Sexually Transmitted Viral Infections
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Herpes Simplex Types 1 and 2
- DNA viruses
- Differ in DNA content
- Share many antigens but several unique
  - Glycoprotein G
- No longer appropriate to refer to viral types as site specific

HSV-2 Seroprevalence in Suburban Practices
- N = 5452
- Seropositives: 25.5%
  - 88% did not know they had genital herpes
  - Percentages support NHANES survey

HSV-2 seroprevalence: men and women
(95% confidence intervals rounded off)

- NHANES 1999-2004 2005-2010
  - 14-19 yo 1.0% (1.2-1.9) 1.2% (0.8-1.5)
  - 20-29 yo 10.6% (8-12) 9.9% (9-11)
  - 30-39 yo 22.1% (20-24) 19.3% (17-21)
  - 40-49 yo 26.3% (24-29) 25.6% (23-28)
  - TOTAL 17.2% (17-19) 16.7% (15-17)

- Little change between these intervals
- Beware of cohort effects


Leone: Sex Transm Dis 2004;31:311-6
HSV Acquisition

- Control group in vaccine trial: HepA vaccine
- N = 3438, 18-30 yrs, f/u 20 months

<table>
<thead>
<tr>
<th>Acquisition</th>
<th>HSV-1</th>
<th>HSV-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Genital</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Both</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>74%</td>
<td></td>
</tr>
</tbody>
</table>

Confirms earlier observations that HSV-1 can be genital or orolabial, but HSV-2 is almost always genital.

Similar presentations: Clinical diagnosis of genital lesions: PPV 83%

Key Points

- If it looks just like genital herpes, it probably is
- Clustering of lesions is a helpful clue
- Unlikely to see intact vesicles, especially in women
- Lesions my coalesce
- Never treat with an occlusive preparation (e.g. petroleum jelly)

Accuracy of the Clinical Diagnosis of Genital Herpes

Langenberg. NEJM 1999;341:1432

Sensitivity = 39%; Specificity = 99%; Positive predictive value = 81%

<table>
<thead>
<tr>
<th>Western Blot Positive</th>
<th>Western Blot Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Diagnosis Positive</td>
<td>60</td>
</tr>
<tr>
<td>Clinical Diagnosis Negative</td>
<td>95</td>
</tr>
<tr>
<td>Total</td>
<td>155</td>
</tr>
</tbody>
</table>

Clinical Features of Typical Recurrent Genital Herpes

- Prodrome: about 30%
  - Itching, burning, tingling
  - Nonspecific
- Grouped lesions
- Begin as blisters
- Rupture to form shallow ulcers
- Heal with crusting
- Course about 5 days
HSV as a cause of benign recurrent lymphocytic meningitis

- 20 patients with BRLM, 7 excluded
- 3/13 had known genital herpes
- 11/13 (84.6%) had HSV DNA in CSF by PCR
- HSV Ab by immunoblot in 13/13
- 10/11 HSV-2

Symptomatic Genital Recurrences

Among patients with initially symptomatic genital herpes, symptomatic recurrences are experienced by

- HSV 1: 14%-25%
- HSV 2: 60%-88%

Persistent HSV-2 shedding

- 377 pts with symptomatic genital herpes
- Swabs for PCR on 30 consecutive days
- Shedding after Dx: percentage of days

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Subclinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>33.6%</td>
<td>26.2%</td>
</tr>
<tr>
<td>1-9 years</td>
<td>20.6%</td>
<td>13.1%</td>
</tr>
<tr>
<td>≥ 10 years</td>
<td>16.7%</td>
<td>9.3%</td>
</tr>
</tbody>
</table>

Phipps w, et al: J Infect Dis 2011;203:100-87

HSV and HIV

- Coprevalent
- In advanced HIV, HSV is sometimes chronic, necrotizing, and difficult to treat
  - May require more toxic drugs, eg: gancyclovir
  - May be caused by ACV-resistant mutants
- HSV activates lymphocytes and may lead to higher viral loads
Genital HSV and HIV
A meta-analysis

- 18 cross-sectional and case-control studies
  - If HSV-2 seropositive, odds ratio for HIV is 4.2 (3.1-5.8)
- 9 prospective cohort or nested case-control studies
  - Prior HSV-2 infection, odds ratio for subsequent HIV is 2.1 (1.3-3.2)
- Yet another example of coprevalence??

