

Epidemiology

ALTHOUGH infection with HSV viruses is common and causes a wide range of clinical syndromes, most infection is actually asymptomatic, occurring in healthy children as well as adults. Clinical disease from herpes infection is more severe and extensive in the immunocompromised.

Traditionally HSV-2 has been associated with genital infection and HSV-1 with oral mucocutaneous disease. There is tropism for type 1 to infect the trigeminal ganglion (causing gingivostomatitis in young children, or



herpes labialis, commonly known as cold sores, in all ages), and for type 2 to infect the sacral ganglion (causing genital herpes). However, these viruses may 'mix and match' anatomical sites, with either type infecting 'above or below the waist'.

In recent years, there has been a change in the epidemiology of genital HSV infection, with significantly higher rates of HSV-1 infection, especially in those from higher socioeconomic groups. This is particularly evident in patients aged 20

and under presenting with genital herpes, in whom HSV-1 may be responsible for up to 70% of cases. This reflects the trend to a shift in seroconversion to HSV-1 from early childhood to young adulthood (see next section).

Significant increases have also been seen in the prevalence of HSV-2 infection in different communities worldwide. For example, in the US between 1978 and 1992 there was a 30% increase in seropositivity for HSV-2 in adults, with a marked shift towards younger age of

acquisition. (This equates to a 30% increase over time, in the era of HIV and safe sex.)

Similar trends have been observed in other countries, including Australia. Reports in pregnant women from various geographical regions also show wide-ranging seroprevalence rates, ranging from 6% to 33%, with rates in Australian antenatal settings being consistently around 14%.^{1,2}

Seroprevalence increases with the number of partners. For example, Kent et al reported a seroprevalence rate of 33% for HSV-2 anti-

bodies in partners of patients with genital herpes in a Melbourne population.³

In another study from Melbourne, high rates of seroprevalence for HSV-2 were found in men who have sex with men (43.0%). In this group the number of HIV-antibody-positive men (61%) was more than twice that of HIV-antibody-negative men (28%) and most men in this group had no awareness of their infection with HSV-2. There was no significant difference for HSV-1 (73%) between the subgroups.⁴

Pathogenesis — how is the virus spread?

PRIMARY HSV-1 infection occurs when a susceptible person, usually a young child, comes into close contact with a person, such as a family member, shedding HSV. Transmission is usually asymptomatic through shedding in saliva or direct contact with a person with herpes labialis.

The primary infection in children is usually asymptomatic, although uncommonly it may present as gingivostomatitis, sometimes severe enough to require hospitalisation for fluid replacement. Symptomatic primary infection is more likely to occur in adolescents and adults.

Seropositivity correlates with the socioeconomic background of the population — in lower socioeconomic groups most HSV-1 seroconversions occur in the first few years of life, and by adulthood 80% or more have HSV-1 antibodies.

However, with improved standards of living, HSV-1 seroprevalence in many developed countries is falling, with a concomitant rise in primary HSV-1 genital infection in young adults. This increasing seroprevalence in adolescents may be due to increasing orogenital contact in susceptible populations.

HSV-2 infection is usually acquired through sexual contact in early adulthood, even in those with pre-existing HSV-1 infection, and is more likely than genital HSV-1 in this group because of the specific tropism for the two serotypes to infect the two different dorsal ganglia.

Thus, clinical infection with one type of HSV is often an initial infection (defined as having pre-existing antibodies to HSV of the non-infecting type) rather than a primary infection (when an individual acquires HSV-2 infection in the absence of antibodies for HSV-1 and 2).

Similarly, prior asymptomatic HSV-2 infection can be followed by symptomatic genital HSV-1 infection, although, because HSV-1 is usually picked up earlier in life, the reverse situation is more common.

The terminology can be confusing. It may be preferable to refer to primary infection with one serotype with or without previous and pre-existing antibodies to the other type.

The number of lifetime sexual partners is an independent risk for HSV-2 infection, and women are generally infected at an earlier age than men. Most transmission occurs via asymptomatic viral shedding from the genital skin or secretions of partners.

One-third of new genital HSV cases occurring in adolescents are thought to be acquired genitally, one-third orally, and the other third from an undefined source. HSV-2 usually causes genital herpes but may uncommonly cause herpes labialis or pharyngitis.

Both HSV-1 and HSV-2 infections may recur clinically. Genital infections caused by HSV-2 are more likely to recur than those caused by HSV-1, and occur more often in the months after primary infection.

Most transmission occurs via asymptomatic viral shedding from the genital skin or secretions of partners.

Common clinical presentations

Orofacial infection

PRIMARY HSV infection of the oropharynx may present as gingivostomatitis, with multiple, shallow painful ulcers on the buccal mucosa, under the tongue and even on the hard palate (making it difficult to differentiate from herpangina caused by coxsackie viruses) or, more often, as an isolated herpes labialis (figure 2).

