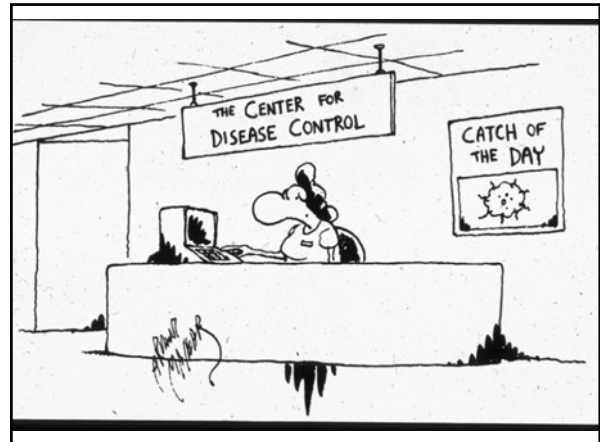


## New Findings in Female Genital Tract Infections Women's Health 2006

Michael F. Rein, M.D.  
Division of Infectious Diseases and International Health  
University of Virginia  
April 23, 2006



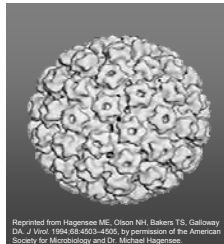
## Human papillomavirus

- Cannot be cultured *in vitro*
- Closed, circular, double stranded DNA
  - 700 base pairs
  - 9 proteins
- Types defined as less than 50% DNA homology

## HPV

Nonenveloped double-stranded DNA virus<sup>1</sup>

- >100 types identified<sup>2</sup>
- 30–40 anogenital<sup>2,3</sup>
  - 15–20 oncogenic<sup>2,3</sup> types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 58<sup>4</sup>
    - HPV 16 (54%) and HPV 18 (13%) account for the majority of worldwide cervical cancers.<sup>5</sup>
  - Nononcogenic<sup>1</sup> types include: 6, 11, 40, 42, 43, 44, 54<sup>4</sup>
    - HPV 6 and 11 are most often associated with external anogenital warts.<sup>3</sup>



Reprinted from Hagensee ME, Cleon NH, Bakers TS, Galloway DA. J Virol. 1994;68:4503–4505, by permission of the American Society for Microbiology and Dr. Nicole Hagensee.

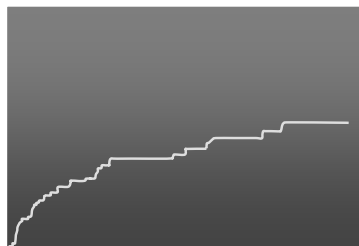
## Structure of Human Papillomavirus

- E<sub>1</sub>: viral plasmid replication
- E<sub>2</sub>: modulates viral transcription (e.g. of E<sub>6</sub> and E<sub>7</sub>)
- E<sub>3</sub>:
- E<sub>4</sub>: filamentous cytoplasmic networks
- E<sub>5</sub>: prevents acidification of endosomes - stimulates transformation
- E<sub>6</sub>: binds to cellular p53 - transformation
- E<sub>7</sub>: binds to retinoblastoma protein - transformation
- L<sub>1</sub>: Major capsid protein - vaccine candidate
- L<sub>2</sub>: Minor capsid protein

## NATURAL HISTORY OF GENITAL WARTS

1. Infection of basal cell
2. Existence as intranuclear episome
3. Superficial migration of cell
4. Productive infection
5. Cell death (koilocytosis): enlarged nucleus perinuclear clear zone

### Infection From Time of First Sexual Intercourse



### Prevalence of HPV in Adolescent and Young Adult Women

Study Author, Year	N	Age Range (Years)	Mean (Years)	HPV Prevalence (%)
Brown, 2005 <sup>1</sup>	60	14–17	15	82%
Tarkowski, 2004 <sup>2</sup>	312	12–19	16	64%
Ho, 1998 <sup>3</sup>	608	NR*	20	58%
Burk, 1996 <sup>4</sup>	604	NR*	20	28%
Bauer, 1991 <sup>5</sup>	467	NR*	23	46%

“Men are scum”

### TRANSMISSION BY FOMITES ?

- Viral proteins identified in:
  - Underwear 14%
  - Examining gloves 50%
  - Instruments 1.6%
  - Laser plume 20%

### PERIANAL WARTS: EPIDEMIOLOGY

Isolated perianal warts:

- Anal intercourse
  - 60/72 (83%) of men
  - 5/7 (71%) of women

Accompanying genital warts:

- 20% of women

### Effect of treatment of male sexual partners on recurrence of warts in women

- Retrospective study: 360 women treated for genital warts
  - 180 male partners examined and treated
  - 180 male partners neither examined nor treated
  - Women resumed unprotected sexual relations after warts had completely resolved for four weeks

Failure Rate	Partners Treated	Partners Untreated
Early	25/180 (13.9%)	25/180 (13.9%)
Late	5/180 (2.8%)	9/180 (5.0%)
Total	30/180 (16.7%)	34/180 (18.9%)