Wald, A, Link K: Abstract 39th IDSA, October 2001

Treatment/suppression of HSV-2 reactivation reduces HIV viral load

- Symptomatic or asymptomatic
- Transient reduction: 0.25-0.5 log
- Hypothetical mechanisms
  - Reduced immune activation
  - Direct effect on HIV: requires phosphorylation
    - Cellular enzymes (inefficient)
  - Other coprevalent viruses
- May not reduce transmission of HIV


Untreated HSV-2 does not accelerate CD4 decline

- 218 HIV+ patients with ART-free interval, CD4 400-900
- 123 HSV-2 +, 161 HSV-1+
- No significant association of CD4 decline with HSV-2 or HSV-1 (~14 cells/year)
- Significant association with HIV viral load and with hepatitis C infection (45 cells/year)


HSV-2 and HIV/AIDS

- HSV activates lymphocytes, may increase production of HIV: suppression of HSV may reverse this
- 60 HIV-1/HSV-2 coinfected men, CD4 392-719
  - Valacyclovir: 500mg bid, 1 gm bid, placebo for 12 weeks
  - Activated CD8 and total CD8, CRP, IL6, SIAM 1
- No significant changes.

Most people with genital herpes don’t know they have it

- Classical symptoms and signs 20%
- Atypical symptoms or signs 60%
- Neither symptoms nor signs 20%

About 20% of patients with genital herpes know they have the infection

Asymptomatic HSV Infection

- Prospective study of incident infections
  - Usually Asymptomatic
  - HSV-1: 74%
  - HSV-2: 63%
- Among women with a history of genital herpes, 25% of recurrences are asymptomatic
  - Never say that asymptomatic sex is safe


Sources of genital herpes infections

- 40% Symptomatic but unrecognized
- 35% Seropositive, asymptomatic
- 25% Known HSV, currently asymptomatic
- 29/43 (67%) had sex while symptomatic


HSV-2 Natural History

- HSV-2 Seropositive: N = 498, 43% men
  - Asymptomatic/subclinical: no diagnosis
  - Symptomatic: previous diagnosis
  - HSV 1-/2+ 54%; 1+/2+ 46%
- ≥ 30 daily swabs
  - Men: penile skin, perineum, perianal
  - Women: vagina, vulva, perineum, perianal
- Fluorescence-based quantitative PCR
  - Positive: >150 DNA copies/ml

Tronstein E, et al: JAMA 2011;305:1441-9
# HSV-2 Natural History

<table>
<thead>
<tr>
<th>Shedding while asymptomatic</th>
<th>Detection ≥ 1 day (pts)</th>
<th>Detection if no lesions</th>
<th>Median $\log_{10}$ virus</th>
<th>Duration of shedding (IQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous Sx</td>
<td>83% (80-81)</td>
<td>13d (12-15)</td>
<td>4.9 (80,000)</td>
<td>5d (3-9)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>68% (59-78)</td>
<td>9d (6-12)</td>
<td>4.5 (30,000)</td>
<td>2d (1-3.5)</td>
</tr>
</tbody>
</table>

Tronstein E, et al: JAMA 2011;305:1441-9

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# Effect of condoms on HSV-2 transmission

- Omentum condoms do pass virus, latex condoms do not
- Latex condoms do not pass viruses
  - Unless they break (4/1000)
  - Unless they are not used correctly (during penile/vulvar or penile/anal contact)

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# Does condom use reduce acquisition of HSV-2?

- 6 pooled, prospective studies, usually control groups for vaccine/suppression trials
- $N = 5384$, 2M followup days
- Overall incidence 7.4 (6.7-8.2) per 100 person-years
- Multivariate analysis:
  - Increase of 25% in condom use reduced incidence by 7%, $P = .01$
  - Use of condoms 100% decreased acquisition by 30%, $P = .01$


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# A common question:

“But I love him. We don’t want to use condoms all the time. What kind of chance am I taking?”

