the diagnosis is often overlooked.

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 pink-red ring around a pale centre. Resolution within 7-10 days is the norm. Recurrent episodes may be managed with continuous antiviral suppression treatment. Stevens-Johnson syndrome (erythema multiforme major) is a related, much less common, but much more serious condition. Clinically, this may be indistinguishable from toxic epidermal necrolysis and hospitalisation for supportive care is indicated.

Education and counselling

It is important to ensure that patients receive accurate up-to-date information about genital herpes. NZHF resources are available to assist patients and clinicians with education and counselling. A range of printed materials can be ordered – please refer to resources listed on inside front cover – primary care practitioners should have access to these resources or be able to advise their patients on how to obtain them. Written materials, such as the NZHF **Myth vs Fact** leaflet and **The Facts** book, should be offered to patients with discussion and further questions encouraged at subsequent visits. Useful resources include the NZHF website **www.herpes.org.nz** and the Herpes Helpline toll free **0508 11 12 13** or the local sexual health clinic for both management advice and/or more information.

It is important to understand the impact that a diagnosis of genital herpes may have.²⁷ Issues that should be raised with patients (and perhaps their partners) include:

- The effect of genital herpes on self esteem and self image
- How herpes will affect their current relationships
- How herpes will affect their ability to form new relationships
- The disclosure of their condition to partners or potential partners
- The lifelong nature of the condition and how this affects them
- Fears concerning transmission or the infectious nature of the disease
- Fears concerning future fertility
- Fears concerning cancer
- Fear of discovery
- Alterations in social activities and lifestyle
- Stress management
- Feelings of isolation
- The attitude of the general public towards this disease

For **Key Information for Health Professionals to Give Patients in Counselling**, see page 42.

People with genital herpes may become anxious or depressed and this may unmask or amplify disorders such as phobias or obsessive-compulsive disorder. Specialist referral may be necessary for severe or complicated cases. In general, assisting the patient to take responsibility for, and control of, their disease and its treatment will help the patient overcome some of the psychological difficulties. **GRADE B**

Recommendations on education and counselling and follow-up are based on internationally accepted standards of practice. **GRADE C**

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.^{29,30} 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.^{29,30} Beyond this time frame, 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. Shorter courses of patient-initiated therapy, e.g. single-day famciclovir³⁰ or two days of aciclovir,³¹ have been shown to be as effective as a longer 5-day course. **GRADE A**

Recommended dosage regimen

If the patient is pregnant, specialist consultation is recommended (see page 22).

In cases of immunocompromised patients, refer to appropriate specialist.

Treatment regimens for intermittent episodes include:

For five days:

- Oral aciclovir 400mg three times daily (recommended)
- Oral aciclovir 200mg five times daily
- Oral valaciclovir 500mg twice daily
- Oral famciclovir 125mg twice daily*

Short-course:

- Oral aciclovir 800mg three times daily for two days (recommended)
- Oral valaciclovir 500mg bd for three days
- Oral famciclovir 1gram bd for one day*

***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.^{32,33} **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.^{34,35}
- To empower the patient, giving them a measure of control over the disease process.
- To allow the patient to have a break from experiencing recurrences of the disease.

In a recent study, suppressive once daily valaciclovir resulted in reduced transmission to an uninfected partner; there was 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

Suppressive therapy should be considered in the following circumstances:

- Frequent and/or severe recurrences or associated psychosocial morbidity. Consider suppressive therapy in conjunction with other management. **GRADE B**
- For HSV-2 positive male partners of pregnant women (see page 28).

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

Recommended dosage regimen

If the patient is pregnant, specialist consultation is required (see page 22). In cases of immunocompromised patients, refer to appropriate specialist.

Recommended treatment regimens for suppressive therapy include:

- Oral aciclovir 400mg twice daily
- Oral aciclovir 200mg four times daily
- Oral valaciclovir 500mg once daily (now available, see Note below)
- Oral famciclovir 250mg twice daily*

Note: Valaciclovir (Valtrex™) is listed for suppressive treatment of recurrent genital herpes, subject to a Special Authority restriction, in the Pharmaceutical Schedule.

- **Initial application:** From any practitioner. Approvals valid for 12 months where the patient has genital herpes with two or more breakthrough episodes in any 6 month period while treated with aciclovir 400mg twice daily.
- **Renewal:** From any practitioner. Approvals valid for 12 months where the treatment remains appropriate and the patient is benefiting from treatment.

*Famciclovir is not currently subsidised or marketed in New Zealand, although this may change as and when generic formulations become available.

The duration of therapy should be negotiated between the patient and the clinician; however, a treatment period of a year is recommended with periodic reassessment. Patients should be given a reasonable break from therapy to reassess their pattern of recurrence to determine whether it has reduced with time. **GRADE C**

20-25% of patients may experience recurrent episodes whilst on suppressive therapy.^{33,36} 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 aciclovir may need to be altered if breakthrough episodes are confirmed; aciclovir has poor oral bioavailability and some patients require multiple doses throughout the day. Alternatively, a trial of Valaciclovir (Valtrex™) may be considered for these patients; Famciclovir is not currently subsidised in New Zealand.

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. At all times this process should be one of negotiation with the patient, as the pattern and severity of recurrent episodes is unpredictable.

Some patients may need to be on suppressive therapy for years. Aciclovir is well tolerated and safety and efficacy data are supportive of longer-term use.³⁷ Neurotoxicity (lethargy, confusion, hallucinations and involuntary movements) has been reported in those with renal impairment.

Intermittent suppressive antiviral therapy

The use of intermittent suppressive therapy is also considered a point for negotiation with the patient. Practitioners should be aware that this type of therapy is an option, particularly for patients who are keen to avoid a recurrence during a specified period, e.g. a holiday, exams, etc. **GRADE C**

Topical antiviral therapy

Topical aciclovir creams may be helpful for mild recurrences in some patients,³⁸ but are less effective than oral aciclovir. Further, not all topical formulations are bioequivalent.³⁹ 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 limited and should be considered as such.²⁵

Management of Genital Herpes in Immunocompromised Individuals

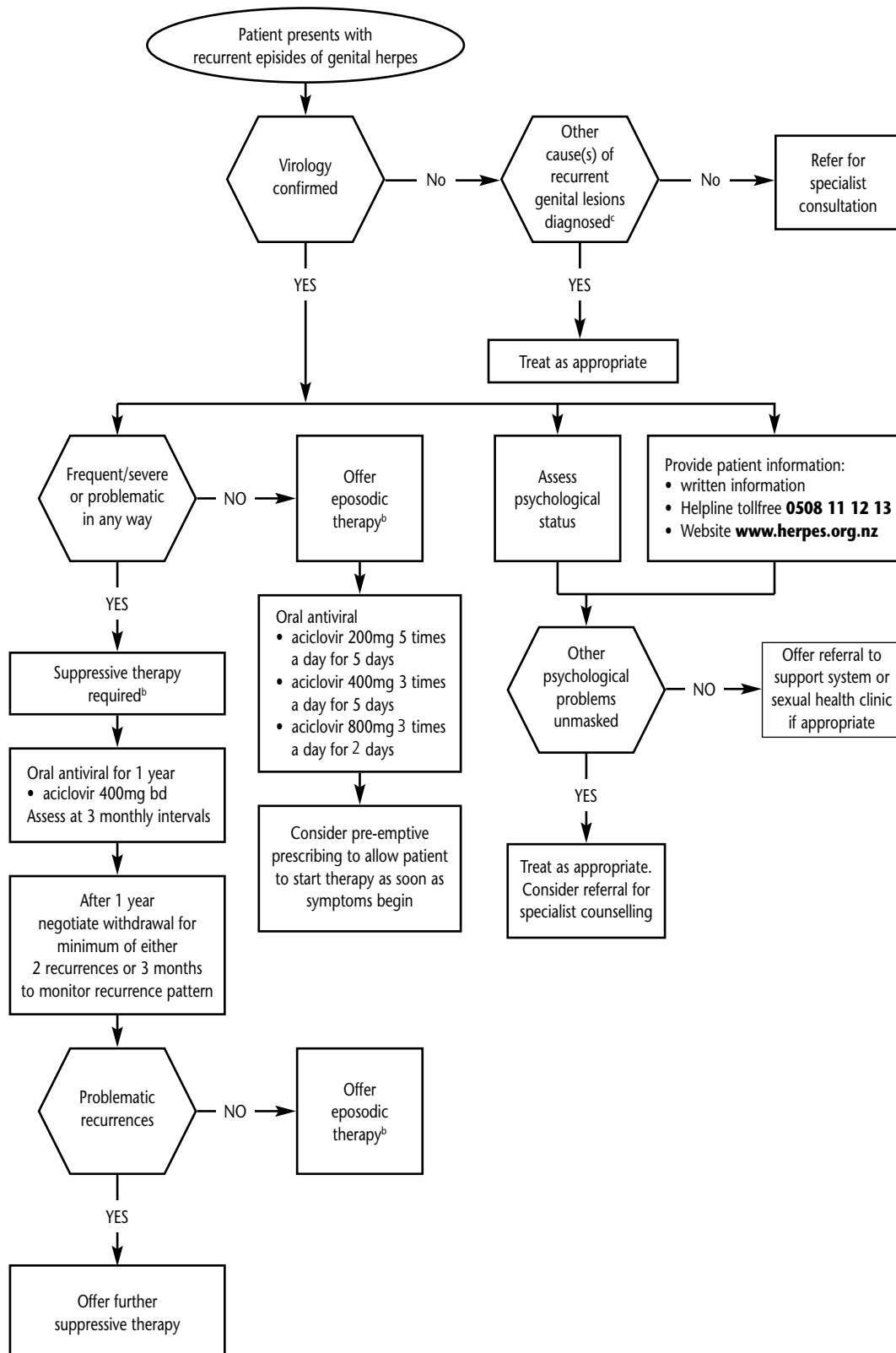
Although rare in immunocompetent individuals, clinically refractory (large, severe and sometimes atypical) lesions due to genital HSV may occur in patients with severe immunodeficiency, including late stage HIV disease. Immunocompromised individuals need referral to specialist care.