There may be accompanying high fevers and regional (submandibular) lymphadenopathy. Autoinoculation from the primary lesions may occur elsewhere on the body (eg, herpetic whitlow or HSV keratoconjunctivitis), although this is rare with recurrences.

Recurrent orolabial infections (herpes labialis, or cold sores) may be triggered by stimuli such as fever, stress, cold, menstruation and ultraviolet radiation. They usually occur on the lips but may develop at other sites on the face, including the inside of the nose. There may be a prodromal tingling or itching at the site of recurrence.

Asymptomatic intermittent oral shedding of HSV in saliva is common and no doubt explains much of the unrecognised transmission of the virus.

Lesions may be widespread in people with eczema (eczema herpeticum, figure 3) and may be severe and/or generalised in the immunocompromised.

Genital infection

Symptomatic primary genital infection can be moderately severe (more likely in women) and last for several weeks. Common symptoms and signs include fever, dysuria, local pain, widespread genital ulceration, inguinal lymphadenopathy, malaise and headache.

Initially, typical blisters may not be evident in women. Local vulval oedema may be all that is seen (figure 4) followed several days later by characteristic shallow ulcers surrounded by erythema (figure 5, page 30).

Women may have no external lesions but present with symptoms of cervicitis, such as a profuse watery discharge. Examination of the cervix shows infection that may resemble neoplasia (figure 6, page 30).

HSV lesions may become secondarily infected by bacteria and/or fungi. Sacral radiculomyelitis may cause urinary retention and sacral neuralgia. Perianal infections and proctitis may also be seen, especially in men who have sex with men.

In contrast to the situation in women, vesicles may be seen at the outset in men (figure 7, page 30) or present as shallow ulcers (figure 8, page 30).

Extragenital sites

Depending on the site of entry of the primary infection, lesions may occur in uncommon sites, for example herpes gladiatorum (figure 9, page 30) in sports players or whitlow in a healthcare worker (figure 10, page 30).

Occasionally genital infections may occur only as pustular or blistering lesions on the thigh or buttock (figure 11, page 30) and be associated with sacral neuralgia.

About 20% of HSV-2-seropositive patients have overt recurrences of genital herpes. Recurrences are more likely to occur in the first six months

Figure 2: HSV stomatitis with widespread ulceration involving the buccal mucosa, typical of primary HSV-1 in a young child.

(Image courtesy of Dr Dominic Dwyer.)



Figure 3: Eczema herpeticum due to HSV-1 in a pregnant patient.



Figure 4: Primary HSV genital infection without typical widespread blistering. Note the marked labial oedema with telltale lesions of HSV on the upper thigh and inner labia, only seen on careful examination after parting the labia.



after the primary episode and the lesions are more often limited in area and severity than those of primary infection (figures 5, 7, page 30).

A further 60% of HSV-2-seropositive patients have genital lesions that they do not recognise as herpes, especially if the lesions are small or atypical (fissures or red patches). However, those with misdiagnosed, unrecognised or atypical lesions can learn to recognise them with appropriate training. The remaining 20% have truly asymptomatic viral shedding (figure 12, page 30).

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Genital HSV-2 recurrences usually last longer than oral HSV-1 recurrences and are more frequent in the 6-12 months after initial infection.

Neonatal infection

Neonatal infection varies in prevalence around the world. It ranges from one in 2500 live births in the US to one in 13,000 births in one maternity hospital in Australia, and a reported incidence on a population-wide basis in Australia of 3.9/100,000 live births.⁵ This range reflects the wide variation in HSV-2 seropositivity in different regions.

Most neonatal HSV infection is transmitted during birth (intrapartum) through an infected birth canal, often associated with asymptomatic maternal genital viral shedding. Neonatal HSV may uncommonly occur in the postpartum period through direct contact with oral lesions or shedding from the mother, siblings or healthcare workers.

On rare occasions, it is transmitted antepartum (ie, congenital infection) from maternal genital infection either via the ascending route through intact or ruptured membranes, or, rarely, through viraemia associated with disseminated infection in the mother. Infection is caused by HSV-1 and HSV-2 in about equal numbers.

Primary maternal genital herpes (symptomatic or asymptomatic) in the last trimester, particularly around the time of labour, has a high rate of transmission to infants (about 50%).

Neonatal HSV may also be acquired from symptomatic or asymptomatic recurrences in the mother. Most babies with neonatal herpes are born to mothers with unrecognised genital herpes and asymptomatic viral shedding (figure 13).

HSV-1 is more likely than HSV-2 to be reactivated in the genital tract and transmitted to the infant, even though clinical recurrences are more likely to be seen with HSV-2.

The clinical picture ranges from disease localised to the skin, eyes and mouth, to encephalitis and disseminated disease. Skin lesions may be present in small numbers, be atypical in appearance or not evident (figures 13, 14, page 31).