It is always dangerous to extrapolate from group statistics to individuals.....but:

In a number of studies of mutually monogamous discordant couples, the infection rate was about 10%/year
What else can be done (and cannot be done) to reduce the risk of giving HSV to a sexual partner?

Key Points
- My approach: first document frequency and severity of recurrences before deciding on suppressive Rx
- Risk of transmission reduced by condom use
- Suppressive therapy reduces but does not eliminate transmission

HSV-2 Suppressive Therapy
- Crossover studies: 4-7 weeks each arm
- Swabs 4X/day, quantitative PCR: 5.4% +
- Bottom Lines
  - Suppressive therapy better than no treatment
  - No significant differences among treatment groups: high dose no better than standard dose
  - Suppressive therapy reduces but does not eliminate shedding

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% swabs+</th>
<th>Episodes/P-Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>18.1%</td>
<td>28.7</td>
</tr>
<tr>
<td>Acyclovir 400 mg bid</td>
<td>4.2%</td>
<td>10.0 - 14.9</td>
</tr>
<tr>
<td>Acyclovir 800 mg tid</td>
<td>4.5%</td>
<td>16.5 - 20.2</td>
</tr>
<tr>
<td>Valaciclovir 500 mg qd</td>
<td>3.3% - 5.8%</td>
<td>22.6</td>
</tr>
<tr>
<td>Valaciclovir 1 gm tid</td>
<td>5.4%</td>
<td></td>
</tr>
</tbody>
</table>

Suppression of HSV reduces but does not eliminate transmission

- Double-blind, placebo controlled
- 1484 monogamous, heterosexual couples
- Discordant with respect to HSV-2
- Source: 9 or fewer episodes/year
- Valacyclovir 500 mg p.o. daily
- Endpoint: symptoms or seroconversion

<table>
<thead>
<tr>
<th></th>
<th>Valaciclovir</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic Acquisition</td>
<td>4 (0.5%)</td>
<td>16 (2.2%)</td>
</tr>
<tr>
<td>HSV-2 Seroconversion</td>
<td>12 (1.6%)</td>
<td>24 (3.2%)</td>
</tr>
<tr>
<td>Overall transmission</td>
<td>14 (1.9%)</td>
<td>27 (3.6%)</td>
</tr>
</tbody>
</table>

45% reduction in overall risk of acquisition
75% reduction in risk of symptomatic acquisition

Possible indications for suppressive therapy

- Long-Term Suppression
  - Frequent recurrences
  - Painful recurrences
  - Psychological distress
  - Protection of partner
- Short Term Suppression
  - Late pregnancy
  - Exams
  - Vacation
  - Important job issue
  - Honeymoon
  - High stress episode

Another common question:

“We both have herpes. Can we give it to each other?”

If you acquired your herpes from different partners, you may be able to transmit it to each other.

If, however, one of you gave herpes to the other, it is very unlikely that you will superinfect each other.
**Dating Services for People with Herpes**

- **The positive:**
  - It is easier to discuss herpes when both partners have it.
  - Shared experience assists in bonding
  - If one is honest about herpes, one may also be honest about other sexual risk factors
- **The negative:**
  - Partners could still infect each other
    - Type 1 vs type 2
    - Subspecies

**Key Points**

- 70% of newly acquired genital herpes is HSV-1, particularly among younger people
- Genital HSV-1 recurs less frequently than does HSV-2

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**HSV-1 Genital Infection**

- **Overall prevalence:** at least 35% of genital herpes
- **In newly acquired cases among young people:** about 70%


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**Why do we expect to see more genital HSV-1?**

- More oral sex, and this among younger people
  - 75% of college students
  - 33%-59% of high school students
  - Less condom use during oral sex
- Fewer very young people experiencing nonvenereal acquisition and therefore first exposed sexually
  - Less crowding
  - Better hygiene
  - More care regarding people with known orolabial HSV and babies (Aunt Edna)
### HSV-1 seroprevalence in men and women

