Genital herpes

An approach for general practitioners in Australia

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BACKGROUND Genital herpes is a common sexually transmitted infection that is most often asymptomatic and remains largely undiagnosed.
OBJECTIVE To discuss the diagnosis, management and treatments available for genital herpes infections.
DISCUSSION Genital herpes is a common infection with significant associated morbidity. Along with diagnosis and appropriate treatment, patient education, counselling and support are essential for effective management.

Hippocrates first used the term 'herpes', from the Greek 'to creep', over 25 centuries ago,[1] and this infection was deemed to be of little significance in contrast to other causes of genital ulcers such as syphilis. Following the discovery of antibiotics during the early part of the century and rapidly changing sexual mores in western society during the 1960s and 1970s, the increasing incidence of primary genital herpes generated media attention, reaching a peak in the early 1980s (Figure 1).

Figure 1. Time Magazine, 1982

In the early 1980s, widespread attention given to the 'gay plague' or Acquired Immune Deficiency syndrome (AIDS), and the subsequent discovery of the HIV virus in 1985, largely overshadowed the genital herpes viruses. The subsequent development of the first effective herpes treatment, Aciclovir, licensed in 1984, generated little interest.

Developments in the past 20 years have seen great steps forward in our knowledge and understanding of herpes simplex viruses (HSV). There have been advances in management, with diagnostic tools such as type specific serology giving us a new understanding of the prevalence of both HSV viruses along with rates of asymptomatic infection and transmission.

Despite these advances, the chronic nature of the herpes simplex infection, and its association with promiscuity continue to keep the infection stigmatised. This may significantly affect many patients, leading to barriers in forming sexual relationships and continuing difficulty disclosing the infection to prospective sexual partners.

This paper hopes to offer Australian general practitioners a useful guide to discussing herpes with patients, to understand the uses and limitations of available tests and the choices in management of HSV infection. The availability of information on the internet, if used correctly, can provide a valuable resource for patient education and destigmatising the infection.

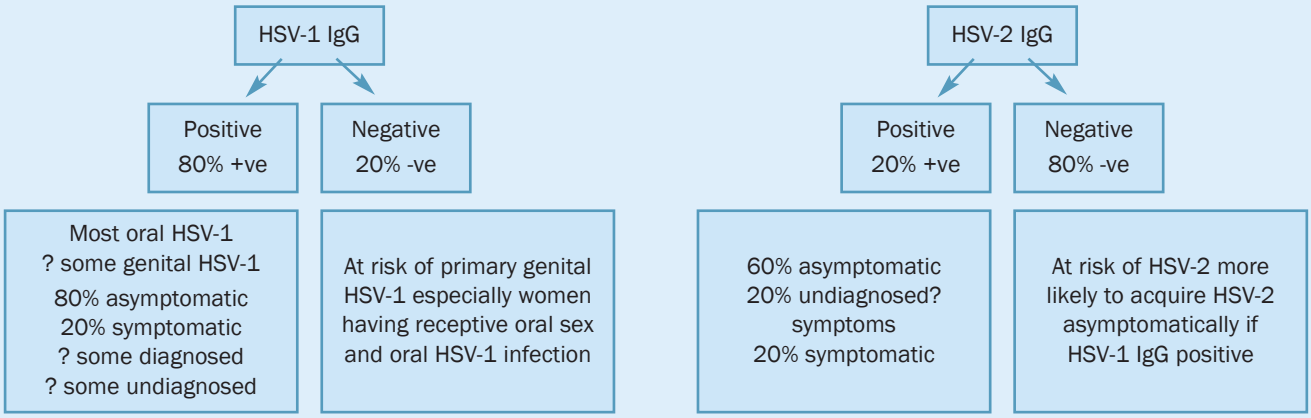
Biology

Both herpes simplex virus (HSV)-1 and HSV-2 can cause oral and genital herpes lesions. Herpes simplex virus 1 and HSV-2 are two of eight human herpes viruses, all of which are well adapted to their natural host. All herpes viruses have the ability to establish latency and hence persist for the life of their host. The site of latency for HSV is the sensory ganglia of nerves innervating the site of initial infection.

