CHRONIC VULVO-VAGINAL HERPES SIMPLEX

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Objectives

- Epidemiology & aetiology
- Symptom control
- Transmission
  - Sexual
  - Pregnancy

- Not covering:
  - Acute HSV
  - HIV co-infection
  - Serodiscordance in pregnancy
EPIDEMIOLOGY & AETIOLOGY
European HSV epidemiology

- Estimated European HSV prevalence 0-49 years:
  - HSV-1: 69% women, 61% men\textsuperscript{1}
  - HSV-2: 21.7% women, 9.7% men\textsuperscript{2}
- Large inter-country differences for age-standardised seroprevalence\textsuperscript{3}
  - HSV-1: Bulgaria (83.9%), Finland (52.4%)
  - HSV-2: Bulgaria (23.9%), England & Wales (4.2%)

Natural history

Infection acquisition

Symptomatic 1st episode (1/3)

Latency (in local dorsal root sensory ganglia)

Asymptomatic shedding

No reactivation

Symptomatic recurrent disease

Potential transmission

Transmission: sexual partners & pregnancy

Symptom control

Alexander L, Naisbett B. *J Infect Dis* 2002;186(S1):S57–S65
Symptoms of recurrent HSV

- Self-limiting, generally minor symptoms
- Ulceration limited to infected dermatome
- Systemic symptoms rare
- Unilateral lymphadenitis in 30%

Recurrence frequency

<table>
<thead>
<tr>
<th>Recurrence frequency</th>
<th>Primary HSV-1</th>
<th>Primary HSV-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st year recurrence rate</td>
<td>1.0</td>
<td>5.0</td>
</tr>
<tr>
<td>2nd year recurrence rate</td>
<td>0.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Diagnosis

• PCR (NAAT): HSV type-specific DNA detection
• Serology: HSV type-specific antibody detection
  • IgM unreliable, IgG = infection at some point
  • Takes several weeks to develop
  • Sensitivity 91-99%, specificity 92-98%
  • Limit use: recurrent/atypical genital disease with negative PCR or transmission concerns

<table>
<thead>
<tr>
<th>HSV-2</th>
<th>Prevalence</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUM</td>
<td>25%</td>
<td>86%</td>
</tr>
<tr>
<td>ANC</td>
<td>5%</td>
<td>50%</td>
</tr>
</tbody>
</table>
Reliability of serology

- **False positives (~4% uninected population)**
  - HSV-1
  - Low positive result (?non-specific IgG binding)
  - Many research studies require x3 above cut off
  - PPV & prevalence (population vs patient)

- **False negatives**
  - African / HIV / post organ transplant
  - Recent infection
  - Failure to seroconvert
  - Up to 1/12 HSV-2 & 1/3 HSV-1: seroreversion
SYMPTOM CONTROL
Management of recurrences

• Supportive: saline bathing, topical petroleum jelly, analgesia, 5% lidocaine ointment

• Episodic:
  • Episodic antivirals reduce duration & severity
  • Early treatment most effective
  • Short-course therapy is more convenient & cost-effective & just as clinically effective

• Suppression:
  • Frequency, severe psychological morbidity, severity, reduction of transmission
  • >20 years of safety data
Episodic therapy regimens

• Recommended short course therapy
  • Aciclovir 800 mg TDS for 2 days
  • Famciclovir 1 g BD for 1 day
  • Valaciclovir 500 mg BD 3 days

• Alternative 5 day courses
  • Aciclovir 400 mg TDS (3–5 days)
  • Aciclovir 200 mg 5 times daily
  • Valaciclovir 500 mg BD
  • Famciclovir 125 mg BD
Suppression therapy

- Aciclovir 400 mg BD (all frequencies of disease recurrence)
- Valaciclovir 500 mg OD (<10 recurrences/annum)
- Valaciclovir 1 g OD (>10 recurrences/annum)

- 2\textsuperscript{nd} stage therapy for poorly controlled patients
  - Aciclovir 400 mg TDS
  - Valaciclovir 250 mg BD
  - Valaciclovir 500 mg BD
  - Aciclovir 200 mg QDS
Recurrence frequency for suppression

• Early trials: recurrence rate >6 recurrences/annum
• More recent studies: much milder disease
• Patients across all spectrums have a substantially reduced recurrence rate
• Recurrence frequency to start suppressive therapy
  • Frequency, impact of disease, transmission risk
  • Cost & inconvenience of treatment
• Majority: occasional symptomatic recurrence
Assess ongoing need annually

- Patient circumstances may alter
- On stopping many do not have a significant alteration in disease frequency/severity
- Short courses of suppressive therapy: fully suppressive effect obtained after 5 days
Do I keep getting recurrences due to my genes?