(95% confidence intervals rounded off)

- **NHANES:**
  - 1999-2004: 39.0% (37-41)
  - 2005-2010: 30.1% (27-33)
  - 20-29 yo: 54.4% (52-57) vs. 49.5% (46-52)
  - 30-39 yo: 63.5% (61-66) vs. 61.8% (59-65)
  - 40-49 yo: 65.3% (63-68) vs. 63.6% (60-67)
  - TOTAL: 57.9% (56-60) vs. 53.9% (52-56)

- Decrease in prevalence in "presexual" ages
- Overall prevalence of antibody is high
- Beware of cohort effects

**Bradley H, et al:** J Infect Dis 2014;209;325-33

### % of Genital Herpes Due to HSV-1

- University of Wisconsin (shhhh)
- First episode
- Culture, monoclonal antibody typing.
- 1993-2001
- 2.5 fold increase in percentage of genital isolates that were HSV 1 (30.9% < 77.6%)
- Especially among younger students (16-21 yo)

**Sex Transm Dis 2003;30:947-800**

### % of Genital Herpes Due to HSV-1

- Tel Aviv, first episode, culture with monoclonal antibody typing. Isolates 1993-2002
- Nongenital: 656/659 (99.55%) type-1
- Genital: 189/285 (66.30%) type-1

<table>
<thead>
<tr>
<th>Age</th>
<th>N</th>
<th>% Genital type 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>132</td>
<td>72.7%</td>
</tr>
<tr>
<td>25-44</td>
<td>140</td>
<td>62.0%</td>
</tr>
<tr>
<td>≥43</td>
<td>54</td>
<td>46.0%</td>
</tr>
</tbody>
</table>

**Sex Transm Dis 2003;30:794-6**

### HSV Types in Cervical Specimens

- HSV PCR on 60,000 cervical specimens
- Jan- Dec 2007
- 14% positive for HSV
- 32% HSV-1
- Among women <24 years old: 47% HSV-1

HSV in genital specimens

- Vaginal swabs from 800 women collected for GC/CT testing
  - Average age 29.8 +/- 9.2 years
- Among 13-30 year-olds
  - HSV-1: 5.26%
  - HSV-2: 4.31%


Consequences

- It is not appropriate to use the terms HSV-1 and HSV-2 respectively for orolabial and genital infections. They refer to viruses, not anatomic sites
- The only sexually transmitted condition your patients cannot get through oral sex is pregnant

Implications of the increase in genital HSV-1

- Type-2 specific serological screening less useful:
  - Cannot reassure individual about genital disease
  - Underestimates prevalence of genital infection
- HSV-1 recurs less frequently than HSV-2: less potential for spread?
- HSV-1 confers partial protection against HSV-2
- HSV-1 is less susceptible to antivirals than HSV-2
- Vaccines against HSV-2 even less useful than they already appear

Genital HSV-1 is less frequently recurrent than HSV-2

53 women, 30 men with primary genital HSV-1 followed 2.7 years

Recurrences during first year:

- 38% none
- 35% 1
- 27% 2 or more

Median time to first recurrence = 233 days (170-335)

Wald et al: Abstract 39th IDSA, October 2001
HSV-1 probably protects against HSV-2

- 1171 HSV-2 Discordant monogamous couples, 19 months followup:
  - Acquisitions of HSV-2/year
    - HSV-1 negative: 39/271 (14.4%)
    - HSV-1 positive: 39/678 (5.9%)

Sprunke et al: Abstract 39th IDSA, October 2001

Case

A 23 year-old woman is entering into a new heterosexual relationship and has been asked by her intended to be evaluated for genital herpes. She has had only penile-vaginal intercourse, six prior sexual partners, and no history of genital or orolabial lesions. She presents having obtained type-specific HSV serology which is positive for HSV-1 and negative for HSV-2, asking for guidance.

Question: What can you tell her regarding possible genital herpetic infection?

