

## **2001 National Guideline for the Management of Genital Herpes**

**Clinical Effectiveness Group (Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases)**

### **Aetiology**

- Herpes simplex virus type 1 (HSV-1, the usual cause of oro-labial herpes) or
- Herpes simplex virus type 2 (HSV-2).

### **Natural History**

- Infection may be primary or non-primary. Disease episodes may be initial or recurrent (figure 1) and symptomatic or asymptomatic.
- Prior infection with HSV-1 modifies the clinical manifestations of first infection by HSV-2<sup>1</sup>.
- After childhood, symptomatic primary infection with HSV-1 is equally likely to be acquired in the genital area or oral areas<sup>1</sup>.
- Following primary infection, the virus becomes latent in local sensory ganglia, periodically reactivating to cause symptomatic lesions or asymptomatic, but infectious, viral shedding.
- New diagnoses of genital herpes (GH) are equally likely to be caused by HSV-1 or HSV-2. However, the median recurrence rate after a symptomatic first episode is 0.34 recurrences/ month for HSV-2 and 0.08 recurrences/ month for HSV-1<sup>2</sup>. Recurrence rates decline over time in most individuals, although this pattern is variable<sup>3</sup>.
- The majority of individuals found to have asymptomatic HSV-2 infections subsequently develop symptomatic lesions<sup>2</sup>.
- Asymptomatic perianal HSV shedding in HIV negative HSV-2 seropositive men who have sex with men is common<sup>4</sup>. In HIV positive HSV-2 seropositive men, both symptomatic and asymptomatic shedding are increased, especially in those with low CD4 counts and those who are also seropositive for HSV-1<sup>5</sup>.

### **Clinical Features**

#### **Symptoms**

- Painful ulceration, dysuria, vaginal or urethral discharge

- Systemic symptoms e.g. fever and myalgia
- The patient may be asymptomatic, and the disease unrecognised.
- Rarely, systemic symptoms may be the only evidence of infection.
- Systemic symptoms are much commoner in primary than in initial or recurrent disease.

### Signs

- Blistering and ulceration of the external genitalia (+/- cervix/rectum)
- Inguinal lymphadenopathy

### Complications

- Autonomic neuropathy, resulting in urinary retention
- Aseptic meningitis

### Atypical GH

- In the United States, only about 20% of those patients who present to physicians with genital symptoms receive a correct diagnosis of GH<sup>6</sup>

## **Diagnosis**

### Virus detection and characterisation

The confirmation and characterisation of the infection and its type, by isolation of HSV from genital lesions (Table 1), are essential for diagnosis, prognosis, counselling, and management (IV, C). Successful diagnosis depends on

- using swabs taken directly from the base of the lesion
- maintaining the cold chain (4°C)
- rapidly transporting specimens to the laboratory and avoiding freeze-thaw cycles.

Local factors (laboratory resources, distance) will determine the testing strategy.

### Serology

- Most commercial tests for HSV antibodies are not type-specific (for example, CFT and many EIAs) and are of no value in the management of GH.
- Type-specific EIAs based on glycoprotein G (gG1, gG2) or western blot assays are becoming available.

- Tests should be evaluated for sensitivity, specificity and reproducibility using sera from cases confirmed by culture, and/or validated established tests before being introduced into clinical practice. Several such validated commercial assays are now available including one near patient test<sup>9,10</sup>.
- Type-specific immune responses can take 8-12 weeks to develop following primary infection.
- In the United Kingdom, serological evaluation of GH requires access to both HSV-1 and HSV-2 type-specific assays.
- Caution is needed in interpreting results because even highly sensitive and specific assays have poor predictive values for low prevalence populations (Table 2).
- The clinical utility of these tests has not been fully assessed. Virus detection remains the method of choice. However, they may be helpful in(111,B)<sup>12</sup>
  - recurrent genital ulceration of unknown cause
  - counselling patients with initial episodes of disease
  - investigating asymptomatic partners of patients with GH
  - evaluating GH during pregnancy.
- The value of screening all genitourinary medicine clinic attenders or antenatal patients for HSV antibodies has not been established<sup>13</sup>.

## **Management**

### **FIRST EPISODE GH**

#### **General advice**

- Saline bathing
- Analgesia
- Topical anaesthetic agents (should be used with caution because of potential sensitisation)

#### **Antiviral drugs**

- oral antiviral drugs are indicated within 5 days of the start of the episode and while new lesions are still forming.
- Aciclovir, valaciclovir, and famciclovir all reduce the severity and duration of episodes (Ib, A)<sup>14,15</sup>. Antiviral therapy does not alter the natural history of the disease<sup>16</sup>.
- Topical agents are less effective than oral agents.
- Intravenous therapy is only indicated when the patient cannot swallow or tolerate oral medication because of vomiting.