Herpes simplex virus is a DNA virus consisting of an outer envelope that assists in the attachment to the host and penetration of host membrane.[2] The differences between HSV-1 and HSV-2 are subtle and clinically indistinguishable, with HSV-1 favouring oral sites (cold sores) while HSV-2 favours genital sites. Although HSV-1 tends to be less severe in recurrent infection, both HSV-1 and HSV-2 may produce a severe primary infection.

Table 1. HSV type specific serology[5]

Commercially available EIA tests have a significant false positive and false negative. Tests are more accurate in those with a clinical history of lesions, but serology is unable to distinguish which HSV type infects which site: oral and/or genital. More accurate type specific serology (Western Blot test) is available from some research centres.



Epidemiology

In Australia approximately 80% of people have acquired HSV-1, usually orally.[3] This infection is usually acquired in childhood and, although transmitted by skin-to-skin contact like HSV-2, is not usually associated with sexual activity and therefore does not carry the same stigma. The clinical features of oral HSV-1 are similar to genital herpes.

The estimated sero-prevalence of HSV-2 in Australia depends on the population studied. Rates vary from 12.5% at an antenatal clinic[3] to 58% in female prisoners.[4] Overall, sero-prevalence of HSV-2 is often quoted as 10-30%. In general up to 80% of infections remain undiagnosed with 60% of these unrecognised, mildly symptomatic outbreaks (Table 1).[5]

Transmission

Infection occurs as a result of intimate, skin-to-skin contact with an infected individual, or via vertical transmission. This includes genital to genital contact, oro-genital contact, ano-oral contact and ano-genital contact. Transmission rates are highest during active lesions however, the majority (up to 70%) of transmission of HSV occurs while patients are asymptomatic.[6] Asymptomatic viral shedding, diagnosed via HSV culture, occurs more commonly with HSV-2 and has been estimated at 3% of days.[7] This rate may be higher with HSV polymerase chain reaction.

Likelihood of HSV transmission is influenced by several factors. Circulating antibodies of prior oro-labial HSV-1 infection will protect the individual against an HSV-1 genital infection and may offer partial protection against HSV-2. Women are at higher risk of acquisition than their male counterparts possibly due to a larger mucosal surface area exposed in females compared to men,[5] and increased frequency of sexual activity with an HSV infected person will also increase the possibility of transmission.[8] The use of barrier protection, such as condoms, has also been found to significantly reduce the transmission of genital herpes to women if used more than 25% of the time.[8] This is believed to be due to gender differences in viral shedding sites. Suppressive therapy probably also decreases transmission however, studies in this field are ongoing.[9] Prophylactic vaccine trials have so far been relatively unsuccessful, except in HSV-1 and HSV-2 sero-negative women.[10]

In sero-discordant couples the transmission is most likely to occur in the first 3-6 months and is estimated at less than 10% per year thereafter.[6] The majority of partners acquiring the infection will do so asymptomatically.

Clinical manifestations and presentations in general practice

Patients presenting to a GP are most likely to be symptomatic, requiring diagnosis or management. They may also be partners of symptomatic individuals requiring information and advice and/or are presenting, requesting serology for diagnosis.