Infants with skin disease, if untreated, develop disseminated disease or encephalitis in only about two-thirds of cases. Therefore a full workup, with a CSF examination plus EDTA-treated blood for HSV detection by PCR, is recommended for suspected neonatal skin disease. Neonatal herpes may recur, necessitating consideration of long-term suppressive antiviral therapy.

Figure 5: Herpes lesions — shallow ulcers with surrounding erythema on the inner labia.



Figure 6: HSV cervicitis with no external lesions.



Figure 7: Recurrent genital herpes showing typical small vesicles. Although this was caused by HSV-2, the viral type cannot be distinguished clinically.

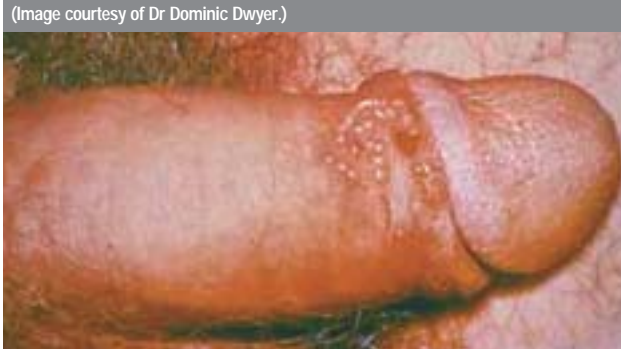


Figure 8: Typical shallow ulcers with typical erythematous margins. (Image courtesy of Dr D Jacobs.)



Figure 9: Herpes gladiatorum. (Image courtesy of Prof S Sacks.)



Genital herpes in pregnancy

Management of genital herpes in pregnant women is complex. The main aim is preventing neonatal transmission during birth.

The risk is low for women with recurrent HSV (ie, documented HSV before becoming pregnant). In these cases, the risk of infant infection is greatest (< 1-3%) when the mother

Figure 10: A whitlow.



Figure 11: Typical pustular lesions of HSV-2 in the sacral neuronal distribution of the buttock.



Figure 12: Diagnosis of genital HSV.

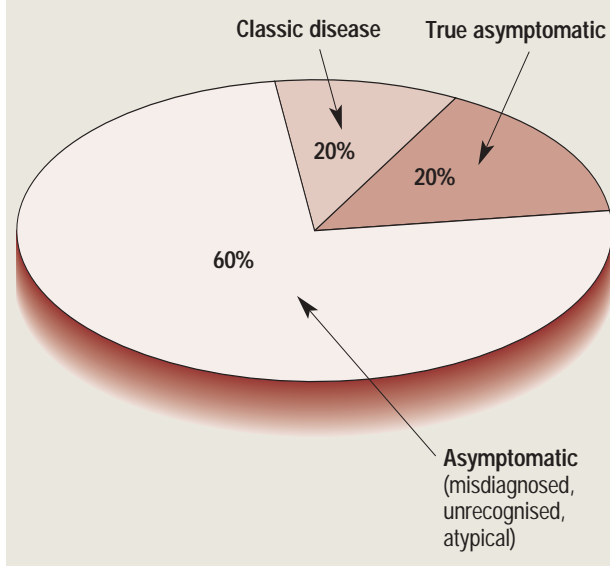


Figure 13: Neonatal HSV. A large, broken vesicular lesion on the underside of the foot of an infant born prematurely, with intrauterine growth retardation and multiple skin vesicles, to a mother who had a recent, non-specific febrile illness without genital symptoms, later confirmed by type-specific serology as primary genital HSV-1.



is shedding the virus in the birth canal, ie, when she has clinically evident genital lesions. A caesarean section is generally indicated, although, because the risk is low, some obstetricians would cover the lesions and allow a vaginal delivery.

The risk of infant infection when the mother is asymptotically shedding the virus in the birth canal is thought

to be lower, in the range of 0.02-3%. Although the risk seems similar in both groups, different ranges are reported in different studies.

When clinical lesions are present, there is a greater viral load and a greater opportunity for transmission. Therefore, if there are no lesions at delivery in a woman with a history of genital herpes, vaginal delivery is appropriate.

Collecting virus cultures during the antenatal period is not predictive of viral shedding intrapartum and is not recommended.

In first-episode or initial infection in a pregnant woman it is important to determine whether the infection is a true primary infection or a recurrent episode with her first clinical lesions occurring during that pregnancy.

For a primary infection, when the mother has seroconverted to the infecting HSV serotype, detected well before 30-34 weeks of gestation, and has no genital lesions in labour, normal vaginal delivery should be allowed.

For women with a primary infection occurring after this period, the development of protective antibodies will not be complete or protective to the unborn child. Antiviral therapy is advocated for these women, and delivery by caesarean section.

Use of forceps, vacuum and suction should be avoided in all cases of genital HSV, whether first episode, initial or recurrent.

In managing a neonate born to a mother with primary-episode or recurrent genital herpes lesions present at the onset of labour (seroconverted well before delivery), specimens should be collected from the baby for virus culture (eg, nose, throat, conjunctival and umbilical swabs, urine and stool).