1. Nothing
2. Genital herpes is very unlikely but is possible
3. She probably has orolabial herpes acquired as a baby and should be careful about fellatio
4. She has genital herpes

Serological Tests for HSV-2 Antibody

- Sensitivity: 80%-98
  - Takes 1-2 weeks for measurable antibody to develop
- Specificity: ≥ 96%
The problem with screening with type-specific HSV serology

- Most people are seropositive for HSV-1
  - By age 30:
    - 50% higher SES
    - 80% lower SES
  - By age 40-50, 90% infected
- In some groups, the majority of genital herpetic infections are now HSV-1
- Screening for HSV-2 alone is risky
- Therefore, in most cases (type-1 positive, type-2 negative) genital HSV infection cannot be ruled out
- If type-2 positive, genital infection is most likely

Type-Specific HSV Serology (CDC 2006)

- Might be useful in the following scenarios:
  - Recurrent or atypical symptoms with negative cultures
  - Clinical diagnosis of genital herpes without laboratory confirmation (?)
  - Partner with genital herpes (especially in pregnancy)
  - Testing reduced risky sexual behavior among pregnant women
- Some specialists think this should be part of a complete STD evaluation in:
  - Multiple sexual partners
  - HIV
  - MSM
- Type-specific screening is not useful in the general population


Short Course Therapy of Recurrent HSV-2 Genital Herpes

Valacyclovir 500 mg orally bid

<table>
<thead>
<tr>
<th></th>
<th>N=362</th>
<th>N=359</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 days</td>
<td>5 days</td>
<td></td>
</tr>
<tr>
<td>Time to lesion healing</td>
<td>4.4 d</td>
<td>4.7 d</td>
</tr>
<tr>
<td>Duration of pain</td>
<td>2.9 d</td>
<td>2.5 d</td>
</tr>
<tr>
<td>Length of episode</td>
<td>4.3 d</td>
<td>4.4 d</td>
</tr>
</tbody>
</table>

Clin Infect Dis 2002;34:958-62

Short Course Therapy of Recurrent HSV-2 Genital Herpes

- Acyclovir 800 mg tid for 2 days vs placebo N= 84
- Duration of viral shedding: 58.5 hrs >25 hrs
- Duration of lesions: 6 d >4 d
- Time to next recurrence: 40.5 d > 48 d (NS)

Clin Infect Dis 2002;34:944-8
Single day Rx of recurrent HSV with famciclovir

- Placebo controlled, Intent to Treat
- Recurrent disease, HSV type 2
- Famciclovir 1000 mg orally twice daily at onset of symptoms
- Time to complete reepithelialization
  - Placebo: 5.0 days
  - Famciclovir: 3.5 days
- p<0.001
- Abortion of lesions (no ulceration)
  - Placebo: 12.7%
  - Famciclovir: 23.3%
  - P=0.003
- Headache: 13.5% vs 5.4%


Other considerations in treatment of HSV

- Higher dose initial therapy (4 gm/day) has no effect on duration of symptoms or rate of recurrences
- Breakthroughs of suppression in normal hosts are not associated with acyclovir resistant mutants

Genital Herpes in Pregnancy

Risk of transmission by vaginal delivery
- Initial HSV acquired near time of delivery
  - Risk 30%-50%
  - No transplacental antibody
  - High genital viral loads
  - Frequent involvement of cervix
- With history of genital HSV or HSV acquired during first trimester
  - Overall risk <1%


Pregnancy: where HSV serology may be useful

- 287 HSV-2 seronegative pregnant women: Partners tested
- % of days with unprotected genital sex by partner serostatus
  - HSV-2 seropositive: 2% vs 8% (P=0.002)
  - HSV-2 unknown: 2% vs 11% (P=0.02)
- HSV-1 discordant couples showed no change in sexual behavior

**Neonatal HSV and Ritual Circumcision**

- *Metzitzah b'peh*: mohel sucks blood away from neonate’s penis
- 11 cases 2000-2011
- Incubation periods: 5-20 days
- Surveillance 2006-2011: 84 cases
  - 45 in males, 22 (59%) HSV-1, 8 untyped
  - 39 in females, 15 (45%) HSV-1, 6 untyped
- Estimated risk in NYC
  - ~1:4100
  - ~3.4X estimated risk of no orogenital contact
- Avoid this practice, legal prohibition pending.