Summary Statements Concerning the Treatment of Genital Herpes

- Oral, not topical, antivirals should be prescribed. Do not confuse the treatment of first episode genital herpes with the '72 hour' herpes zoster rule.
- Analgesia and topical anaesthetic jellies can be suggested if necessary. Encourage intake of oral fluids. Patients should be advised to bathe herpetic lesions in salt water, and women be advised to urinate in a warm bath to prevent pain.
- Effective episodic treatment of recurrent herpes requires prompt initiation of therapy during the prodrome or within one day of symptom onset. Sufficient quantities of medication may be prescribed with instructions to start treatment as soon as symptoms begin.
- Suppressive therapy should be considered for those with frequent and/or severe recurrences or associated psychosocial morbidity. Consider suppressive therapy in conjunction with other management.
- Standard therapy in New Zealand for suppression of herpes recurrences is oral aciclovir 400mg twice daily. The recommended period of treatment is 12 months, with review at 3-month intervals. Repeat year-by-year, if necessary.
- Withdrawal of therapy should be for a sufficient length of time to establish whether the pattern of recurrence has changed, for example, a minimum of two recurrences or for 3 months.
- Current generic brands of aciclovir are fully subsidised and, in 2009, cost:

aciclovir	200mg x 25 tabs = \$2.50	ex manufacturer
aciclovir	400mg x 56 tabs = \$7.50	ex manufacturer
aciclovir	800mg x 35 tabs = \$8.30	ex manufacturer

Management of Recurrent Episodes of Genital Herpes



- a In cases of immunocompromised patients or herpes proctitis, refer to specialist.
- b Use in pregnancy requires specialist consultation.
- c Recommend self-applied swab or early presentation for viral swab if recurrence.

GENITAL HERPES IN PREGNANCY

KEY PRACTICE 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.
- All women should be asked by their primary caregiver at their first antenatal visit if they or their partner have ever had genital herpes and given information on the potential risks of transmission in pregnancy; this includes the risk of genital HSV-1 from oral-genital contact.
- Women with genital herpes lesions during their pregnancy should be referred to a specialist obstetrician and/or a sexual health physician.
- The risk of maternal-fetal transmission (MFT) is highest with primary genital herpes infection during labour or within 6 weeks of delivery. 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.
- Recurrent lesions at term are a relative (not absolute) indication for caesarean section. The risk of MFT is low from recurrent lesions during labour, although may be greater with HSV-1 than HSV-2.
- Suppressive aciclovir from 36 weeks gestation may reduce the chance of a recurrence at term and hence the need for caesarean section. This should be used selectively rather than routinely, for example for women who have had an episode during pregnancy.
- 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 (see **Neonatal HSV Infection**, page 29).

Concerns around herpes infection during pregnancy tend to relate to the risk of neonatal infection. Disseminated maternal infection in pregnancy 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.⁴⁰

Neonatal herpes is a rare but potentially serious infection, which may be associated with significant morbidity and mortality. About 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) and in 5% of cases the infection is acquired post partum.⁴¹

Primary maternal infection before the 20th week of pregnancy may be associated with miscarriage,⁴² 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.⁴³ 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.⁴⁴

Antenatal recurrent disease, where HSV is not shed at delivery, does not have an adverse effect on neonatal outcome and the risk of intrauterine fetal infection from recurrent maternal HSV infection appears to be very low. 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.⁴⁵

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.^{46,47} **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 57%, while vertical transmission rates of 25% are found in those with a non-primary first episode (infection with one virus type in the presence of antibodies to the other virus type) near or at the time of delivery.

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.^{46,48} If lesions are present at delivery, there is a small but still reasonable risk of transmission of 0.25-3% because of protection from maternal antibodies passing across the placenta.⁴⁷

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.⁴⁹

Of infants with proven HSV infection, 80% have no documented history of herpes infection in either the mother or her partner.⁵⁰

Mode of delivery

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

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%).⁴⁷ 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, HSV-1 vs HSV-2 isolation at the time of labour, the use of invasive monitoring, premature delivery and young maternal age. None of the 140 women with viral shedding due to HSV-2 reactivation infected their babies compared to 2/11 women with HSV-1 reactivation. Of 26 first episode cases, transmission occurred in eight. 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-2.⁵¹

However 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.⁴³

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, the ACOG guideline states that there is no evidence that there is a duration of premature rupture of membranes beyond which the fetus does not benefit from caesarean delivery.⁵²

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.⁵³

In the case of recurrent genital herpes, maternal antibodies are protective and it has been argued that the benefits of caesarean section are low in this group of women, even if lesions are present at the time of delivery. Policy in the USA has been to offer delivery by caesarean section if the woman has signs or symptoms of a recurrence at the onset of labour and there is data to support this approach, as discussed above.⁴⁷ In the Netherlands, however, 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 (26 cases of neonatal herpes 1981-1986 compared to 19 cases 1987-1991).⁵⁴ A follow-up audit 1999–2005 concluded that a low rate of neonatal infection in The Netherlands continues despite a low caesarean section rate to prevent neonatal infection and there was therefore not a need to revise the current guidelines in that country.⁵⁵ 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.⁵⁶⁻⁵⁸ It has also been shown that the presence of symptoms at delivery correlates relatively poorly with the detection of HSV from genital sites or lesions by culture or PCR.⁵⁹

Use of prophylactic aciclovir

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.^{54,60-62} 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.^{63,64} **GRADE B**

However, there are theoretical concerns that maternal aciclovir therapy may suppress the production of neutralising antibodies to the immunogen, glycoprotein D, thus having an effect on passive immunity to the fetus, and may suppress rather than treat newborn infections, thus leading to a delay in presentation of neonatal disease.

In the absence of definitive data, it is recommended that prophylactic aciclovir from 36 weeks should be used selectively, rather than routinely offered, for women with a history of recurrent genital herpes e.g to those women who have had an episode in the current pregnancy. This may be updated when more information on the effects of aciclovir on the neonate is available.

Management of Pregnant Women with First Episode Genital Herpes

First and second trimester acquisition

Management of the woman should be in keeping with her clinical condition using aciclovir in standard doses as indicated (see page 28). **GRADE C**

Provided delivery does not ensue, the pregnancy should be managed expectantly and vaginal delivery anticipated. Continuous aciclovir in the last 4 weeks of pregnancy reduces 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 27.

