INTRODUCTION

First infection with either herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2) is termed primary infection and results in either symptomatic disease at the site of viral entry (i.e. around the mouth or around the genital area) or asymptomatic and hence unrecognized disease. In addition there may be systemic symptoms as with other acute viral illnesses. Following infection, the virus becomes latent in the local sensory ganglion, periodically reactivating to cause symptomatic lesions or asymptomatic, but none the less infectious, viral shedding. Genital herpes can be caused by either HSV-1 (the usual cause of oro-labial herpes) or by HSV-2. Infection with either virus can cause an identical initial illness. However, subsequent recurrence frequency is greater for HSV-2 than HSV-1 disease. The majority of patients will suffer from atypical lesions where signs may be easily confused with other genital infections or dermatoses. Clinical diagnoses alone in atypical cases should, whenever possible, be avoided.

Transmission risk

Risk of transmission appears to be greatest during lesional recurrences or prodrome. Patients should be advised to abstain from sexual contact during this time. Transmission can occur in the absence of lesional recurrence as a result of subclinical viral shedding. Efficacy of condoms to prevent sexual transmission has not been formally assessed. Risk of transmission is greater from men to women than vice versa. Prior infection with HSV-1 reduces the HSV-2 seroconversion risk in serodiscordant couples.

DIAGNOSIS

Clinical

Although classical genital herpes can be recognized by the presence of typical papular lesions progressing to blister and ulcer formation, associated with local adenitis and in recurrent cases proceeded by prodromal symptoms, the features in many patients can be highly variable. The majority of patients will suffer from atypical lesions where signs may be easily confused with other genital infections or dermatoses. Clinical diagnoses alone in atypical cases should, whenever possible, be avoided.

Laboratory

Virus detection and characterization

The confirmation of the infection is essential and characterization of its strain is recommended for diagnosis, prognosis-counselling and management. Laboratory diagnosis is based on direct detection of HSV from genital lesions which may be atypical (Table 1). The quality of samples is critical and specimens should be collected using swabs directly from the base of the lesion. HSV is a labile virus and successful virus culture depends on maintaining the cool chain (4°C), rapidly transporting specimens to the laboratory and avoiding freeze–thaw cycles. Local factors (laboratory resources, distance) should be considered in deciding on the testing strategy. The stage of the lesion will determine the success of virus detection. Negative diagnostic tests do not exclude infection. Patients may require reassessment on a number of occasions for a definitive diagnosis to be made.

Serology

Most currently available commercial tests for HSV antibodies are not type-specific (e.g. complement-fixation test (CFT) and many enzyme immunoassays (EIAs)). These tests are rarely of value in the management of genital HSV. However, type-specific commercial assays are becoming available and are either EIAs based on glycoprotein G (gG1, gG2) or Western blot. Type-specific immune responses can take 8–12 weeks to fully develop following primary infection.

Full serological assessment of genital HSV requires access to both HSV-1 and 2 type-specific antibody assays, because of the high proportion of cases due to HSV-1 infection. HSV-1 type-specific assays are consistently less sensitive and specific than those for HSV-2.
The value of screening all STD clinic attendees or antenatal patients for HSV antibodies has not been established. Tests should be fully evaluated for sensitivity, specificity, reproducibility against virus culture and/or validated established tests (e.g. Western blot) before being introduced into clinical practice.

The value of these tests for patient management has not been fully assessed but they are likely to contribute in cases with recurrent genital ulceration of unknown cause, for counselling patients with initial episodes of disease and the asymptomatic partners of patients with HSV-2 infection.

As adverse psychological sequelae may follow the identification of an asymptomatic chronic infection, protocols for use of type-specific antibody of tests need to be developed in individual centres.

**MANAGEMENT**

**First-episode genital herpes**

**Indications for therapy**

First episodes of genital herpes are frequently associated with a prolonged disease course. Untreated, many patients suffer general and local complications. Therapy can be highly effective and should be instigated on clinical suspicion alone.

**Antivirals**

Patients presenting within 5 days of the start of the episode, or while new lesions are still forming, should be given oral antiviral drugs. Aciclovir, valaciclovir and famciclovir are all effective in reducing the severity and duration of episode.\(^9\,10\)

Topical agents are less effective than oral agents.

The only indication for the use of intravenous therapy is when the patient is unable to swallow or tolerate oral medication because of vomiting. Intravenous therapy does not alter the natural history of genital herpes infection.\(^11\)

The regimens recommended are (all for 5 days):

- Aciclovir 200 mg 5/day, or
- Famciclovir 250 mg 3/day, or
- Valaciclovir 500 mg 2/day.

Choice should be made by individual clinicians taking cost of therapy and likely compliance into account.

**Supportive measures**

Saline bathing and the use of appropriate analgesia is recommended. Caution should be exercised in using topical anaesthetic agents because of the potential for sensitization.