Observe for signs of sepsis and collect EDTA-treated blood and CSF for HSV PCR if signs of sepsis and/or meningitis occur.

Because asymptomatic neonatal infection usually develops into overt disease, the infant should be treated with IV aciclovir (Aciclovir, Acihexal, Lovir, Zovirax) if cultures are positive, even if there are no clinical signs.

If a baby is asymptomatic and cultures are negative, parents should be advised to report early signs of infection in the baby, such as lethargy, fever, poor feeding or skin lesions.

In babies born to mothers with a history of genital herpes but no symptoms at delivery, routine virus culture of the newborn is not recommended, but parents should be advised to report early signs of infection. Routine antenatal screening for HSV antibodies is not indicated.

When the mother has an initial infection (no antibodies against the HSV serotype) or a severe HSV infection close to delivery, or the infant has clinical signs of neonatal HSV:

- Perform swabs at birth on the eye, throat, umbilicus and rectum and collect a urine sample.
- Arrange HSV PCR on blood and CSF.
- Conduct a full blood examination (for low

platelets) and LFTs (elevated).

- Perform an eye examination for corneal ulcers or keratitis.

Ophthalmic infection

In HSV-1 keratitis, patients may complain of pain, photophobia, blurred vision, tearing and or redness, and the infection may be recognised on slit-lamp examination as a unilateral dendritic (branching) erosion or ulcer (figure 15).

Initial infection occurs at the corneal epithelium, where, after replication, the virus enters the sensory nerve endings, travels along axons and becomes latent in the trigeminal ganglion.

Ocular HSV-1 infection is the major cause of

non-traumatic blindness in developed countries. If recurrences are severe and frequent, they may involve deeper corneal layers, leading to interstitial or disciform keratitis and possible loss of vision. Suppressive therapy should therefore be considered in conjunction with specialist ophthalmic care.

Encephalitis

Adult herpes encephalitis is a severe focal encephalitis caused by direct viral invasion of the brain (usually by HSV-1), typically involving the frontotemporal and parietal areas. It is uncommon (about one in one million of the population a year) and occurs in all age groups.

Figure 14: Pustular lesions due to HSV-1 seen on the scalp of a newborn. The lesions were asymptomatic in the mother at delivery.



Figure 15: Typical herpetic dendritic ulcer of the eye. (Courtesy of Dr Luba Robman, Centre for Eye Research, Melbourne.)



Diagnosis

Viral detection

WHEN possible, all patients with suspected HSV (especially genital herpes) who require antiviral therapy should have a definitive diagnosis. However, laboratory confirmation should not delay appropriate therapy.

Until recently, virus isolation by culture was the laboratory gold standard. Culture is most sensitive when lesions are fresh and moist. A fresh vesicular lesion should be ruptured, and the fluid collected using a dacron/rayon-tipped plastic swab and placed into appropriate viral transport medium.

The specimen should be stored at 4°C (not frozen) and processed immediately or as early as possible within 48 hours. Cultures can be taken from other mucocutaneous sites such as endocervical, anogenital, throat and conjunctival sites. In the neonate and/or in suspected disseminated infection, urine, CSF and EDTA-treated blood should be taken for culture.

Time to diagnosis is about 48 hours, but may be up to 10 days. A modified culture using shell vial or spin amplification can reduce the time to diagnosis to 1-3 days.

Direct antigen detection methods are more rapid than virus isolation and more sen-

sitive than culture. Indirect fluorescent antibody detection performed on samples from skin or mucous membrane lesions may also determine serotype and has a sensitivity of about 95%. It can also be used to confirm typing on cultures (figure 16).

Lesion samples for this technique require cells, not just vesicular fluid, to be collected. After the vesicle is broken, the swab must be rubbed firmly over the lesion to collect cells. Time to result is one day.

Genomic detection by PCR, including real-time PCR, is highly sensitive and is the technique of choice for examining lesions that have begun to crust, as well as CSF in suspected encephalitis or meningoencephalitis.

PCR diagnosis takes anywhere from a few hours (RT-PCR) to 1-7 days, depending on the frequency of the PCR runs within the diagnostic laboratory. It is increasingly used to diagnose genital infection.

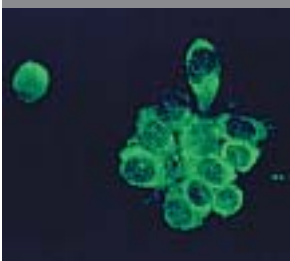
PCR testing has confirmed that asymptomatic shedding from genital sites is far more frequent than indicated from research using viral cultures and also that it occurs more frequently than clinical recurrences.

In recent HSV vaccine trials involving about 36,000 patients, PCR was found to

Who should be tested with type-specific serology?