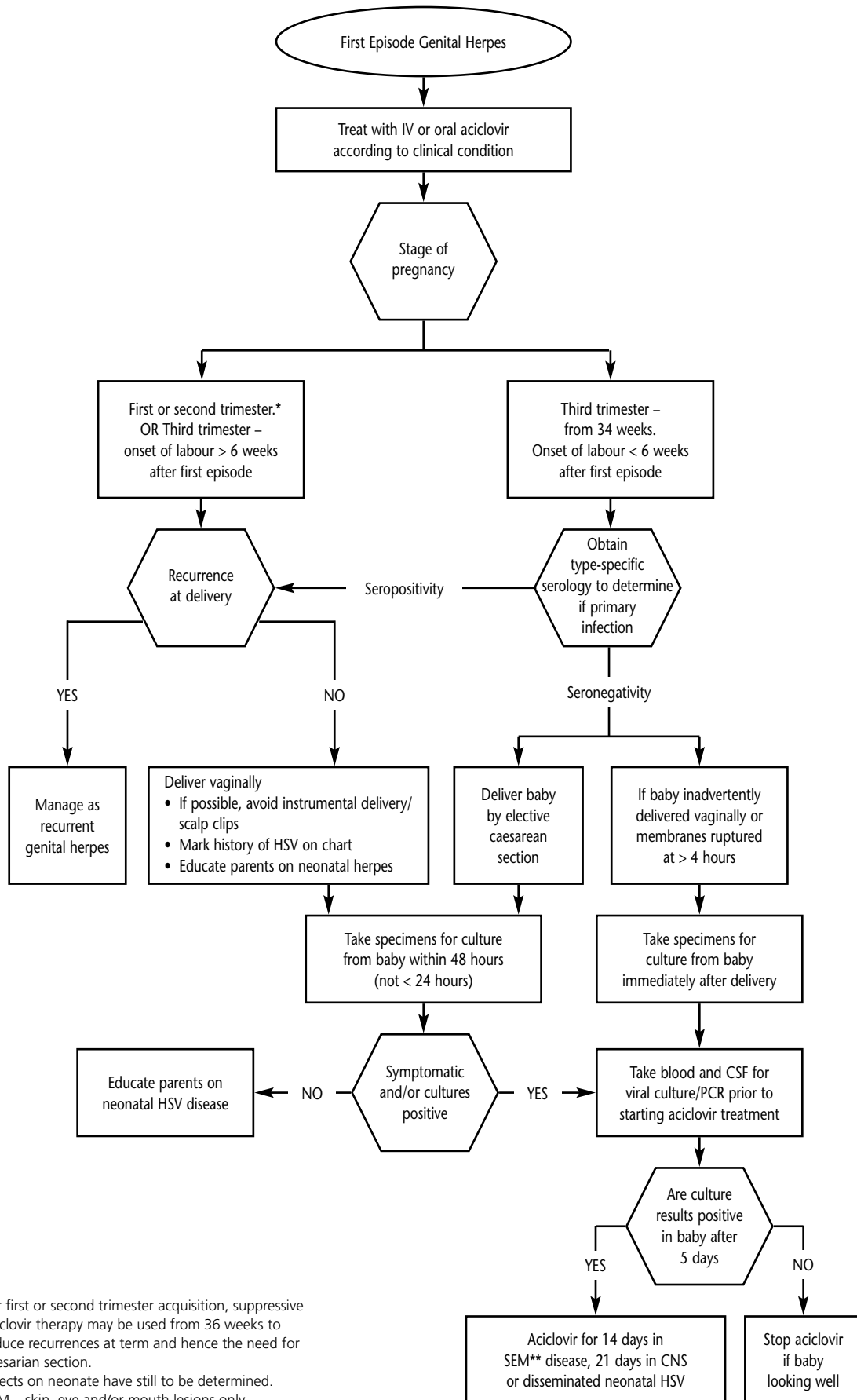
Third trimester acquisition

Note: The first clinical episode may not be due to a primary infection, as previous infection may not have been recognised. Type specific culture or 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. Consider treatment with aciclovir (see page 28).

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 treatment of mother with aciclovir and request an urgent referral to a paediatrician experienced in HSV infection (see **Neonatal HSV Infection**, page 29). **GRADE C**

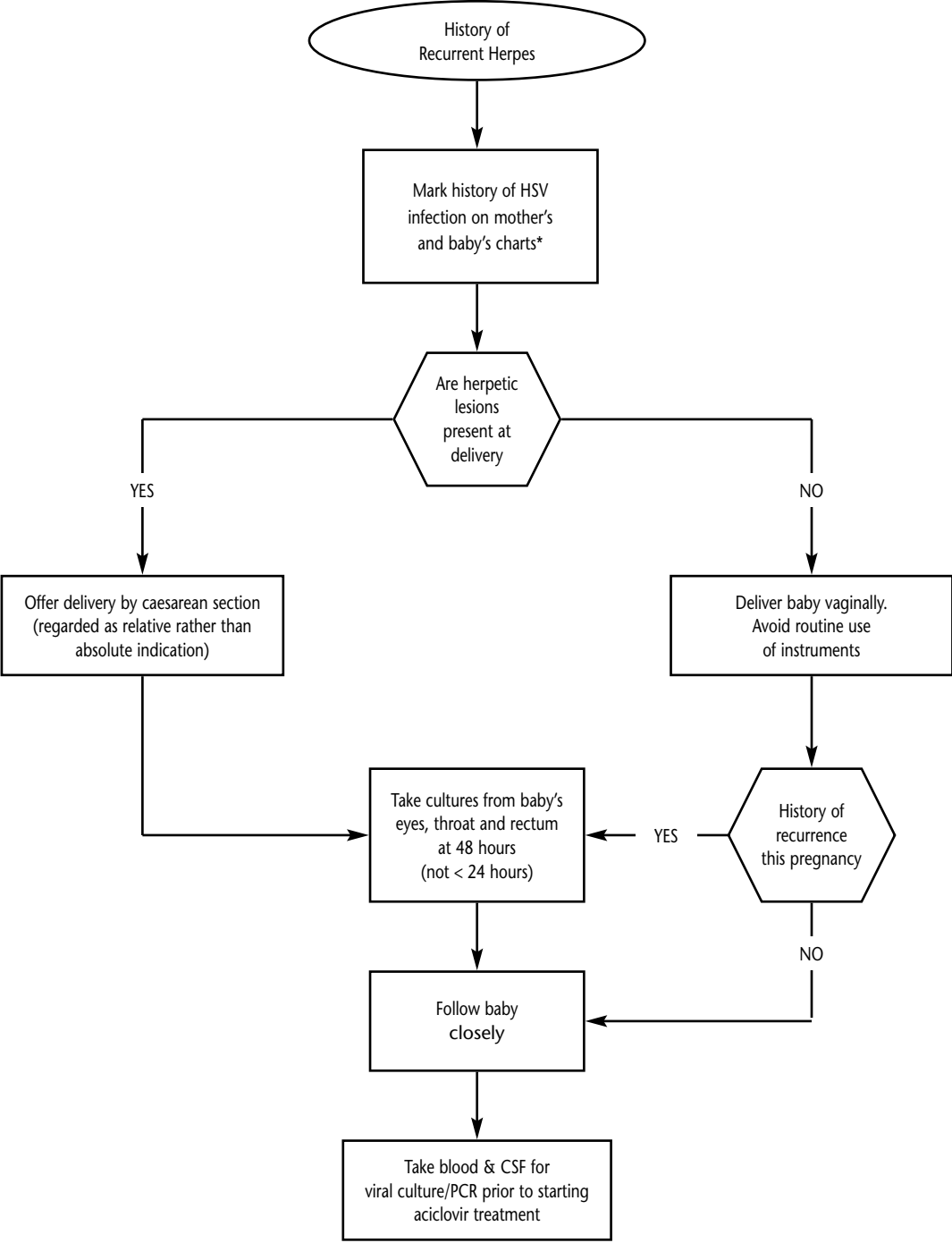
Management of First Episode Genital Herpes in Pregnancy (in consultation with a specialist)



* For first or second trimester acquisition, suppressive aciclovir therapy may be used from 36 weeks to reduce recurrences at term and hence the need for caesarian section. Effects on neonate have still to be determined.

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

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



* For women with recurrences during pregnancy, suppressive aciclovir therapy can be considered to reduce recurrence at term and hence the need for caesarean section. Effects on the neonate have still to be determined.