**Counselling**

Counselling of patients with first-episode genital herpes should include a discussion of the following topics: possible source(s) of infection, natural history including risk of subclinical viral shedding, future treatment options, risk of transmission by sexual and other means, risks of transmission to the foetus during pregnancy and the advisability of the obstetrician and midwife being informed, sequelae of infected men infecting their uninfected partners during pregnancy, the possibility of partner notification.

**Management of complications**

Hospitalization may be required for:

- Urinary retention
- Meningism
- Severe constitutional symptoms
- Adverse social circumstances.

If catheterization is required, suprapubic catheterization is preferred both on theoretical grounds (to prevent ascending infection) and practical grounds.

**Special situations — HIV-positive patients with first-episode genital herpes**

There are no controlled trials on duration and dose of treatment. Some clinicians advocate a 10-day course of treatment.

**Follow up**

Patients are followed up until the episode has resolved and counselling is considered complete.
Further follow up may be required to exclude other causes of genital ulceration that may be co-existent. Patients should be invited to reattend should recurrences be problematic.

**Recurrent genital herpes**

**Indications for therapy**

Genital herpes recurrences are self-limiting and generally cause minor symptoms. Decisions about how best to manage clinical recurrences should be made in partnership with the patient. Management strategies include supportive therapy only, episodic antiviral treatments and suppressive antiviral therapy. The most appropriate strategy for managing an individual patient may vary over time according to recurrence frequency, symptom severity and relationship status. For most patients management will need to be supportive only, with simple local measures such as saline bathing or topical petroleum jelly being adequate.

**Episodic antiviral treatment**

Oral aciclovir, valaciclovir and foscarnet are effective at reducing the duration and severity of recurrent genital herpes. The reduction in duration is a median of 1–2 days for most patients. Valaciclovir is no more or less effective than aciclovir. Foscarnet has not been compared with aciclovir. Valaciclovir and foscarnet have not been compared. Both foscarnet and valaciclovir have a twice-a-day dosing regimen which is easier to take than a 5-a-day regime. It is likely that patient-initiated treatment started early in an episode is most likely to be effective. Valaciclovir aborted one in 10 lesional recurrences when initiated by patients early in the course of an episode.

The recommended regimens are all for 5 days:

- Aciclovir 200 mg 5 a day or
- Valaciclovir 500 mg twice daily, or
- Foscarnet 125 mg twice daily, plus supportive measures including saline bathing, petroleum jelly.

**Suppressive therapy**

All trials of suppressive therapy have been done in patients with a recurrence rate equivalent to ≥6 recurrences/annum. However, it is likely that patients with a lower rate of recurrence will also reduce their rate of recurrence with treatment. The frequency of recurrence at which it is worth starting suppressive therapy is a subjective issue and needs to balance the frequency of recurrence against the cost and inconvenience of treatment.

Patients with culture-proven genital herpes who have a recurrence rate equivalent to ≥6 episodes of genital herpes annually are highly likely to experience a substantial reduction in recurrence frequency on suppressive antiviral therapy.

Experience with suppressive antiviral therapy is most extensive with aciclovir. Safety and resistance data on patients on long-term therapy now extends to over 11 years of continuous surveillance.

**Recommended regimens**

The optimal daily dose of suppressive aciclovir therapy is 800 mg. The only published clinical dose-ranging study concluded that a dose of 200 mg 4 times a day was clinically superior to 400 mg twice daily. However, ability to comply with a 4 times a day regimen should determine prescribing decisions for individual patients.

Suppressive therapy using foscarnet (250 mg twice daily) has only been compared with placebo and not against the current standard of care. Twice-daily valaciclovir (250 mg twice daily) has been shown to be as effective as twice-daily aciclovir (400 mg twice daily) in all patients. Patients with less frequent recurrences (<10 per annum) may be adequately suppressed on once-daily valaciclovir (500 mg once daily). Patients with more frequent disease (>10 attacks per year) require higher doses of once-daily valaciclovir to maintain control (1000 mg once daily). Once-daily aciclovir does not suppress genital herpes recurrences.

Therapy should be discontinued after a maximum of a year of continuous antiviral therapy to reassess recurrence frequency. Twenty per cent of patients will experience a reduction in recurrence frequency compared with pre-suppression symptomatic levels. The minimum period of assessment should include two recurrences. It is safe and reasonable to restart treatment in patients who continue to have an unacceptably high rate of recurrence.

Short courses of suppressive therapy to prevent clinical symptoms may be helpful for some patients (e.g. for holidays, exams, etc.).

**Viral shedding and transmission on suppressive therapy**

Subclinical shedding of infectious virus occurs in some individuals with genital HSV-1 and/or HSV-2. Viral shedding is more likely to occur in patients with genital HSV-2 infection, in the first year after infection or in individuals with frequent symptomatic recurrences. In one study, aciclovir 400 mg twice daily substantially reduced both the number of women with subclinical viral shedding and the number of days on which viral shedding occurred. The evidence in men is awaited. The effect of antiviral drugs on rate of sexual transmission has not been established.