- combined oral and topical treatment is of no benefit.
- There is no evidence for benefit from courses longer than five days. However, it may be prudent to continue therapy beyond five days if new lesions are still appearing at this time.

Recommended regimens (all for five days):

- Aciclovir 200 mg five times daily
- Famciclovir 250 mg three times daily
- Valaciclovir 500 mg twice daily.

Management of complications

- Hospitalisation may be required for urinary retention, meningism, and severe constitutional symptoms.
- If catheterisation is required, suprapubic catheterisation is preferred (IV, C).
  - to prevent theoretical risk of ascending infection
  - to reduce the pain associated with the procedure
  - to allow normal micturition to be restored without multiple removals and recatheterisations

HIV positive patients

Some clinicians advocate a 10-day course of treatment (IV, C). Lesions unresponsive to therapy may be due to drug resistant HSV and drug susceptibility testing of the virus isolate should be considered (see below).

**RECURRENT GH**

- Recurrences are self-limiting and generally cause minor symptoms.
- Management decisions should be made in partnership with the patient.
- Strategies include
  - supportive therapy only
  - episodic antiviral treatments
  - suppressive antiviral therapy.
- The best strategy for managing an individual patient may change over time according to recurrence frequency, symptom severity, and relationship status.

General advice (IV,C)

- Saline bathing
- Vaseline

- lignocaine gel

#### Episodic antiviral treatment (Ia, A)

- Oral aciclovir, valaciclovir<sup>17</sup>, and famciclovir<sup>18</sup> reduce the duration (by median of 1-2 days<sup>19, 20, 21</sup>) and severity of recurrent GH.
- Patient initiated treatment started early in an episode is most likely to be effective<sup>20</sup>.

#### Recommended regimens (all for five days)

- Aciclovir 200 mg five times daily
- Valaciclovir 500 mg twice daily
- Famciclovir 125 mg twice daily

#### Suppressive antiviral therapy

- Patients who have taken part in trials of suppressive therapy have had at least six recurrences per annum. Such patients have fewer or no episodes on suppressive therapy (1b,A). Patients with lower rates of recurrence will probably also have fewer recurrences with treatment.
- Patients should be given full information on the advantages and disadvantages of suppressive therapy. The decision to start suppressive therapy is a subjective one, balancing the frequency of recurrence with the cost and inconvenience of treatment.
- Safety and resistance data on patients on long-term therapy with aciclovir<sup>22</sup> now extend to over 13 years of continuous surveillance (III, B).

#### Recommended regimens (1b, A)

- Aciclovir 400mg twice daily
- Aciclovir 200mg four times daily
- Famciclovir 250mg twice daily<sup>18</sup>
- Valaciclovir 250mg twice daily (250mg tablets not available in the UK)<sup>17</sup>
- Valaciclovir 500mg daily
- Choice of treatment depends on patient compliance and cost (table 3)
- Suppressive therapy should be discontinued after a maximum of a year to reassess recurrence frequency. The minimum period of assessment should include two recurrences. Patients who continue to have unacceptably high rates of recurrence may restart treatment. (IV, C).
- Short courses of suppressive therapy may be helpful for some patients (IV, C).

#### ASYMPTOMATIC VIRAL SHEDDING

- occurs in individuals with genital HSV-1 and those with genital HSV-2.

- occurs most commonly in
  - patients with genital HSV-2 infection
  - in the first year after infection
  - in individuals with frequent symptomatic recurrences
- is an important cause of transmission
- may be reduced by aciclovir 400 mg twice daily (Ib, A) <sup>23,24</sup>.

### **Counselling**

- Diagnosis often causes considerable distress<sup>25</sup>. Most people with recurrences adjust over time but antiviral treatment can probably reduce anxiety, assist adjustment and improve quality of life <sup>26,27</sup> (II, B).
- Counselling should be as practical as possible and address particular personal situations; issues for someone in a long-term relationship are likely to be different from those for someone seeking a partner.
- Failure by the patient to control everyday stresses does not affect recurrences<sup>25</sup>. For most patients one or two counselling sessions with an invitation to return in case of difficulty should be enough.
- Patients who have failed to adjust to the diagnosis after a year should be considered for more intensive counselling interventions.