Management of Pregnant Women with Recurrent Genital Herpes

Document the history in both mother's and infant's notes. Symptomatic recurrences during third trimester are usually brief and vaginal delivery is appropriate if no lesions are present at delivery.⁴⁴ 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 (see above) and should be used selectively rather than routinely. **GRADE B**

Sequential cultures in the third trimester to predict viral shedding at delivery are not indicated.⁶⁵ Caesarean section should not be performed in women who do not have lesions at delivery.⁴⁴ **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.⁴⁴ **GRADE C**
- Ideally, this scenario should be discussed by the primary caregiver with the woman early in pregnancy.
- Caesarean section does not itself provide total protection.⁶⁶
- 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 aciclovir may be considered based on anecdotal evidence, although there have been no trials to assess the value of such therapy.
- In women who have recurrences in late pregnancy, starting aciclovir 400mg tds should 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 aciclovir.⁶⁷ This recommendation is consistent with the principles of episodic treatment.

Investigation and surveillance in the neonate

See **Management of Neonatal HSV Infection**, page 33.

Use of Aciclovir in Pregnancy and Breastfeeding

Data collected via the Aciclovir Pregnancy Register (1984-99) found the observed rates and types of birth defects for 1,234 pregnancies exposed to aciclovir did not differ significantly from those in the general population.⁶⁸ Some studies on the use of valaciclovir (an aciclovir prodrug) from 36 weeks gestation have addressed toxicity issues and identified no safety concerns in mothers, fetuses or neonates.^{53,69} Monitoring in the neonates included assessment of white cell counts, renal and hepatic function. The studies were underpowered to confirm safety with certainty, but the results, in conjunction with the lack of reported adverse events from other trials of prophylactic aciclovir and valaciclovir in late pregnancy, are reassuring.

While aciclovir is not licensed for use in pregnancy, there is substantial clinical evidence supporting its safety. Women who are inadvertently exposed to aciclovir in early pregnancy can be informed that the available information is reassuring and the use of aciclovir can be recommended where clinically indicated.

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

First episode:

- Aciclovir 200mg orally five times daily for five days.

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:

- Aciclovir 400mg orally three or four times daily, or 200mg four times daily (with more frequent dosing indicated because of increased clearance in pregnancy).

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.⁷⁰ **GRADE B**

Prematurity

One study has shown 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.⁷¹ 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. Little data is available on the management of preterm premature rupture of membranes in association with primary herpes simplex infection.

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 3,192 pregnant women and their partners identified that 22% of women were at risk of HSV-1 or HSV-2.⁷² 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.
- 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.
- 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.⁷³

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, the United Kingdom 1.65, and the Netherlands 3.2)^{55,74,75} is lower than reported for Scandinavia (Sweden 6.5)⁷⁶ and North America (the United States 4.0, and Canada 5.9).^{77,78}

Marked differences in incidence can also exist within countries. For example, in the United States the incidence of neonatal HSV infection in Seattle is 31-48, in Atlanta 15-20 and in California 12.1 cases per 100,000 live births.^{47,79,80} While reliable New Zealand data are lacking, in Australia the incidence is estimated at 3.2 per 100,000 live births.⁸¹

These differences in rates may be explained, at least in part, by variations in HSV-1 and HSV-2 seroprevalence rates, which influence the risk of acquiring first episode genital infections during pregnancy.^{79,82} Other possible explanations include different sexual practices, maternal age, types of hospitals surveyed and neonatal and paediatric post-mortem rates. It is fortunate that neonatal HSV infection is a rare disease given the potential for exposure as, for example, 20-30% of the childbearing population in the United States is seropositive for HSV-2.⁸³

Current data collection and case definitions are inadequate to provide sufficiently accurate incidence and epidemiological data, yet these are essential to guide effective education and prevention strategies.⁸⁰

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.⁸⁴

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 at least 85% of neonatal HSV infection.⁸⁵ 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.⁸⁴

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.^{46,47} The risk is greatest when a previously seronegative woman has a primary first episode of genital herpes near the time of delivery. Under such circumstances the risk of neonatal HSV infection is 57%, while vertical transmission rates of 25% are found in those with a non-primary first episode (infection with one virus type in the presence of antibodies to the other virus type).

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.^{46,48} If lesions are present at delivery, there is a small but still significant risk of transmission of 0.25-3%.⁴⁷ 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.⁴⁷ Recent studies report an increasing proportion of genital and neonatal herpes infection from HSV-1 strains.⁷⁸

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 fathers, other family members and medical staff.

Disease Classification

Intrauterine HSV infection

This 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 far better than that for newborns with more long-standing intrauterine infection and complications such as hydranencephaly.⁴⁴

Neonatal HSV infection

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.⁷⁸

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.^{50,86} Fever may be absent initially.⁸⁴ Mortality is highest in those with an altered conscious state, seizures, disseminated intravascular coagulation, and if born preterm.^{44,66}

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

Table 2: Classification of neonatal HSV infection^{44,66,87-89}

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

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 and the liver is the most commonly involved organ from primary viraemia. Multiple organs are seeded by a secondary viraemia, particularly the lung and adrenal glands. Focal embolisation of the brain may occur late in the illness. 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 or encephalitis. Vesicular skin lesions may not be present. Mortality in untreated patients is approximately 90% and many untreated survivors are severely impaired.

Central nervous system (CNS) disease

Almost one-third of neonates with HSV infection will have only encephalitis. It is believed that this represents axonal transmission of the virus to the brain. A history of recurrent genital herpes in the mother can act as a warning sign, since maternal transplacental antibodies may prevent disseminated disease, but not the virus spreading to the brain.⁹⁰ Infants usually present between 10 days and 4 weeks of age with symptoms of fever or temperature instability, lethargy 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, and elevated protein concentrations, both of which increase over the first few days. At presentation many are devoid of skin lesions. Untreated, the mortality rate approaches 50% with most survivors suffering severe neurological impairment. Even with the use of high dose aciclovir, morbidity has shown little improvement.

Skin, eyes and/or mouth (SEM) infection

Nearly half of neonates with HSV infection will present with lesions confined to the skin, eyes or mucous membranes. This proportion has increased in recent decades and is attributed to recognising and treating SEM infection before it progresses to more severe manifestations of the disease.^{78,88} 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.

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.⁹¹ It is also likely that a widespread rash represents underlying viraemia and greater risk of insidious reactivation later in infancy.

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.⁹² 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 techniques can detect HSV-DNA in the CSF, which may explain the emergence of new neurological deficits.⁹³

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. Most cases will present without identifiable risk factors and many with disseminated or CNS disease will initially lack skin lesions to assist in a timely diagnosis.

Management of suspected neonatal HSV infection

Successful management relies upon 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.^{50,86}

Consequently, most 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, thrombocytopenia, 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.⁹⁴

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.⁸⁹ **GRADE A** Aciclovir should also be considered for an unwell infant without clinical improvement and negative bacterial cultures at 48-72 hours.⁹⁵

Diagnosis

As neonatal HSV infection may occur in the absence of skin lesions, other diagnostic methods are required. These confirm the diagnosis and determine the extent of disease.⁴⁴ Acquisition of material for viral culture, from sites such as the eyes (conjunctiva), mouth, nasopharynx, urine and rectum, and from skin lesions (when present) is undertaken.

GRADE A

Liver function tests, including serum transaminases, as well as viral culture and PCR of CSF determine the extent of disease.^{91,96} These tests are performed on all infants suspected of neonatal HSV infection. **GRADE A**

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**

PCR

PCR is a rapid, highly sensitive and specific technique that avoids problems that may affect culture results such as inadequate quantity of specimen, bacterial contamination, and inadvertent inactivation of virus by sub-optimal handling and sample transport delays. Stringent quality control is necessary because of potential contamination by 'carryover' DNA from other biological samples.¹⁹ Interpretation and determination of significance of PCR results needs to be correlated with clinical presentation and course.⁹⁷ A negative 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.

Suitable specimens for PCR include:

- CSF
- Peripheral WBC (EDTA or CPD sample – not heparin)
- Vesicle fluid

Culture

Viral culture should provide a result within 2-4 days and is highly sensitive for HSV in mucocutaneous lesions. However, in contrast to PCR, fewer than 20% of neonates with CNS disease have positive CSF cultures.