- Those whose lesion culture is negative or whose culture type is unknown (important for prognosis).
- Those whose lesion culture is negative, but whose aetiology is undetermined (sensitivity is poor for lesion culture in about 40% of recurrent infections).
- Those with recurrent symptoms suggestive of HSV.
- Those not recognising signs or symptoms as being due to HSV.
- High-risk patients:
 - Partner is positive.
 - Patient has other STI or has HIV.
 - Pregnant women with unrecognised HSV-2.
 - Those at risk for HSV-1 and 2 seroconversion.

Figure 16: HSV in culture confirmed as HSV-2 by indirect fluorescent antibody detection using monoclonal antibody.



be more sensitive than culture by a factor of four (12.2% recurrences detected by PCR versus 3% by culture).

HSV can also be detected in tissue specimens such as brain by microscopy (haematoxylin-eosin staining or Pap staining of ectocervical smears) and immunohistochemistry. However, these techniques have largely been superseded by PCR, which is well adapted for samples requiring less invasive collection.

Serology

Antibody assays

HSV antibody testing can distinguish between primary infections and recurrent disease only if pre- and post-lesion sera are available. If a patient has already been infected with a strain of

HSV not causing the current infection, diagnosing primary infection by seroconversion measuring total HSV antibody is not useful.

HSV type-specific antibody assays are now available, although they vary in reliability. The gold standard of type-specific serology is Western blot assay seroconversion, which can take up to 12 weeks from the primary infection, although sero-reversion is rare.

Western blot shows progressive evolution of bands with time, virtually giving a personal profile of band results, allowing one to define how a particular infection may have been transmitted. The technique is not readily available in diagnostic laboratories — only in reference laboratories.

Various enzyme immunoassays are available, most of which now use recombinant antigens. Their sensitivity varies depending on the antigen preparation.

Type-specific enzyme immunoassays can be used to determine seroprevalence in populations and confirm new infections (for example, HSV-2 genital infection against a background of HSV-1 antibodies from childhood herpes labialis). This can aid risk assessment of HSV seroconversion in pregnancy (see Author's case study — Genital

herpes in pregnancy, page 32) and determine previous exposure to either virus.

Of the various commercial assays, the following are approved by the Food and Drug Administration in the US, have a high sensitivity (especially for HSV-2, less so for HSV-1 for unknown reasons), are type-specific IgG-based kits and are of diagnostic value:

- HerpesSelect Focus — ELISA or Immunoblot (Focus) (HSV-1 and HSV-2).
- POCKit HSV-2 — (Biokit) (HSV-2).
- Captia ELISA (Trinity) (HSV-1 and HSV-2).

Median time to seroconversion is about 20 days for Focus and shorter for POCKit. Sero-reversions can occur.

HSV type-specific IgM can be detected by enzyme immunoassays during acute infection, usually within a few days of appearance of clinical lesions, but possibly taking up to three weeks.

As an isolated finding, an HSV type-specific IgM after an episode of clinical recurrence does not necessarily mean a recent primary infection — it can be found during a recurrence from a past infection. Individual episodes of recurrent genital herpes cannot be reliably diagnosed by serological testing.

Treatment and prevention

Non-genital herpes

HERPES labialis in healthy individuals rarely requires oral treatment. Topical antivirals may limit disease if used early, particularly if the patient has a prodrome and can apply the cream rapidly.

In cases of gingivostomatitis, aciclovir IV should be used initially (10mg/kg tds). Ocular HSV infections require antiviral therapy to prevent scarring and are best managed in conjunction with an ophthalmologist.

Genital herpes

Oral agents available in Australia for genital HSV include the nucleoside analogues aciclovir, famciclovir (Famvir) and valaciclovir (Valtrex) (table 1). These agents are effective in acute first-episode infection and in recurrent genital herpes, either as episodic therapy

(intermittent use at the onset of a recurrence) or suppressive therapy (continuous use to reduce the frequency of recurrences).

Antiviral therapy reduces the number of lesions and, when used for suppression, reduces the frequency of recurrences and virus shedding significantly. Although transmission is not completely prevented.

Early treatment (within 72 hours of development of lesions) is necessary for maximal effect, particularly in recurrences. Patients using episodic treatment should start therapy during the prodrome. Unfortunately, antivirals do not prevent the development of neural latency.