**SPECIAL SITUATIONS**

**Management of herpes in immunocompromised individuals**

Although rare in immunocompetent individuals, clinically refractory lesions due to genital HSV are a major problem in patients with severe immunodeficiency, including late-stage HIV diseases. The algorithms in Figure 1 is modified from a paper...
published following a consensus symposium on the management of resistant herpes simplex\textsuperscript{20}. In addition there is evidence from a randomized, double blind, placebo-controlled trial that cidofovir gel (0.1% or 0.3% applied once daily for 5 days), achieves complete healing or >50% decrease in lesional area in up to 50% of patients. However cidofovir has only been compared with placebo and not against current standard of care (foscarnet or trifluridine)\textsuperscript{21}.

**Suppressive antiviral therapy**

There is no evidence to suggest that immunocompromised patients on suppressive therapy for frequently recurring genital herpes need other than the standard regimen.

**Management of partners**

There is no evidence on which to base recommendations for partner notification. On an individual basis it may be appropriate to offer to see partners to help with the counselling process. Partner notification in relation to pregnancy is discussed below.

It is worth bearing in mind the following points when counselling patients.

- Asymptomatic shedding plays a major role in the transmission of HSV infection
- Partner notification is an effective way of detecting asymptomatic individuals when combined with type-specific antibody testing\textsuperscript{22}
- Up to 50% of asymptomatic HSV-2 seropositive women can be taught to recognize genital herpes recurrences after counselling. It may be possible to prevent transmission by educating patients to recognize symptomatic recurrences\textsuperscript{23}
- Although there is no definitive evidence that either antiviral treatment or patient education/counselling alters transmission rates of HSV at a population level, it seems logical to increase awareness of the diagnosis in patients when appropriate, with the aim of preventing further onward transmission.

**Management of pregnant women with first-episode genital herpes**

*First and second trimester acquisition*

- Management of the woman should be in line with her clinical condition and will often
involvethe use of either oral or intravenous aciclovir in standard doses
- Providing that delivery does not ensue, the pregnancy should be managed expectantly and vaginal delivery anticipated
- Continuous aciclovir in the last 4 weeks of pregnancy may prevent recurrence at term and hence the need for delivery by Caesarean section.

**Third trimester acquisition**
- Caesarean section should be considered for all women, particularly those developing symptoms within 6 weeks of delivery, as the risk of viral shedding in labour is very high
- If vaginal delivery is unavoidable, aciclovir treatment of mother and baby may be indicated.

**Management of pregnant women with recurrent genital herpes**
- Sequential cultures during late gestation to predict viral shedding at term are not indicated.
- Caesarean section to prevent neonatal herpes should not be performed in women who do not have genital lesions at delivery
- Symptomatic recurrences of genital herpes during the third trimester will be brief; vaginal delivery is appropriate if no lesions are present at delivery
- The benefits of obtaining specimens for culture at delivery, in order to identify women who are asymptomatically shedding HSV, are unproven.

**Management of women with genital lesions at onset of labour**
- There is evidence that the risks of vaginal delivery for the foetus are small and must be set against risks to the mother of Caesarean section.

**Note:** None of the antiviral drugs is licensed for use in pregnancy. There is most experience with aciclovir, which should therefore be used in preference to famciclovir or valaciclovir if clinically indicated.

**Prevention of acquisition of infection**
Any strategy for prevention of neonatal herpes needs to involve both parents.
- All women should be asked at their first antenatal visit if they or their partner have ever had genital herpes
- Female partners of men with genital herpes, but without a history of genital herpes, should be strongly advised not to have sex at the time of lesional recurrence. Conscientious use of condoms during pregnancy may diminish risk of acquisition
- Pregnant women should be advised of the risk of acquiring HSV-1 as a result of orogenital contact
- Identical susceptible women by means of type-specific antibody testing has not been evaluated in terms of costs and benefits
- All women, not just those with a history of genital herpes, should undergo careful vulval inspection at the onset of labour to look for clinical signs of herpes infection
- Mothers, staff and other relatives/friends with active oral lesions should be advised about the risk of postnatal transmission.

**Management of the neonate**

*Babies born to mothers with first-episode genital herpes at the onset of labour*
- HSV culture of urine and stool, from the oropharynx, eyes and surface sites to allow early identification of infected babies
- The potential benefits and risks of starting intravenous aciclovir without waiting for the results of these cultures should be discussed
- If aciclovir is not started immediately the neonate should be closely monitored for signs of lethargy, fever, poor feeding or lesions.

*Babies born to mothers with recurrent genital herpes at the onset of labour*
- One set of specimens for viral culture collected after delivery may help with early identification of infection
- Parents should be advised to report early any signs of infection (lethargy, fever, poor feeding or lesions).

**References**
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