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**Future Rx for genital herpes**

- Standard therapies: nucleoside analogs,
  - Inhibit DNA polymerase
  - Require phosphorylation
- New thrapy: Pretelivir
  - Inhibits helicase-primase
    - Separates (unwinds) DNA strands
    - Synthesizes RNA primer
  - Does not require phosphorylation
  - Active against nucleoside-resistant isolates
  - May be used for combination therapy


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**Antiherpes drugs in early pregnancy**

- N = 838K, Denmark
  - Medical Birth Register
  - Prescription Drug Register: during first trimester
    - Acyclovir
    - Valacyclovir
    - Famciclovir
- Major birth defects, Prevalence Odds Ratio
  - Antiviral drug: 2.2%
  - No antiviral drug: 2.4%
  - Prevalence Odds Ratio: 0.89 (0.65-1.22)
- Note:
  - Cannot assess effect on individual birth defects
  - Prescriptions filled not drug used

Pasternak et al: JAMA 2010;304:859-866
Mills JL, Carter TC: JAMA 2010;304:905-6

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**Future Rx for genital herpes**

- HSV-2 seropositive with Hx of outbreaks, HIV-
  - Median duration 11 years
  - 147 completed study
  - Daily genital swabs and diary

<table>
<thead>
<tr>
<th>Dose: mg/d (X 4 wks)</th>
<th>0</th>
<th>5</th>
<th>25</th>
<th>75</th>
<th>400mg/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shedding % d</td>
<td>16.6</td>
<td>18.2</td>
<td>9.3</td>
<td>2.1</td>
<td>5.3</td>
</tr>
<tr>
<td>Lesions %d</td>
<td>9.0</td>
<td>12.5</td>
<td>3.3</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Recurrences N</td>
<td>12</td>
<td>18</td>
<td>12</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

Next: comparison with standard therapies

“HSV-Eraser Program”
- Two-step program of vitamins and supplements
  - Step 1: 10 days, destroys "ICP47" which "cloaks" the virus
  - Step 2: 11-13 days, stimulates the immune system to destroy the virus
  - In 3 weeks, blood tests completely negative (OMG)
- 100% effective in 479 people
- Big PHARMA suppressing data
- Standard antiherpes meds are highly toxic
- $399 ➔ $199 ➔ $99 ➔ $39
- OMG!!
- Researchers do not exist
- ICP47 does: effectively blocks the major histocompatibility complex class I antigen presentation pathway (J Virol 1998)
- Physiologically impossible (for so many reasons)
- Toxicity: I wasted ½ hour that I will never get back

If colposcopy negative...
- 2796 women with abnormal pap or high-risk HPV
- No visible lesions on colposcopy
- Single random cervical biopsy
  - CIN 1: 5.7%
  - CIN 2: 1.3%
  - CIN 3: 1.4%
- If carrying HPV 16 or 18: CIN 2 or 3 24.7%
  

**Antimicrobial resistance: it's not just far bacteria any more**
- 211 HSV clinical samples, 2008-2012, many from immunocompromised patients
- Genotype: thymidine kinase (UL23) and Pol (UL30)
- Acyclovir plaque reduction
- Resistance: ?clinical significance
  - Resistant: 30.7%
  - Susceptible: 34.9%
  - Uncertain: 23.8%
- Type specific resistance
  - HSV 2: 53.8%
  - HSV 1: 34.9%
  

**Some Legal Implications of HSV**
Transmission of HSV covered by homeowner’s policy

- A man gave genital herpes to a sexual partner.
- She sued him.
- It was covered by his homeowner’s policy.
- The insurance company could not show that he intended harm.
- Insurance company permitted to add exclusion.