Aciclovir has been widely used for more than 20 years and has a good

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Table 1: Indications and treatment regimens for antiviral agents in HSV infection

Infection	Treatment
Non-genital HSV (initial or recurrent)	<ul style="list-style-type: none"> ■ Aciclovir 200mg orally five times daily for five days; or ■ (Herpes labialis): aciclovir 5% topically four-hourly while awake, for five days; or ■ (HSV keratitis): aciclovir 3% ophthalmic ointment five times daily for 14 days or for at least three days after healing
Genital HSV (initial)	<ul style="list-style-type: none"> ■ Aciclovir 400mg orally eight-hourly daily for five days; or ■ Famciclovir 125mg orally 12-hourly for five days; or ■ Valaciclovir 500mg orally twice daily for five days
Genital HSV (recurrent episode)	As for initial genital HSV but valaciclovir 500mg orally for three days
Genital HSV (suppression of recurrences)	<ul style="list-style-type: none"> ■ Aciclovir 200mg orally 12-hourly daily for up to six months; or ■ Famciclovir 250mg orally twice-daily for up to six months; or ■ Valaciclovir 500mg orally daily for up to six months ■ In pregnancy, consider suppressive aciclovir 400mg, but orally tds from 36 weeks' gestation for those with multiple clinical recurrences
Severe initial HSV, HSV encephalitis or disseminated HSV	<ul style="list-style-type: none"> ■ Aciclovir 10mg/kg IV three times daily for at least 14 days ■ In neonates use aciclovir 20mg/kg IV eight-hourly for 21 days. Long-term aciclovir as suppressive therapy may be needed for recurrent encephalitis or recurrent neonatal HSV episodes

from previous page safety profile. Laboratory-confirmed resistance to this drug is rare in the immunocompetent host; treatment failure is more likely to result from non-compliance or problems with drug absorption (for example, diarrhoea).

The decision to use antivirals for suppressing recurrences of genital herpes needs to be taken on an individual basis. The severity and number of recurrences and their effects on the patient's physical and mental wellbeing need to be assessed. In general, more than six recurrences a year is a reasonable threshold at which to consider use of suppressive therapy for 3-6 months.

Suppression can allow the patient a 'herpes-free period' so they can better adjust to having HSV infection, get used to what represents a relatively minor recurrence, and in some cases break the cycle of infection.

Severe HSV infection (for example, encephalitis and herpes in the neonate or

immunocompromised patient) requires hospital treatment. Intravenous aciclovir is the mainstay treatment, possibly with follow-up oral antivirals depending on the clinical problem.

A high dose of 20mg/kg/day in a 1-2-hour infusion should be given for neonatal infection. Treatment at this dose should be continued for at least 14 days, then case-dependent decisions regarding continuing treatment or changing antivirals made after assessing the newborn.

In neonates with disseminated HSV infection, recurrences and unusual presentations are not uncommon. They may require prolonged treatment with aciclovir for at least 21 days after the last positive culture result, and for at least 3-4 months to as long as a year if infection recurs.

Foscavir (Foscarnet) or vidarabine is used for aciclovir-resistant HSV in immunocompromised patients. Ganciclovir (Cymevene, Vitrasert) is also effective against HSV, as well as varicella-zoster

virus and cytomegalovirus.

Antivirals are just one component of the management of patients with newly diagnosed genital herpes.

Significant emotional and psychosexual disturbance can result from a diagnosis of genital HSV. It is therefore important to resolve potential myths and misconceptions when the diagnosis is made to reduce the frequency of such outcomes.

Underscoring the commonality of HSV-2 infection in our community is the fact that one in seven healthy pregnant patients is seropositive, although most would not be aware of their status.

A person may have been exposed to HSV, shed the virus unknowingly and transmitted it to their partner, so an initial episode does not necessarily mean that the partner has been unfaithful.

Although patients often want to know the source of the infection, this cannot always be determined. They are also often concerned

about the risk of transmission to other parts of their bodies, their partners, children and unborn children.

People with genital HSV need accurate information and should be involved in management decisions and, if necessary, they (and their partners) referred to specialists or counsellors. Psychological sequelae are less likely to be an issue when the virus and infection are well explained.

Education about the symptoms of recurrent infection is important, as many people do not recognise that HSV is the cause of minor genital symptoms such as fissures, non-vesicular lesions, burning, tingling or a 'cut feeling', dysuria and itching.

Patients with laboratory-confirmed infections and their partners also require screening for other sexually transmitted infections (syphilis, HIV, hepatitis B, chlamydia, gonorrhoea and trichomoniasis).

When used appropriately, condoms can reduce transmission by about 50%.

More information on herpes is available at the Australian Herpes Management Forum web site: www.ahmf.com.au.

Vaccines

Vaccines for genital herpes have been under development for years, with results from various clinical trials being largely disappointing overall.

One recent trial with vaccine containing a truncated form of recombinant HSV-2 glycoprotein D plus alum and monophosphoryl lipid A (MPL) adjuvants elicited humoral and cell-mediated responses as well as being protective for the occurrences of genital herpes disease in some women (those seronegative for both HSV-1 and 2), but not in men (irrespective of HSV serological status) or women with pre-existing HSV-1 seropositivity.⁶

Other vaccine candidates are DNA vaccine, antigenic vaccine and a live mutant strain of the type 2 virus, d15-29, but we await data from clinical trials.

Author's case studies

Genital herpes in pregnancy

Presentation

A 25-year-old woman presented to the emergency department with vaginal discharge, itching and dysuria. She had been seen by her GP and given clotrimazole cream, without relief. There was no clinical exam and no genital swabs were collected. Her menstrual period was overdue by several weeks.