Suitable specimens for viral culture include:

- CSF
- Blood
- Vesicle fluid
- Throat swab
- Nasopharyngeal aspirate
- Eye (conjunctival) swab
- Stool or rectal swab
- Urine

Direct immunofluorescence

This is the least sensitive diagnostic technique and is no longer recommended.

In addition, a sexual history from the parents is taken. The mother's lead maternity caregiver is asked to obtain cultures or PCR of maternal genital secretions and to perform total and type-specific HSV serology. This is important, even when the presentation is weeks after the delivery. Infant acute and convalescent serum to determine seroconversion may aid long-term evaluation when clinical suspicion is high but cultures or PCR results are negative. However, in general, serology plays no role in the diagnosis of neonatal HSV disease.

Treatment

Intravenous aciclovir (20mg/kg every 8 hours) decreases the mortality and morbidity of neonatal HSV infections.^{89,91,98} Early therapy improves neurological outcome. The treatment duration is 14 days for SEM disease and 21 days for CNS and disseminated infections.⁹⁸ The recommendation for the longer course of aciclovir also includes those infants with SEM disease but who have abnormal CSF parameters, including HSV DNA detected by PCR. **GRADE A & B**

Infants with persistent HSV DNA in the CSF following completion of antiviral therapy are more likely to die or suffer serious neurological impairment than infants whose post-therapy CSF specimens are PCR negative.^{98,99} All infants with HSV CNS involvement therefore should have a lumbar puncture at the end of aciclovir therapy to determine if the CSF is PCR negative for HSV. Those who remain PCR positive should continue receiving intravenous aciclovir until viral DNA in the CSF is no longer detected.^{66,91} **GRADE B**

As a rule neonatal HSV infections are presumed to be susceptible to aciclovir as the frequency of resistant strains is very low in this population. Use of agents such as foscarnet should only be considered if there is a slow response to therapy or if an initial improvement is followed by a subsequent deterioration.¹⁰⁰ **GRADE C**

A role for routine suppressive aciclovir therapy for neonatal HSV infection to prevent cutaneous recurrences and neurological complications once therapeutic courses have been completed has not been established.⁹³ A recent small study of infants with CNS or disseminated disease found no acute neurological deterioration using suppressive aciclovir for 2 years.¹⁰¹ Further studies are required before aciclovir can be recommended routinely for long term suppressive therapy.¹⁰² **GRADE B**

General management points

A monocytic leukocytosis in the CSF is suspicious of CNS HSV infection.⁴⁴ Treatment with aciclovir should be instituted before cultures or PCR results are available. After 5 days, aciclovir can be discontinued if the clinical course is no longer compatible with HSV CNS disease, all cultures (including PCR) are negative and a CT or MRI head scan is normal or does not suggest HSV encephalitis. Be aware however that a negative initial CSF culture or 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.^{91,103} Consequently, perform serial lumbar punctures when microbiological tests are negative, but clinical suspicion remains high. **GRADE B & C**

Empirical treatment with aciclovir of suspected disseminated HSV infection is recommended if after 48 hours the infant is critically ill despite antibiotic therapy, if bacterial cultures are negative, and if there are signs of progressive liver dysfunction with coagulopathy.¹⁰⁴ **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.¹⁰⁵ **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**

Management of cutaneous recurrences is difficult. Recurrences are more commonly associated with HSV-2 infections and a poorer prognosis.^{92,106} The benefit of routine suppressive therapy has not been established. Data from an uncompleted clinical trial indicate that oral aciclovir (300mg/m² three times daily) prevents HSV recurrences after SEM disease, but almost half the infants experienced neutropaenia while on treatment.⁹³ While controversial,¹⁰² it is recommended that if there are two such episodes during the first 6 months of life suppressive oral aciclovir be considered and the white blood cell count monitored.¹⁰⁷ It must be realised however that treatment failures resulting in serious disease have still been reported during aciclovir suppressive therapy.¹⁰⁸ **GRADE B & C**

When a cutaneous recurrence is accompanied by fever and especially irritability, a CSF examination, including HSV DNA PCR, should be performed and if abnormal 3 weeks of intravenous aciclovir 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. Couple separation is not uncommon.¹⁰⁹ 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** (see page 42).

- 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 staff 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 staff 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?"
- It is very important for health professionals to address transmission; how the baby did and did not become infected. Parents may prefer to believe that the baby was infected from contaminated medical equipment or a staff member with a 'cold sore' to mitigate the burden of parental responsibility for the baby's infection.
- 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 42 for Key Information for Health Professionals to Give Patients and consider referring to the NZHF Helpline toll free 0508 11 12 13

Anticipatory Management of Newborn Infant with Known Risk for Neonatal HSV

High risk

This category involves a subgroup of infants born to mothers with their first episode of genital herpes during 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.⁴⁶ Although not completely protective, 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.⁴⁶ **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 culture and PCR testing (see above) and initiation of anticipatory aciclovir therapy. 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 is continued for at least 5 days. It can be discontinued at this time if the neonate remains well, viral cultures and molecular diagnostic testing have not identified HSV, and the CSF studies including PCR results are normal. 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.⁹⁸ **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 cultures, 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.
- Advise mothers about hand washing and caution those with vesicular breast lesions 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.
- 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 cultures

- Cultures should be taken at 48 hours of age (not at birth or within the first 24 hours of life because of possible contamination by maternal cervico-vaginal secretions).
- Cultures should be obtained from eyes (conjunctiva), mouth, nasopharynx, urine and rectum.
- Further clinical and laboratory evaluation, as for suspected neonatal HSV infection, followed immediately by aciclovir therapy is mandated, if cultures are positive.⁸⁹ **GRADE A**

Breastfeeding and use of oral aciclovir

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.⁷⁰ **GRADE B**

GENITAL HSV INFECTION IN CHILDHOOD

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.¹¹⁰ The appearance of aphthous genital ulcers is also usually preceded by a history of fever, malaise and headache, but viral cultures are negative. Epstein-Barr virus and cytomegalovirus infections have also been reported to cause genital ulceration. Any genital ulcers should therefore be swabbed and cultured 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 culture or PCR 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. Also 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.¹¹¹

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 DSAC (Doctors for Sexual Abuse Care) doctor with special training in the area of recognition of child sexual abuse.

Adolescents

If genital herpes is present, a history suggesting aetiology should be carefully documented as for pre-adolescent children. During the interview it is important to ensure privacy. The adolescent should be asked whether they are sexually active and whether their involvement in sexual activity has been consensual. If non-consensual activity is reported and they are under the age of 17, then referral to the local Police, and Children Youth & Family (CYF) Sexual Abuse Team (SAT), should be seriously considered. It is preferable that this referral be made with the consent of the adolescent and his/her parents. If consent is not given and there are serious concerns about the safety of the young person then referral can be still be made under the protection of the Children & Young Persons' Act.

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

KEY POINT

All children with suspected genital herpes infection should be referred for specialist assessment and management.

Key Issues in Health Professionals' Counselling Management

Genital herpes is a common 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.¹¹²⁻¹¹⁵

EMOTIONAL FEELINGS RELATED TO THE DIAGNOSIS OF GENITAL HERPES

- Grief
- Guilt
- Embarrassment
- Sense of isolation
- Loss of assertiveness
- Unworthiness
- Shock
- Dirtiness
- Anger
- Sense of injustice
- Confusion
- Fear
- Surprise
- Denial

Good therapeutic management acknowledges these emotional responses and addresses the patient's feelings and concerns. The patient who presents with genital herpes for the first time is very vulnerable. The clinician/counsellor should acknowledge how difficult it must have been for the patient to present for treatment.¹¹⁶

Often the diagnosis is unexpected. The physician/counsellor should never be dismissive of the patient's disease; for some patients a diagnosis of genital herpes may be the most challenging health disruption they have ever experienced, given the stigma associated with sexually transmitted infections. The clinician/counsellor should show their empathy for the patient and allow the patient to talk. The counselling needs to take place at the patient's pace and not be rushed. If the patient is referred elsewhere for counselling, the diagnosing clinician should still address the acute issues at the first presentation.^{26,117}

Not all patients will want to take up the offer of counselling and support. Nevertheless, it is very important to offer it to all so that they can make this decision.