Counselling should cover:

- natural history
- the use of antiviral drugs for symptom control; current uncertainties about impact on infectivity should be discussed
- risks of transmission by sexual and other means, related to the actual situation of the patient
  - Patients should be advised to abstain from sexual contact during lesional recurrences or prodromes.
  - Transmission may occur as a result of asymptomatic viral shedding. Seropositive patients with unrecognised recurrences can be taught to recognise symptomatic episodes after counselling and this may prevent onward transmission<sup>28</sup>.
  - Efficacy of condoms to prevent sexual transmission has not been formally assessed

- Pregnancy issues for both men and women (see below)
- Partner notification
  - is an effective way of detecting individuals with unrecognised disease<sup>29</sup>
  - may clarify whether a partner is infected or not (utilising type-specific antibody testing if necessary). This may help to relieve anxiety about transmission or reinforce the need to reduce the risk of transmission
  - may help with the counselling process
  - awareness of the diagnosis in a partner or ex-partner may prevent further onward transmission.

### **Management of herpes in pregnancy**

Guidelines for GH in pregnancy are categorised into management of first episodes and recurrent episodes. Accurate clinical classification is difficult<sup>30</sup>. Viral isolation and typing and the testing of paired sera (if a booking specimen is available) may be helpful.

#### **FIRST EPISODE GH**

##### **First and second trimester acquisition**

- Management should be in line with the clinical condition with the use of either oral or intravenous aciclovir in standard doses (IV, C).
- Aciclovir is not licensed for use in pregnancy; however, there is substantial clinical experience supporting its safety.
- Vaginal delivery should be anticipated (IV, C).
- Continuous aciclovir in the last 4 weeks of pregnancy reduces the risk of both clinical recurrence at term and delivery by Caesarean section (CS) (Ib, A)<sup>31</sup>.

##### **Third trimester acquisition** (IV, C)

- If a true first episode is confirmed (see above) CS should be considered for all women, particularly those developing symptoms after 34 weeks of gestation, as the risk of viral shedding in labour is very high.
- CS for the prevention of neonatal herpes has not been evaluated in randomised controlled trials and may not be completely protective against neonatal herpes

- If vaginal delivery is unavoidable, aciclovir treatment of mother and baby may be indicated.

#### RECURRENT GH (III, B)

- Sequential cultures during late pregnancy do not predict viral shedding at term<sup>32</sup>.
- If there are no genital lesions at delivery, CS to prevent neonatal herpes should not be performed.
- Symptomatic recurrences during the third trimester are likely to be brief; vaginal delivery is appropriate if no lesions are present at delivery.
- Continuous aciclovir in the last four weeks of pregnancy may modestly reduce the risk of clinical recurrence at term but not of CS. Aciclovir reduces, but does not eliminate, viral shedding<sup>33</sup>.
- Continuous aciclovir in the last four weeks of pregnancy may be cost-effective compared with no therapy or with CS<sup>34</sup>.
- The benefits of obtaining specimens for culture at delivery to identify women who are asymptotically shedding HSV are unproved.

#### GENITAL LESIONS AT THE ONSET OF LABOUR (III, B)

- Current practice in the United Kingdom is for delivery by CS, despite lack of evidence for its effectiveness.
- The risks of vaginal delivery for the fetus are small and must be set against risks to the mother of CS<sup>35</sup>.

#### PREVENTION OF ACQUISITION OF INFECTION (IV, C)

- maternal risk of HSV acquisition in pregnancy varies geographically and local epidemiological surveillance should guide strategy for prevention<sup>36</sup>.
- All women should be asked at their first antenatal visit if they or their partner have ever had GH.
- Asymptomatic female partners of men with GH should be strongly advised not to have sex during recurrences. Conscientious use of condoms throughout pregnancy, especially the third trimester, may reduce the risk of acquisition, but this is unproven.
- Pregnant women should be advised of the risk of acquiring HSV-1 as a result of oro-genital contact.
- Identifying susceptible women by means of type specific antibody testing has not been shown to be cost-effective<sup>13</sup>.

- All women, not just those with a history of GH, 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 herpes in immunocompromised individuals

- clinically refractory lesions due to genital HSV are a major problem in patients with severe immunodeficiency, including late stage HIV disease.
- a consensus symposium on management of aciclovir resistant HSV led to the publication of guidelines<sup>37</sup> (modified in figure 1).

#### SUPPRESSIVE ANTIVIRAL THERAPY

A standard suppressive regimen should be used for immunocompromised patients who have frequently recurring GH.

The relative costs of antivirals are given in table 3.