Examination

Genital examination showed vulval swelling, plus ulcerative lesions on the inner thigh (see figure 4, page 29).

Investigations

A pregnancy test was positive. Culture of the vulva was positive for *Candida albicans* as well as HSV-2.

Management

The patient was given clotrimazole cream and blood was taken for HSV antibody testing.

The test for total HSV antibodies was positive, and type-specific antibody testing showed antibodies to HSV-1 only. A repeat blood in several weeks time showed seroconversion to HSV-2.

The patient was counselled that:

- She'd had a recent HSV-2 infection, plus thrush.
- HSV transmission to the baby usually occurred at delivery, but the risk of transmission was very low if no lesions were present during labour.
- If symptoms or signs of a recurrence occurred at delivery, a caesarean section would be performed to minimise risk of transmission.

The baby was closely monitored for HSV infection (including swabs taken for viral culture or PCR) and was to be treated with antiviral therapy only if there was evidence of clinical HSV infection.



The risk of transmission to the newborn is very low if no lesions are present during labour.

Take-home points

- It is always important to confirm a clinical diagnosis of genital herpes.
- Neonatal HSV infection occurs in one in 11,000-13,000 deliveries in Australia, with the risk highest in primary infection just before delivery (about 33%), compared with recurrences (< 1%) and asymptomatic infection.
- Careful clinical examination at the time of delivery is probably the best way to determine if there is active genital infection, although asymptomatic viral shedding may occur.
- Aciclovir therapy from 36 weeks of pregnancy can be considered in women with confirmed recurrent genital herpes.

A young woman with a first infection

Presentation

AN 18-year-old woman presents to her GP with profuse watery vaginal discharge and dysuria. She has a regular boyfriend of four months and no previous partners. She is extremely anxious and concerned that her

boyfriend has been unfaithful to her, as she believes he has had no sexual partners before her.

Examination

Genital examination shows a few ulcerative lesions on the inner labia minora, plus significant oedema and inguinal lymphadenopathy.

Investigations

A swab of the labial lesion was collected for microscopy and culture.

Management

It is important to ensure a definitive diagnosis is made in such a setting, for example, microscopy and culture of the lesions to ensure this is not a case of *Candida albicans* infection. Sexual and travel histories should be taken to ensure uncommon pathologies (for example, syphilis, chancroid) are not a possibility.

Discuss with the patient the fact that about one in 20 healthy sexually active people may have been in contact with HSV-2 and, if there is a history of previous partners, HSV-2 is a likely diagnosis. If this is so, the partner may never have had overt clinical lesions and can be totally unaware that they carry and therefore are capable of transmitting HSV-2.

Also, when sexual contact has been orogenital, or a partner's genital infection is HSV-1 and there is HSV-1 serological discordance within a partnership or there is HSV-2 oral discordance, HSV-1 is the likely possibility (ie, one does not have to presume that the partner has been unfaithful).

In this patient, the culture from the lesion came back as positive for HSV-1. The information above was reinforced, including the fact that HSV-1 genital lesions are less likely to cause recurrences in the genital tract than HSV-2.

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Online resources

The Australian Herpes Management Forum web site: www.ahmf.com.au

GP's contribution



DR MARCIA MANNING
Greenwich, NSW

TL, a nurse, has been a patient in my practice for about five years. When she was 26 she presented to her previous GP with dysuria, frequency and high fever, one week after starting a new sexual relationship with the man whom she later married.

She said that the dysuria was so painful that she could not go to work, that the urine culture showed no infection and that she had seen a urologist, who changed the antibiotic she had been prescribed but found no explanation for her symptoms.

When the dysuria continued she attended a sexual health clinic. The doctor had done a speculum examination and seen ulcers on her cervix, which were, on testing, positive for HSV.

Over the next few years she had many episodes of recurrent blisters, but they were almost exclusively on the thigh or buttock. On one occasion she described a typical patch of blisters over the medial right knee.

Her husband denied any history of genital sores but, after they had been together for a few years, he started getting episodes suggestive of HSV. They had two children, one by caesarean because of the presence of blisters, but they separated after a few more years and



TL then did not have a sexual partner for the next five years.

She is now 38 and embarking on a new relationship. She has never had to discuss her HSV status with a new partner. She gets only about one episode a year of clinical HSV recurrence and is keen to avoid discussion of this.

Questions for the author

If TL takes valaciclovir 500mg daily, would the risk of transmission to her new partner be negligible (it would be a private script but she is thinking that she would like to take it for the next few months).

It would markedly reduce the risk, but not to zero.

Would doubling the dose confer a lower risk of transmission?

No.

If her partner has not had a cold sore since adolescence, does that mean he is more immunocompetent and perhaps less susceptible to HSV-2?

No. Many patients who are seropositive are either asymptomatic or their original infection was unrecognised.