It is important that counselling and education about genital herpes take place in the appropriate setting. The following points should be considered:

- Comfortable setting
- Patient dressed
- Minimal interruptions
- Confidentiality assured
- Adequate time
- Attentive listening
- Avoidance of pejorative and prejudicial terms
- Empathic attitude
- Written information to take away and read
- Encouragement to return with list of questions

The education process may include answering questions about the natural history of the disease including the likely triggers for reactivation. Few solid data exist, but patient experience suggests that stress appears to be associated with recurrences in some patients. Advice on how to manage stress and lead a healthy lifestyle (exercise, good diet, etc.) should be given with care. Too much advice on lifestyle may be stressful for the patient, heightening feelings of guilt and the belief that the disease is self-inflicted.

Correct management of genital herpes is time-intensive. The likely impact of the disease on the patient and how well they are coping should be assessed. Psychological issues and concerns should start to be addressed at the first session. Many patients will be worried about the risk of having acquired HIV or other STIs or that they are seen to be promiscuous and may be worried about the doctor's opinion of them. In all cases (whether primary, non-primary or first symptomatic reactivation) the emotional consequences and perceived social stigma of the disease need to be addressed. The diagnosis of genital herpes will provoke a shock reaction in many patients and cause feelings such as guilt, anger, confusion and a sense of isolation.¹¹⁷⁻¹²¹ Patients with genital herpes are usually very concerned about the diagnosis of the disease, its potential impact on their lives and how their family and friends will view them. Common concerns of patients relate to the social stigma of the disease, transmitting the disease, fear of telling potential sexual partners who may then reject them and how it will affect their sex life and their social activities.¹¹⁴

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

COMMON CONCERNS OF PATIENTS WITH GENITAL HERPES

- Fear of discovery
- 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

Patients should be reassured that they are not alone in having genital herpes. The clinician or counsellor is encouraged to offer information about local herpes support groups and/or the NZ Herpes Foundation (toll free **0508 11 12 13**) or refer for specialist counselling to the local Sexual Health Clinic.

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.

- Approximately 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.
- 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. If this happens there is effective 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.
- Over 75% of people get herpes from a partner who has no history of ever having had herpes.
- Getting genital herpes in a long-term relationship does not assert that the other partner has been unfaithful. However, a full sexual health screen may be reassuring.
- Genital herpes is more common in women as it is easier to transmit from men to women, than from women to men.
- Oral to genital transmission of HSV-1 is very common. 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.
- Only a small percentage of people with genital herpes get frequent recurrences.
- There is a very effective oral antiviral medication if genital herpes is problematic.
- 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.

Herpes and Pregnancy (Key Information continued)

- 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.

Ensure patients have access to the NZHF patient pamphlets and/or the Helpline toll free 0508 11 12 13, or www.herpes.org.nz

References

1. Looker KJ, et al. An estimate of the global prevalence and incidence of herpes simplex virus type 2 infection. *Bull World Health Organ* 2008;86:805-812A.
2. Eberhart-Phillips J, et al. Herpes simplex type 2 infection in a cohort aged 21 years. *Sex Transm Infect*, 1998: 216-218.
3. Eberhart-Phillips JE, et al. Rising incidence and prevalence of herpes simplex type 2 infection in a cohort of 26 year old New Zealanders. *Sex Transm Infect* 2001;77(5): 353-357.
4. Dickson N, et al. Risk of herpes simplex virus type 2 acquisition increases over early adulthood: evidence from a cohort study. *Sex Transm Infect* 2007;83(2):87-90.
5. Haddow L, et al. Increase in rates of herpes simplex virus type 1 as a cause of anogenital herpes in western Sydney, Australia, between 1979 and 2003. *Sexually transmitted infections* 2006;82(3):255-259.
6. Gray E, et al. Herpes simplex type 1 versus Herpes simplex type 2 in anogenital herpes; a 10 year study from the Waikato region of New Zealand. *N Z Med J*, 2008:43-50.
7. Perkins N. personal communication, 2006.
8. Corey L, et al. Evaluation of new anti-infective drugs for the treatment of genital infections due to herpes simplex virus. *Clin Infect Dis* 1992;15(Suppl.1):S99-S107.
9. Wald A. Herpes simplex virus type 2 transmission: risk factors and virus shedding. *Herpes* 2004;11 Suppl 3: 130A-137A.
10. Langenberg A. Interrupting herpes simplex virus type 2 transmission: the role of condoms and microbicides. *Herpes*, 2004;147A-154A.
11. Martin E, et al. A pooled analysis of the effect of condoms in preventing HSV-2 acquisition. *Arch Intern Med*. 2009;169(13):1233-1240.
12. Cowan FM, et al. Relationship between antibodies to herpes simplex virus (HSV) and symptoms of HSV infection. *J Infect Dis* 1996;174(3):470-5.
13. da Silva LM, et al. Herpes simplex virus type 1 shedding in the oral cavity of seropositive patients. *Oral Dis* 2005; 11(1):13-6.
14. Wald A, et al. Oral shedding of herpes simplex virus type 2. *Sex Transm Infect*, 2004:272-6.
15. Wald A, et al. Frequent genital herpes simplex virus 2 shedding in immunocompetent women. Effect of acyclovir treatment. *J Clin Invest*, 1997:1092-7.
16. Corey L, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004;350(1):11-20.
17. Langenberg AGM, et al. A Prospective Study of New Infections with Herpes Simplex Virus Type 1 and Type 2. *N Engl J Med* 1999;341(19):1432-1438.
18. Scouler A. Using the evidence base on genital herpes: optimising the use of diagnostic tests and information provision. *Sex Transm Infect* 2002;78(3):160-165.
19. Post JC, Ehrlich GD. The Impact of the Polymerase Chain Reaction in Clinical Medicine. *JAMA* 2000;283(12): 1544-1546.
20. Bryson Y, et al. Treatment of first episodes of genital herpes simplex virus infection with oral acyclovir. A randomized double-blind controlled trial in normal subjects. *N Engl J Med* 1983;308(16):916-921.
21. Mertz GJ, et al. Double-blind placebo-controlled trial of oral acyclovir in first-episode genital herpes simplex virus infection. *JAMA* 1984;252(9):1147-1151.
22. Berger JR, Houff S. Neurological complications of herpes simplex virus type 2 infection. *Arch Neurol* 2008; 65(5):596-600.
23. Corey L, et al. Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med* 1983;98(6):958-72.
24. Engstrom M, et al. Prednisolone and valaciclovir in Bell's palsy: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet Neurol* 2008;7(11):993-1000.
25. Beauman JG. Genital herpes: a review. *American family physician* 2005;72(8):1527-34.
26. Carney O, et al. A prospective study of the psychological impact on patients with a first episode of genital herpes. *Sex Transm Infect* 1994;70(1):40-45.
27. Green J. Psychosocial issues in genital herpes management. *Herpes* 2004;11(3):60-2.
28. Wald A, et al. Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. *N Engl J Med*, 2000:844-50.
29. Tyring SK, et al. A randomized, placebo-controlled comparison of oral valacyclovir and acyclovir in immunocompetent patients with recurrent genital herpes infections. The Valaciclovir International Study Group. *Arch Dermatol*, 1998:185-91.
30. Aoki FY, et al. Single-day, patient-initiated famciclovir therapy for recurrent genital herpes: a randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2006;42(1):8-13.
31. Wald A, et al. Two-day regimen of acyclovir for treatment of recurrent genital herpes simplex virus type 2 infection. *Clin Infect Dis*, 2002:944-8.
32. Mertz GJ, et al. Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection. A multicenter double-blind trial. *JAMA* 1988; 260(2):201-206.
33. Kaplowitz LG, et al. Prolonged continuous acyclovir treatment of normal adults with frequently recurring genital herpes simplex virus infection. The Acyclovir Study Group. *JAMA* 1991;265(6):747-751.
34. Patel R, et al. Impact of suppressive antiviral therapy on the health related quality of life of patients with recurrent genital herpes infection. *Sex Transm Infect*, 1999:398-402.
35. Romanowski B, et al. Patients' preference of valacyclovir once-daily suppressive therapy versus twice-daily episodic therapy for recurrent genital herpes: a randomized study. *Sex Transm Dis*, 2003:226-31.
36. Tyring SK, et al. Oral famciclovir for the suppression of recurrent genital herpes: the combined data from two randomized controlled trials. *J Cutan Med Surg* 2003; 7(6):449-54.
37. Tyring SK, et al. Valacyclovir for herpes simplex virus infection: long-term safety and sustained efficacy after 20 years' experience with acyclovir. *J Infect Dis* 2002; 186 Suppl 1:S40-6.
38. Corey L, et al. A trial of topical acyclovir in genital herpes simplex virus infections. *N Engl J Med* 1982; 306(22):1313-1319.
39. Trottet L, et al. Are all aciclovir cream formulations bioequivalent? *Int J Pharm*, 2005:63-71.