#### Auditable outcome measures

- Virological confirmation should be attempted in all patients. Target 100%.
- At least one viral isolate should be typed. Target 100%.
- Patients presenting early in the course of first episode GH should be offered antiviral therapy. Target 100%.
- Patients with a diagnosis of GH should be offered counselling, support, and written information. Target 100%.
- Suppressive therapy should be offered to all patients with more than six recurrences annually. Target 100%.
- If suppressive therapy is commenced, a clear plan of duration of treatment should be entered in the notes and the patient should be reviewed in accordance with this. Target 100%.

#### **Authors**

Herpes Simplex Advisory Panel (special interest group of the MSSVD): Simon Barton (Chelsea and Westminster Hospital), David Brown (Public Health Laboratory Service),

Frances M Cowan (University College London), Susan Drake (Birmingham Heartlands Hospital), John Green (Paterson Centre, London), George Kinghorn (Royal Hallamshire Hospital), Patricia Munday (Watford General Hospital), Raj Patel (University of Southampton), Deenan Pillay (University of Birmingham), Anne Scoular (Glasgow Royal Infirmary), Derek Timmins (Royal Liverpool University Hospital), Paul Woolley (Withington Hospital), Mark Whitaker (General Practitioner, Didsbury).

### **Membership of the CEG**

Clinical Effectiveness Group: chairman, Keith Radcliffe (MSSVD); Imtyaz Ahmed-Jushuf (AGUM); Mark FitzGerald (AGUM); Janet Wilson (Royal College of Physicians GU Medicine Committee); Jan Welch (MSSVD).

### **Conflict of interest**

The Herpes Simplex Advisory Panel is a special interest group of the MSSVD. It is currently sponsored by an educational grant from GlaxoWellcome. All panel members have undertaken research and been funded to attend meetings by GlaxoWellcome and/or SmithKline Beecham.

### **Evidence base**

Drug therapy: Cochrane search strategy for randomised controlled trials combined with herpes genitalis in MeSH and GH (free text).

Diagnosis: MeSH "Herpes-genitalis-diagnosis," "Herpes-simplex-diagnosis," "Sensitivity," "Specificity."

Neonatal herpes:MeSH "Neonatal herpes," "pregnancy complications-infectious," "Herpes near pregnancy" (free text).

Hand searching of reference lists of articles was undertaken.

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### Definitions

**Initial episode:** First episode with either HSV-1 or HSV-2. Dependent on whether the individual has had prior exposure to the other type, this is further subdivided into:

**Primary infection:** first infection with either HSV-1 or HSV-2 in an individual with no pre-existing antibodies to either type.

**Non-primary infection:** first infection with either HSV-1 or HSV-2 in an individual with pre-existing antibodies to the other type.

**Recurrent episode:** recurrence of clinical symptoms due to reactivation of pre-existent HSV-1 or HSV-2 infection after a period of latency.

*Table 1 Detection of HSV in lesions, available tests*

	<b>Virus culture “the gold standard”</b>	<b>Antigen detection (immunofluorescence on smears)</b>	<b>Antigen</b>	<b>Nucleic Acid</b>
<b>Source</b>	Swabs/scraping	Smear/tissue section	Swabs/ scraping	Swabs/ scraping
<b>Sensitivity</b>	High; >90% from lesions	Low	80%	Highest (used for research studies)
<b>Specificity</b>	High	High	High	Controls for cross- contamination important
<b>Advantages</b>	Allows virus typing and antiviral sensitivity using Monoclonal antibodies	Low cost	Low cost; fast; may be useful late in episode <sup>7,8</sup>	Allows virus typing, high sensitivity
<b>Disadvantages</b>	Sample transport, labour intensive, expensive	Insensitive	Insensitive, no viral typing	No commercial assay, expensive

*Table 2 Positive predictive values for HSV-2 antibody assays*

	<b>Prevalence</b>	<b>Positive predictive value*</b>
Sexually transmitted infection clinic <sup>9</sup>	25%	86%
General population antenatal clinic <sup>11</sup>	5%	50%

- For an assay with 95% sensitivity and specificity

*Table 3 Relative costs of antiviral drugs for treating genital herpes\**

<b>Indication</b>	<b>Treatment duration</b>	<b>Aciclovir</b>		<b>Famciclovir</b>	<b>Valaciclovir</b>
		<b>Generic</b>	<b>Zovirax</b>		
<b>First episode</b>	5 days	£5.54	£20.22	£84.35	£23.50
<b>Recurrence</b>	5 days	£5.54	£20.22	£28.12	£23.50
<b>Suppression</b>	1 year	£194	£966	£4104	£857

\*Source of costing DMG tariff MIMS November 2000 (Different prices may be negotiated by NHS hospital trusts).

Figure 1 Management of herpes in immunocompromised individuals