General questions for the author

What is the incidence of reactions to, and side effects of, aciclovir, valaciclovir and famciclovir? Are there class effects?

These agents are well tolerated, and sensitivity is very uncommon.

Is there any known incidence of asymptomatic transmission to neonates that goes undetected and remains quiescent?

There are no data on this to date. Asymptomatic HSV in the mother could be transmitted to the infant; however, it is thought that if infected, the neonate would develop the disease. We are currently researching this.



How To Treat Quiz

Herpes simplex infections
— 15 July 2005

INSTRUCTIONS

Complete this quiz to earn 2 CPD points and/or 2 PDP points by marking the correct answer(s) with an X on this form. Fill in your contact details and return to us by fax or free post.

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1. Viruses from the Herpesviridae family are DNA viruses that have the property of latency. Which ONE is not a member of this family?

- a) Rotavirus
- b) Cytomegalovirus
- c) Epstein-Barr virus
- d) HSV

2. Which ONE statement about HSV infections in Australia is correct?

- a) Primary HSV-1 infection in children usually presents as gingivostomatitis
- b) Condoms, correctly used, reduce the transmission of HSV by 90%
- c) The rate of seroprevalence for HSV-2 in men who have sex with men is less than 25%
- d) HSV-1 seroprevalence in children is decreasing

3. Danielle, 17, presents with a painful red eye, and fluorescein stain shows a dendritic ulcer. On questioning she explains she has been unsuccessfully treating herself for thrush. Examination is consistent with genital HSV infection. What management are you most likely to institute (choose THREE)?

- a) 3% aciclovir ointment applied to the eye five times a day for five days only
- b) Aciclovir 400mg three times daily for

five days

- c) Famciclovir 125mg twice daily for five days
- d) Valaciclovir 500mg twice daily for five days

4. Which TWO of the following are achieved by using antiviral therapy?

- a) Prevention of neural latency
- b) Reduction in the number of lesions
- c) Cessation of viral shedding
- d) Reduction in the frequency of recurrences when used for suppression

5. Danielle's infection is proved to be due to HSV-1 and she is anxious that she will transmit the infection to any future partners. You explain that it is important for her to recognise the symptoms of recurrence. Which ONE symptom is she least likely to experience with a recurrence?

- a) Vesicles
- b) Non-vesicular lesions
- c) Urinary retention
- d) Fissuring of the skin

6. Jodie, 30, is pregnant. She had documented HSV infection before the pregnancy. How should she be managed during the pregnancy (choose ONE)?

- a) Even if there are no lesions at the time of

delivery, a caesarean section is indicated

- b) Viral cultures collected in the third trimester can predict viral shedding intrapartum
- c) If there are genital lesions at the time of delivery, delivery is usually by caesarean section, although a vaginal delivery may be considered if the lesions can be covered
- d) Even if there are no lesions at the time of delivery, routine virus cultures should be performed on the newborn

7. Meg, 25, is 35 weeks pregnant and has a primary HSV genital infection. Which TWO management options would you be most likely to choose when she delivers?

- a) Vaginal delivery, if there are no clinical signs at the time of delivery
- b) Automatic antiviral therapy to the newborn as prophylaxis
- c) Antiviral therapy during the remainder of the pregnancy
- d) Routine viral cultures on the newborn

8. In which ONE patient is type-specific serology least likely to provide useful information?

- a) One with culture-positive genital ulceration
- b) An HIV positive patient
- c) A patient with recurrent genital

symptoms and no ulceration

- d) A patient with a history of genital ulceration one week ago

9. HSV-2 is identified as the cause of Meg's infection. Which TWO statements about HSV-2 genital infection are correct?

- a) Very few (< 10%) of HSV-2-seropositive patients have genital lesions that they do not recognise as herpes
- b) Recurrences of genital infections are more likely with HSV-2 than HSV-1 infections
- c) In women, vesicles and ulcers are always seen early in the presentation
- d) The number of lifetime sexual partners is an independent risk for HSV-2

10. Twelve months later Meg attends with a new partner. They are considering unprotected sexual intercourse and request information about the risk of transmission. Her partner has no history of infection. Which ONE option would be least helpful to them?

- a) Arrange type-specific enzyme immunoassays for both partners
- b) Discuss the symptoms and management of recurrences
- c) Screen Meg for evidence of viral shedding
- d) Antiviral therapy

CONTACT DETAILS

Dr: Phone: E-mail:

RACGP QA & CPD No: and/or ACRRM membership No:

Address: Postcode:

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer. Your CPD activity will be updated on your RACGP records every January, April, July and October.

NEXT WEEK The next How to Treat reports on the changing management of diabetes. The author, Associate Professor Peter Colman, is director, department of diabetes and endocrinology, Royal Melbourne Hospital, Victoria.

Australian Doctor
Education.

HOW TO TREAT Editor: Dr Lynn Buglar
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