Standard exclusions to homeowners policies

“Medical payments to others do not apply to bodily injury or property damage which arises out of the transmission of a communicable disease by an insured”

Recent interpretations suggest that this applies only to person-to-person transmission by direct physical contact and not to diseases transmitted by airborne particles or food or water contamination, even when the transmission may be traced to human carelessness.

$15,000,000 Lawsuit for battery, negligence, and emotional distress

- Transmission of HSV and HPV
- The plaintiff “does not bear the burden of completely eliminating the possibility that the defendant’s conduct did not cause her injury......a plaintiff does not need to prove her case beyond a reasonable doubt.”
- And people think medical terminology is confusing!

Las Vegas Sun On-line 1/13/00
Herpes Lawsuit

- Civil lawsuit, No criminal proceeding
- Defendant:
  - Knew he had herpes: admitted immediately after coitus
  - “Thought he was no longer contagious”
- Claim
  - Battery: intentionally engaging in an activity (sex) that resulted in harm (herpes)
  - Negligence: breach of duty by infecting
- Verdict:
  - eHarmony
  - Comparative negligence: Man 75%, Woman 25%
  - $900,000

Chow, A: FindLaw.com 2012; June 7; reported in The Oregonian

The importance of the medical record

- A physician has been successfully sued because of a failure to document in the medical record that the patient had been informed about asymptomatic shedding.
- One should advise the patient to inform sexual partners of the diagnosis and document in the medical record that one has done so!

Molluscum Contagiosum

- Caused by a poxvirus
- Spread by direct contact
  - Kids - trunk
  - Adults - genital area, thighs, buttocks
- 1-3 mm with central umbilication
- Self limited: 6-9 months
  - “Squeezers and scrapers”
  - Risk of autoinoculation
- May be disseminated in advanced HIV
  - Lesions resemble those of cryptococcosis
  - Cryotherapy

Sexually transmitted vaccinia

- Vesiculopapular rash and contact to recently vaccinated partner
- Lesions of labia and vagina
- Virus present until scab separates from skin: 2-3 weeks
- Contact transmission: note digital-genital contact

MMWR 2010;59:773-5
Ebola

- Virus can be isolated from the semen for more than 60 days among those few lucky people who survive
- As transmission occurs by contact of infected secretions with broken skin or with mucous membranes, specifically sexual transmission seems possible
- The same is apparently true of other hemorrhagic fever viruses

A little about HPV

Effect of HPV vaccine on sexual behavior

- After vaccination for HPV, no difference in:
  - Engaging in high-risk behavior
  - Number of sexual partners
  - Age at sexual debut
  - Use of contraception (actually higher in recipients)


Sex toys and HPV

- 12 bisexual women, 18-29 yo, each given two vibrators and cleaning solution (which?)
  - Thermoplastic elastomer (rabbit style)
  - Soft silicone
  - Swabbed for HPV DNA testing
    - Immediately after use
    - After cleaning
    - 24 hours later
- 9 women HPV-positive, each had ≥ 1 vibrator +
- Positive for HPV: Immediate p-clean p-24 hrs
  - Plastic 8 5 2
  - Silicone 6 4 0

Cohen R Reuters News Service; bit.ly/1I36aab Sex Trans Infect, online 4/14/2014
HPV NAAT in screening

- Cobas HPV test® (Roche Diagnostics)
- Primary screening for women ≥ 25 yo
- 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68
- Management:
  - 16,18: colposcopy
  - Other types: pap smear to dx need for colposcopy

FDA: Press release April 24, 2014

HPV NAAT in screening

- Cobas HPV test® (Roche Diagnostics)
- Approved in 2011 in conjunction with or as followup to pap testing for women ≥ 30 yo
- Followup to abnormal cytology for women ≥ 21 yo
- Cohort study: 47208 women ≥ 25 yo, routine cervical exams, 3 years followup
- Positive by either test and subset negative by both tests had followup colposcopy and cx biopsy
  - Relative sensitivity for ≥ CIN3
    - HPV DNA: 58.3% (44.0-75.0)
    - Comparator: 42.6% (31.8-55.4)
  - Positive predictive value among women referred for colposcopy
    - HPV DNA: 12.5% (10.7-13.9)
    - Comparator: 6.5 (5.5-7.5))