40. Frederick DM, et al. Fatal disseminated herpes simplex virus infection in a previously healthy pregnant woman. A case report. *J Reprod Med* 2002;47(7):591-6.
41. Garland SM. Neonatal herpes simplex: Royal Women's Hospital 10-year experience with management guidelines for herpes in pregnancy. *Aust N Z J Obstet Gynaecol* 1992;32(4):331-4.
42. Brown ZA, et al. Genital herpes complicating pregnancy. *Obstet Gynecol* 2005;106(4):845-56.
43. Corey L, Wald, A. *Sexually Transmitted Diseases*. 3rd ed: McGraw-Hill, 1999.
44. Arvin A, Whitley, RJ., Gutierrez, KM. Herpes simplex infections. In: Remington JS KJWC, Baker CJ, editor. *Infectious diseases of the fetus and newborn infant*. 6th ed. Philadelphia: Elsevier Saunders, 2006:845-866.
45. Eskild A, et al. Herpes simplex virus type-2 infection in pregnancy: no risk of fetal death: results from a nested case-control study within 35,940 women. *BJOG* 2002;109(9):1030-5.
46. Brown ZA, et al. The Acquisition of Herpes Simplex Virus during Pregnancy. *N Engl J Med* 1997;337(8):509-516.
47. Brown ZA, et al. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA* 2003;289(2):203-9.
48. Randolph AG, et al. Cesarean delivery for women presenting with genital herpes lesions. Efficacy, risks, and costs. *JAMA* 1993;270(1):77-82.
49. Ozouaki F, et al. Genital shedding of herpes simplex virus type 2 in childbearing-aged and pregnant women living in Gabon. *Int J STD AIDS*, 2006:124-7.
50. Elder DE, et al. Neonatal herpes simplex infection: keys to early diagnosis. *J Paediatr Child Health* 1995;31(4):307-11.
51. Brown EL, et al. Effect of maternal herpes simplex virus (HSV) serostatus and HSV type on risk of neonatal herpes. *Acta obstetrica et gynecologica Scandinavica* 2007;86(5):523 - 529.
52. ACOG. ACOG practice bulletin. Management of herpes in pregnancy. Number 8 October 1999. Clinical management guidelines for obstetrician-gynecologists. *Int J Gynaecol Obstet* 2000;68(2):165-73.
53. Smith JR, et al. The management of herpes simplex virus infection in pregnancy. *Br J Obstet Gynaecol* 1998; 105(3):255-60.
54. Wald A. Genital herpes. *Clin Evid* 2002(8):1608-19.
55. Poeran J, et al. The incidence of neonatal herpes in The Netherlands. *J Clin Virol* 2008;42(4):321-5.
56. RCOG. Management of Genital Herpes in Pregnancy, 2002.
57. AHMF. Herpes Simplex in Pregnancy, 2004.
58. BASHH. 2007 National Guideline for the Management of Genital Herpes. BASHH 2008:1-26.
59. Gardella C, et al. Poor correlation between genital lesions and detection of herpes simplex virus in women in labor. *Obstet Gynecol* 2005;106(2):268-74.
60. Scott L, et al. Acyclovir suppression to prevent cesarean delivery after first-episode genital herpes. *Obstet Gynecol* 1996;87(1):69-73.
61. Brocklehurst P, et al. A randomised placebo controlled trial of suppressive acyclovir in late pregnancy in women with recurrent genital herpes infection. *Br J Obstet Gynaecol* 1998;105(3):275-80.
62. Watts DH, et al. A double-blind, randomized, placebo-controlled trial of acyclovir in late pregnancy for the reduction of herpes simplex virus shedding and cesarean delivery. *Am J Obstet Gynecol*, 2003:836-43.
63. Sheffield JS, et al. Acyclovir Prophylaxis to Prevent Herpes Simplex Virus Recurrence at Delivery: A Systematic Review. *Obstet Gynecol* 2003;102(6):1396-1403.
64. Ramsey P, Andrews W. Antiviral suppression to prevent recurrence of herpes simplex virus (HSV) infections in pregnancy: a meta analysis. *Am J Obstet Gynecol* 2003; 189(6):S98.
65. Arvin A, et al. Failure of antepartum maternal cultures to predict the infant's risk of exposure to herpes simplex virus at delivery. *N Engl J Med* 1986;315(13):796-800.
66. Kimberlin DW, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. *Pediatrics* 2001;108(2):223-9.
67. Sauerbrei A, Wutzler P. Herpes simplex and varicella-zoster virus infections during pregnancy: current concepts of prevention, diagnosis and therapy. Part 1: herpes simplex virus infections. *Med Microbiol Immunol* 2007;196(2):89-94.
68. Stone KM, et al. Pregnancy outcomes following systemic prenatal acyclovir exposure: Conclusions from the international acyclovir pregnancy registry, 1984-1999. *Birth Defects Res A Clin Mol Teratol* 2004;70(4):201-7.
69. Andrews WW, et al. Valacyclovir therapy to reduce recurrent genital herpes in pregnant women. *Am J Obstet Gynecol* 2006;194(3):774-81.
70. Sheffield JS, et al. Acyclovir concentrations in human breast milk after valaciclovir administration. *Am J Obstet Gynecol* 2002;186(1):100-2.
71. Major CA, et al. Expectant management of preterm premature rupture of membranes complicated by active recurrent genital herpes. *Am J Obstet Gynecol*, 2003:1551-4; discussion 1554-5.
72. Gardella C, et al. Risk factors for herpes simplex virus transmission to pregnant women: a couples study. *Am J Obstet Gynecol* 2005;193(6):1891-9.
73. Cleary KL, et al. Type-specific screening for asymptomatic herpes infection in pregnancy: a decision analysis. *BJOG* 2005;112(6):731-6.
74. Braig S, Chanzy B. Management of genital herpes during pregnancy: the French experience. *Herpes* 2004; 11(2):45-7.
75. Tookey P, Peckham CS. Neonatal herpes simplex virus infection in the British Isles. *Paediatr Perinat Epidemiol* 1996;10(4):432-42.
76. Malm G, et al. Neonatal herpes simplex: clinical findings and outcome in relation to type of maternal infection. *Acta Paediatr*, 1995:256-60.
77. Stone KM, et al. National surveillance for neonatal herpes simplex virus infections. *Sex Transm Dis* 1989;16(3): 152-6.
78. Kropp RY, et al. Neonatal herpes simplex virus infections in Canada: results of a 3-year national prospective study. *Pediatrics* 2006;117(6):1955-62.
79. Nahmias AJ. Neonatal HSV infection Part II: Obstetric considerations – a tale of hospitals in two cities (Seattle and Atlanta, USA). *Herpes* 2004;11(2):41-4.
80. Gardella C, et al. Neonatal herpes - the forgotten perinatal infection. *Sexually transmitted diseases* 2008; 35(1):22-4.
81. Morris A, et al. Australian Paediatric Surveillance Unit : progress report. *J Paediatr Child Health* 2002;38(1):8-15.