- Role of human variation in severity unclear
- Genome-wide association study on 223 Europeans with HSV-2
- Severity measured by viral shedding rate (correlates with lesion rates) over ≥30 days
- Adjusted for age, sex, and ancestry
- No genome-wide significant associations with HSV-2 viral shedding rate

Kleinstein S et al. Genes Immun 2018
TRANSMISSION
Transmission

- 50% transmit in 1st 6/52
- Mean time to transmission 3.5/12 (40 sex acts)
- Then ~3%/year
- Long term relationships: most eventually transmit
- Risk reduction: selective abstinence during prodromes & recurrences, condoms, suppression, disclosure

Wald A et al. JID 2006;194:42-52
Condoms & disclosure

• 100% condom use ↓ transmission by 30%¹
• Risk of acquisition ↓ 7% for every additional 25% of the time condoms used
• Risk ↑ with ↑ frequency of UPSI
• Disclosure delays time to transmission from 6 weeks to 9/12²

2. Wald A et al. JID 2006;194:42-52
Suppression

1484 heterosexual immunocompetent monogomous partners serodiscordant for HSV-2

<table>
<thead>
<tr>
<th></th>
<th>VCV 500mg OD 8/12</th>
<th>Placebo 8/12</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant HSV-2</td>
<td>0.5%</td>
<td>2.2%</td>
<td>0.25</td>
</tr>
<tr>
<td>Acquisition of HSV-2</td>
<td>1.9%</td>
<td>3.6%</td>
<td>0.52</td>
</tr>
<tr>
<td>Shedding from infected partner</td>
<td>2.9% days</td>
<td>10.8% days</td>
<td></td>
</tr>
<tr>
<td>Recurrence rate in infected partner</td>
<td>0.11/month</td>
<td>0.40/month</td>
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No significant difference between ACV & VCV in suppressing frequency & quantity of shedding

Shedding

- Lifetime shedding rate 18% (↓ with time)
- ~30 episodes/yr (hrs-wks, median 13hrs)
- 80% asymptomatic
- Peak viral production varies (→ over time)
- High shedders remain high shedders
- Shedding = surrogate marker for recurrence frequency

Ramchandani M et al. Sex Transm Infect 2017;0:1-3
Can I catch HSV-2 again?

- 2 samples 5/12 apart: Africa, Peru & US
- Prevalence of dual strains = 3.7% (adjusted = ~7%)
- Risks: Africa, HIV+ x4 risk (CD4>350)
- Dual strains fairly rare
  - ? Immune response
  - ? Primary infection less likely than superinfection

Pregnancy

- Neonatal HSV: localised, encephalitis, disseminated infection
- Recurrent HSV: low risk for neonatal HSV even with lesions at delivery (0-3%)
- Recurrent disease during pregnancy
  - Avoid episodic therapy where possible
  - Case-by-case if severe/complicated disease
  - Avoid newer antivirals & titrate dose down to minimum effective
Maternal antiviral prophylaxis

- Suppressive aciclovir 400mg TDS from 36/40
  - Can’t estimate effect on neonatal HSV
  - ↓ recurrence at delivery (RR 0.28, NNT 10)
  - ↓ Caesarean section for HSV (RR 0.30, NNT 10)
  - ↓ shedding at delivery (RR 0.14, NNT 17)

- 200 women in Uganda, prophylaxis BD from 28-36/40 or placebo, all prophylaxis from 36/40
  - No reduction in PPROM / HSV-2 shedding / low birth weight
  - ↓ preterm delivery (RR 0.41) & admission to special care (RR 0.43)

2. Nakubulwa et al. Reproductive Health 2017;14:31
Recurrent genital lesions at onset of labour

- May consider Caesarean section considered for women with recurrent genital herpes lesions at the onset of labour
- Risk of neonatal herpes following vaginal delivery is small
- Balanced against risks to the mother of Caesarean section
- If there are no genital lesions at delivery, there is no indication for a Caesarean section to prevent neonatal herpes
Tak!

Available on the IUSTI website:

2017 European guidelines for the management of genital herpes

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