Key point: Some different schedules of vaccination provide some protection

If someone is late for or misses an appointment for the vaccine, do not give up hope

Alternative Schedules for HPV4 Vaccine

N = 809 11-13 yo, Viet Nam
GMT Antibody levels 1 month after final dose: Type-specific competitive immunoassay.
Noninferior = lower bound of 95% CI > 0.5

Alternative Schedules for HPV4 Vaccine

<table>
<thead>
<tr>
<th>Schedule (Mo)</th>
<th>GMT Antibody Levels (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type 16</td>
</tr>
<tr>
<td>0,2,6</td>
<td>5808 (4196-6799)</td>
</tr>
<tr>
<td>0,3,9</td>
<td>5369 (4632-6222)</td>
</tr>
<tr>
<td></td>
<td>0.92 (0.71-1.20)</td>
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<tr>
<td>0,6,12</td>
<td>5716 (4877-6701)</td>
</tr>
<tr>
<td></td>
<td>0.98 (0.75-1.29)</td>
</tr>
<tr>
<td>0,12,24</td>
<td>3692 (3145-4335)</td>
</tr>
<tr>
<td></td>
<td>0.64 (0.48-0.84)</td>
</tr>
</tbody>
</table>

Implications:
- Significance of differences in antibody levels unclear, but they are not great
- Perhaps more important for duration than for immediate duration of protection
- If a patient is late for a dose, it probably makes little difference

3 HPV vaccine doses within 356 days

<table>
<thead>
<tr>
<th>Age</th>
<th>% completed</th>
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<tbody>
<tr>
<td>9-12</td>
<td>38</td>
</tr>
<tr>
<td>13-18</td>
<td>40</td>
</tr>
<tr>
<td>19-26</td>
<td>36</td>
</tr>
<tr>
<td>&gt; 26</td>
<td>25</td>
</tr>
</tbody>
</table>

Year of first dose

<table>
<thead>
<tr>
<th>Year of first dose</th>
<th>% completed</th>
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<tbody>
<tr>
<td>2006</td>
<td>51</td>
</tr>
<tr>
<td>2007</td>
<td>47</td>
</tr>
<tr>
<td>2008</td>
<td>36</td>
</tr>
<tr>
<td>2009</td>
<td>21</td>
</tr>
</tbody>
</table>


Fewer doses of HPV Vaccine

- Costa Rican study, bivalent HPV vaccine vs HepA vaccine
- “Efficacy” = reduction in type 16/18 HPV infection persisting for ≥ 10 mo after last dose
- 3 doses: N = 5967, efficacy = 81%
- 2 doses: N = 802, efficacy = 84%
- 1 dose: N = 384, efficacy = 100%

2 vs 3 doses of HPV vaccine

- Canadian women 9-13 yr old
  - HPV 4 at 0,2,6 months (261)
  - HPV 4 at 0,6 months (259)
- Ratio of geometric mean titres 1 mo after last dose
  - HPV 16: .95 (.73-1.23)
  - HPV 18: .68 (.54-.85)
- However: significant differences at 24 and 36 months

Dobson SRM et al: JAMA 2013;309:1793-1802

Effectiveness of fewer doses of HPV-4 vaccine

- 1 million Swedish women: 10-24 yo, first dose of HPV-4 age 10-16, 2006-2010
- 20,383 cases of condyloma acuminate
- 322 cases in recipients of HPV-4 vaccine

<table>
<thead>
<tr>
<th>Doses</th>
<th>Incidence rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.18 (0.15-0.22)</td>
</tr>
<tr>
<td>2</td>
<td>0.29 (0.21-0.40)</td>
</tr>
<tr>
<td>1</td>
<td>0.31 (0.20-0.49)</td>
</tr>
<tr>
<td>0</td>
<td>1.0</td>
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</tbody>
</table>