82. Freedman E, et al. Epidemiological, clinical and laboratory aids for the diagnosis of neonatal herpes – an Australian perspective. *Herpes* 2004;11(2):38-44.
83. Fleming DT, et al. Herpes Simplex Virus Type 2 in the United States, 1976 to 1994. *N Engl J Med* 1997;337(16):1105-1111.
84. Kimberlin DW. Herpes simplex virus infections of the newborn. *Seminars in perinatology* 2007.
85. Whitley RJ, et al. The natural history of herpes simplex virus infection of mother and newborn. *Pediatrics*, 1980:489-94.
86. Whitley RJ. Neonatal herpes simplex virus infections. *J Med Virol*, 1993:13-21.
87. Kimberlin DW. Herpes simplex virus infections in neonates and early childhood. *Semin Pediatr Infect Dis* 2005;16(4):271-81.
88. Whitley RJ, et al. Changing presentation of herpes simplex virus infection in neonates. *J Infect Dis*, 1988: 109-16.
89. Whitley R, et al. A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. *Infectious Diseases Collaborative Antiviral Study Group. N Engl J Med* 1991;324(7):444-9.
90. Nahmias AJ. Neonatal HSV infection Part I: continuing challenges. *Herpes* 2004;11(2):33-7.
91. Kimberlin DW, et al. Application of the polymerase chain reaction to the diagnosis and management of neonatal herpes simplex virus disease. *National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. J Infect Dis* 1996;174(6):1162-7.
92. Whitley R, et al. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. *The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. N Engl J Med* 1991; 324(7):450-4.
93. Kimberlin D, et al. Administration of oral acyclovir suppressive therapy after neonatal herpes simplex virus disease limited to the skin, eyes and mouth: results of a phase I/II trial. *Pediatr Infect Dis J* 1996;15(3):247-54.
94. Caviness AC, et al. Clinical and laboratory features of neonatal herpes simplex virus infection: a case-control study. *Pediatr Infect Dis J* 2008;27(5):425-30.
95. Caviness AC, et al. The prevalence of neonatal herpes simplex virus infection compared with serious bacterial illness in hospitalized neonates. *J Pediatr* 2008;153(2):164-9.
96. Diamond C, et al. Viremia in neonatal herpes simplex virus infections. *Pediatr Infect Dis J*, 1999:487-9.
97. Kimberlin DW. Neonatal herpes simplex infection. *Clin Microbiol Rev* 2004.
98. Kimberlin DW, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics* 2001;108(2):230-8.
99. Troendle-Atkins J, et al. Rapid diagnosis of herpes simplex virus encephalitis by using the polymerase chain reaction. *J Pediatr*, 1993:376-80.
100. Levin MJ, et al. Development of acyclovir-resistant herpes simplex virus early during the treatment of herpes neonatorum. *Pediatr Infect Dis J* 2001;20(11):1094-7.
101. Tiffany KF, et al. Improved neurodevelopmental outcomes following long-term high-dose oral acyclovir therapy in infants with central nervous system and disseminated herpes simplex disease. *Journal of perinatology : official journal of the California Perinatal Association* 2005;25(3):156-61.
102. Gutierrez K, Arvin AM. Long term antiviral suppression after treatment for neonatal herpes infection. *Pediatr Infect Dis J* 2003;22(4):371-2.
103. De Tiege X, et al. Limits of early diagnosis of herpes simplex encephalitis in children: a retrospective study of 38 cases. *Clin Infect Dis* 2003;36(10):1335-9.
104. Scott LL. Perinatal herpes: current status and obstetric management strategies. *Pediatr Infect Dis J* 1995;14(10): 827-32; discussion 832-5.
105. Sakaoka H, et al. Two outbreaks of herpes simplex virus type 1 nosocomial infection among newborns. *J Clin Microbiol* 1986;24(1):36-40.
106. Kimura H, et al. Relapse of neonatal herpes simplex virus infection. *Arch Dis Child Fetal Neonatal Ed*, 2003: F483-6.
107. Frenkel LM. Challenges in the diagnosis and management of neonatal herpes simplex virus encephalitis. *Pediatrics*, 2005:795-7.
108. Fonseca-Aten M, et al. Herpes simplex virus encephalitis during suppressive therapy with acyclovir in a premature infant. *Pediatrics* 2005;115(3):804-9.
109. Kimberlin DW. Neonatal HSV infections: the global picture. *Herpes* 2004;11(2):31-2.
110. Huppert JS, et al. Vulvar ulcers in young females: a manifestation of aphthosis. *J Pediatr Adolesc Gynecol* 2006;19(3):195-204.
111. Kelly P, Koh J. Sexually transmitted infections in alleged sexual abuse of children and adolescents. *J Paediatr Child Health* 2006;42(7-8):434-40.
112. Fortenberry JD, et al. Relationships of Stigma and Shame to Gonorrhea and HIV Screening. *Am J Public Health* 2002;92(3):378-381.
113. Fortenberry JD. The effects of stigma on genital herpes care-seeking behaviours. *Herpes* 2004;11(1):8-11.
114. Green J, et al. Determinants of disclosure of genital herpes to partners. *Sex Transm Infect*, 2003:42-44.
115. Patel R. Supporting the patient with genital HSV infection. *Herpes* 2004;11(3):87-92.
116. Sankar P, Jones NL. To tell or not to tell: primary care patients' disclosure deliberations. *Arch Intern Med* 2005;165(20):2378-83.
117. Nack A. Damaged goods: Women managing the stigma of STD's. *Deviant Behavior: An Interdisciplinary Journal* 2000;21(2):95-121.
118. Breitkopf CR. The theoretical basis of stigma as applied to genital herpes. *Herpes* 2004;11(1):4-7.
119. Inhorn M. Genital herpes: An ethnographic inquiry into being discreditable in American society. *Med Anthropology Quarterly* 1986;17:59-63.
120. Lee J, Craft, E. Protecting oneself from a stigmatized disease... once one has it. *Deviant Behavior: An Interdisciplinary Journal* 2002;23(3):267-299.
121. Swanson JM, et al. Clinical features and psychosocial factors in young adults with genital herpes. *Image J Nurs Sch* 1995;27(1):16-22.

Members of the Professional Advisory Board (PAB) of the Viral Sexually Transmitted Infection Education Foundation 2009

Sexual Health Physicians

Dr Jane Morgan (Chairperson)

Dr Edward Coughlan

Dr Janet Say

Dr Nicky Perkins

NZ Dermatological Society

Dr Darian Rowan

NZ Committee of the Royal Australian and New Zealand College of Obstetrics and Gynaecology

Dr Ron Jones (Chairperson, NZHPV Project)

Dr Anne Robertson

Dr Richard Speed

Paediatric Society of New Zealand

Dr Lesley Voss

NZ College of General Practitioners

Dr Phil Jacobs

Virology

Dr Kitty Croxson

Family Planning

Dr Christine Roke

Counselling

Catherine Cook

Nursing

Claire Hurst

Georgina McPherson (NZHPV Project)

Jessie Crawford

Patient Advocate

Jo Patrick

Project Co-ordinator

Claire Hurst, PO Box 2437, Auckland

Tel: 09 433 6526 Fax: 09 360 2835 Email: info@herpes.org.nz

Index

Barrier Methods	6
Condom Use	6
Congenital Infection	22
Costs of Antivirals	20
Counselling	
First Episode	13
Recurrences	16
Key Issues	40
Common Concerns	41
Key Information.....	42
Culture	7
Diagnosis	
First Episode	7
Recurrences	7
Diagnostic Procedures	7
Education	
First Episode	12
Recurrences	17
Epidemiology	4
Episodic Therapy	17
Examination	
First Episode	11
Recurrences	15
Follow-up	13
History and Examination	
First Episode	11
Recurrences	15
Key Information to Give to Patients in Counselling	42
Laboratory Testing Methods.....	7
Management in Childhood	39
Management of First Episode	10
Algorithm	14
Management in Pregnancy	
First Episode	24
Algorithm	25
Recurrences	27
Algorithm	26
Use of Aciclovir in Pregnancy and Breastfeeding	27
Special Cases – Male Partner HSV Positive	28
Neonatal Herpes	29
Pharmacological Treatment	
First Episode	12
Recurrences	17
Pharmacological Treatment in Pregnancy	
First Episode	24
Recurrences	27
Serology Testing	8
Suppressive Therapy	18
Transmission	5
Treatment – Summary Statements	20

International Resources

The International Herpes Management Forum (IHMF)

Established in 1993 to improve the awareness, understanding, counselling and management of HSV infections.

The IHMF website publicises IHMF activities, press releases and disseminates information published in the *Management Strategies in Herpes* series.

For further information contact:

IHMF Secretariat

Wicker House

High Street

Worthing

West Sussex, BN11 1DJ

UNITED KINGDOM

Tel: +44 (0) 1903 288188

Fax: +44 (0) 1903 210296

www.ihmf.org

The International Herpes Alliance (IHA)

A patient-driven sister organisation to the IHMF, established in 1999 to ensure patients receive optimal management.

The IHA provides patient focussed information and referral to regional herpes support groups.

www.herpesalliance.org

*Supported by an educational grant from
New Zealand District Health Boards*