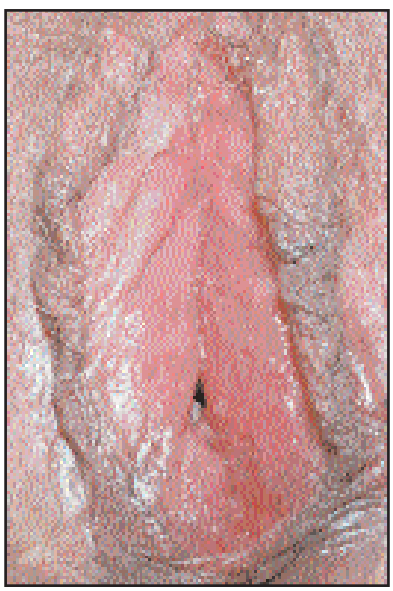


Figure 2. Painful genital herpes lesions

Table 2. Comparison of primary and recurrent genital herpes

	Primary	Recurrence
Systemic symptoms: headache, fever, myalgias	Usually	Seldom
Genital symptoms: pain, itch, ulceration	Severe	Mild to moderate
Lymphadenopathy	Yes	Occasionally
Complications: constipation, erectile dysfunction, urinary retention	Occasionally, due to sacral radiculopathy	No
Duration of lesions	Up to 3 weeks	<1 week
Prodrome	Seldom	Usually
Extragenital lesions	Yes, if infected at nongenital sites	Yes, in distribution of sacral dermatomes

The severity and frequency of genital herpes clinical manifestations may depend upon infection with either HSV-1 or HSV-2, prior immunity to HSV-1 and patient response to the infection. A true primary outbreak, where the patient is first infected (ie. no prior antibodies) with either HSV-1 or HSV-2, may present 2-20 days postexposure and tends to be more severe than recurrent lesions (Table 2), marked by systemic symptoms and prolonged duration of painful lesions (Figure 2).

However, even for those doctors specialising in the area, cases of genital herpes recurrences may be clinically indistinguishable from a primary outbreak,[11] and it is always unwise to be 'certain' that the infection was recently acquired unless confirmed with positive HSV IgM serology and negative HSV IgG. Some recurrent outbreaks, while being IgG positive may also produce a transient IgM.

Recurrent symptomatic genital herpes lesions may be preceded by a prodrome of shooting pains in the legs and hips or an itching, tingling or burning in the genital area followed by skin erythema, varying from person to person. In both primary and recurrent genital herpes the classic presentation is characterised by clusters of clear fluid filled vesicles which burst, crust over and dry out.

Genital herpes does not always present classically, and atypical presentations are listed in Table 3. Due to the establishment of latent infection in the sacral nerve root ganglia, recurrences may manifest as a sacral neuralgia or lesions in nongenital areas, in the distribution of the sacral dermatomes, including buttocks, perianally and posterior lower limbs.

For many, the morbidity associated with genital herpes is dependent on the

Table 4. Antiviral medication for genital herpes

	Primary herpes	Recurrent herpes	suppression therapy
Aciclovir	200 mg 5/day PO for 5-10 days	200 mg 5/day PO for 5 days	200 mg tds PO or 400 mg bd
Valaciclovir	500 mg bd PO for 5-10 days	500 mg bd PO for 5 days	500 mg daily PO increase to bd if >10 episodes/year
Famciclovir	not licensed in primary herpes	125 mg bd PO for 5 days	250 mg bd PO

Table 3. Atypical presentations of genital herpes

- erythema
- rash
- skin fissuring
- pain or burning
- genital itch

frequency of recurrences. More frequent recurrences on the genital sites are associated with HSV-2 infection, recent acquisition (within the first six months) and other unknown host factors. Some other factors thought to be involved in triggering recurrences may include fatigue, menstruation, sexual intercourse and trauma.

Diagnosis

Clinical diagnosis of genital herpes can be difficult. Most often the infection is asymptomatic, however, mildly symptomatic cases may be misdiagnosed and self treated by patients as other conditions, eg. candidiasis. In Australia over 90% of genital ulceration is caused by HSV. Rare causes of genital ulcers may include traumatic ulceration, syphilis, donovanosis and scabies, and noninfectious causes such as Behcet's syndrome, recurrent apthous ulcers, fixed drug reactions and inflammatory bowel disease.

There are a variety of tests available for HSV-1 and HSV-2 detection. The direct detection tests are the preferred form of diagnosing HSV lesions as serological testing will not identify site of infection, nor confirm clinical signs and symptoms are due to an HSV infection.

Direct detection tests

Confirmation of a genital HSV infection can be made only via a direct detection test, eg. HSV culture, HSV immunoflourescence (IF) or HSV DNA detection. These tests are type and site specific and are only useful for those patients presenting with clinical lesions. A negative result does not preclude HSV, however, a positive culture or HSV polymerase chain reaction test result is thought of as the current 'gold standard'.

False positive results may occur with IF and significant amounts of virus must be present for a positive HSV culture. Crusted lesions should be scraped firmly with the crust removed and blisters should be pierced and the fluid absorbed on a swab and then placed in the appropriate container. Primary episodes are more likely to return positive results than recurrences.

Serology

Commercially available HSV serology tests, unless interpreted correctly can be more confusing than helpful, as these tests may give false positive and negative results. Type specific serology is available at a cost to the patient from some research laboratories.

Serological testing, while not site or symptom specific, may be useful in particular settings, but given the high prevalence of both HSV-1 and HSV-2, serology has a limited place in the diagnosis of genital herpes. Counselling about the positive and negative aspects of serological testing should be advised, before serology testing. Partners of HSV-2 positive patients may already be sero-positive for HSV-2 but asymptomatic and following testing may be then be 'labelled' with an asymptomatic infection. If sero-negative for HSV-2 they may become infected in the future, with no guarantee of ensuring they will never become infected.

Management

As the majority of HSV positive individuals have asymptomatic or mildly symptomatic infection, management may be limited to information and counselling alone. For those with frequent painful recurrences and whose symptoms are significantly impacting on their lifestyle, oral antiviral treatment may be appropriate. Patients should be encouraged to be involved with their own care and may elect to use either forms of treatment or none at all depending on personal circumstances and life events. A high frequency of attacks in the first few months after a primary episode should prompt suppressive therapy for six months to minimise adjustment to the disease.

Currently there are three antiviral agents licensed in Australia for the treatment of genital herpes (Table 4). All agents are well tolerated with few side effects, differing only in oral bioavailability and hence dosing frequency. Oral treatments can be taken episodically for individual outbreaks, where they shorten the duration of symptoms, or used daily as suppressive therapy, to prevent outbreaks and decrease asymptomatic viral shedding.

Pregnancy

While almost all cases of neonatal herpes are acquired perinatally via contact with the infection during delivery, the rate of infection is low when compared to the numbers of women infected who give birth vaginally. In Australia, approximately 2.6:100 000 neonates acquire the infection[12] and the risk is greatest from a woman with primary HSV infection at delivery.

Transmission is estimated at about 50% for those who acquire genital HSV-2 in the third trimester, compared to the risk of transmission in women with recurrent HSV-2 infection at less than 1%. It is thought that maternal antibodies in recurrent disease are protective.

While available antiviral medications are not licensed for specific use in pregnancy, with most carrying a category B rating, they have been used in pregnancy with little ill effect. It is essential that possible primary outbreaks are diagnosed and managed promptly and effectively. In recurrent infection, management during pregnancy and labour vary.

Avoidance of antivirals in the first trimester is usually encouraged, and advice sought from specialist referral should symptoms be severe. Management during pregnancy should be discussed with the obstetrician and/or midwife or specialist sexual health service.

Herpes and human immunodeficiency virus (HIV)

Herpes, and other sexually transmitted diseases that cause genital ulceration, are important risk factors in the acquisition and transmission of HIV, especially in countries with a high HIV sero-prevalence.[13] In profoundly immunosuppressed individuals lesions may take much longer to heal and resistance to the standard antiviral drugs has been documented.

Conclusion

Herpes simplex viruses are well adapted to the human host. The infections are extremely common and most often asymptomatic, infecting many millions of people, usually with little serious morbidity and mortality.

The associated shame and stigma make it difficult for people to discuss genital HSV infection, unlike that of cold sores (HSV-1). This relates directly to its association with sex and notions of promiscuity, often causing more psychological damage than the physical symptoms of the infection.

Reassurance, normalisation of the infection, accurate information, including good websites and written resources, and effective treatment is all that may be needed to relieve an individual of a burden which they may have had for many years.

Websites

For doctors
http://www.ihmf.com
http://www.acshp.org.au
For patients
http://www.thefacts.com.au
http://www.herpes.com.au

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