*Treatment of male partners had no effect on recurrence rate.*

### Significance of coincident latent infection

- Detected by DNA hybridization (PCR might be more sensitive)
- 45% carriage up to 10 mm from wart
- Correlates with recurrence
  - Present: 67% recurrence
  - Absent: 9% recurrence
- PCR +, cytology - : 20% develop lesions within 18 months

### Evidence supporting HPV as a cause of cervical cancer

- Epidemiologically, cancer of the cervix is a sexually transmitted disease
  - More frequent in women with more sexual partners
  - Associated with other STDs
- Isolation from most lesions
- Prospective studies confirm increased risk
- Mechanism of malignant transformation partially defined

### Historical Risk Factors for Cervical Carcinoma

- Not a nun
- Broken marriage
- Multiple marriages
- Extramarital sexual contacts
- Premarital sexual activity
- Early age of first marriage
- Early age of first coitus
- Multiple sexual partners
- Husband with multiple sexual partners
- History of prostitution

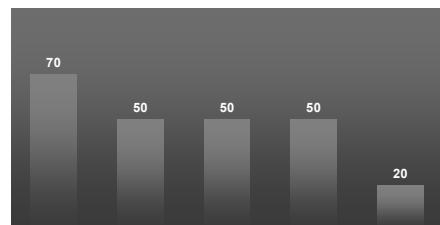
### Oncogenic HPV Types Are a Necessary Cause of Cervical Cancer

- Infection with oncogenic HPV types is the most significant risk factor in cervical cancer etiology.<sup>1</sup>
- First ever identified cancer solely attributed to an infectious agent.<sup>2</sup>
- Analysis of 932 specimens from women in 22 countries indicated prevalence of HPV DNA in cervical cancers worldwide = 99.7%.<sup>1</sup>
- Most common HPV types identified in cervical cancer: HPV 16, 18, 31, 33, and 45<sup>3</sup>
  - Over two thirds of cervical cancer cases associated with HPV 16 or 18 infection<sup>3</sup>

### Risk of malignancy

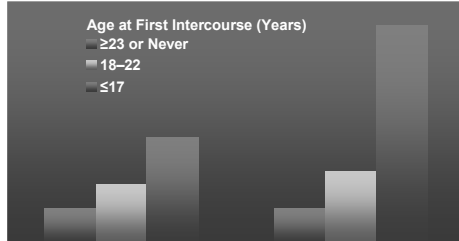
- Low: 6, 11
- Intermediate:
  - 30's, 50's, 60's
- High: 16, 18

### Cancer Types Attributable to HPV Other Than Cervical Cancer<sup>1</sup>



## Risk of Cervical Lesions and Cancer in Women Exposed to HPV at a Young Age<sup>1</sup>

Relative risks for CIN and invasive cancer increase with decreasing age of first sexual intercourse



## Prevalence of Abnormal Cervical Cytology by Age

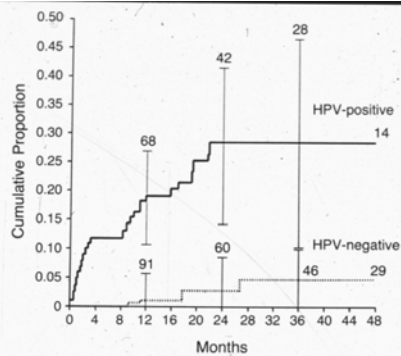


Figure 2. Cumulative Proportion of 241 Women with Negative Cervical Cytologic Tests on Enrollment in Whom Biopsy-Confirmed Cervical Intraepithelial Neoplasia Grade 2 or 3 Developed.

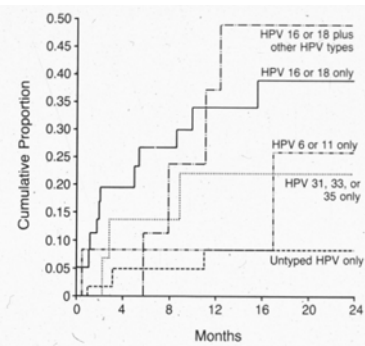


Figure 3. Cumulative Proportion of 110 Women with HPV DNA in Whom Biopsy-Confirmed Cervical Intraepithelial Neoplasia Grade 2 or 3 Developed, from the Time of the First Detection of HPV DNA in a Cervical Specimen.

## Prospective Study of HPV in 1075 Newly Sexually Active Women

- Cumulative 3 year risk of:
  - HPV: 44% (40-48)
  - Second HPV type: 26 % (20-32)
- Median duration HPV: 13.7 mo (8.0-25.4 IQR)
- High grade CIN, 28 cases
  - Risk maximal @ 6 mos after HPV diagnosis
  - Median interval 26 months

Woodman CVB et al: Lancet 2001;357:1831-6

## HPV Integration and Malignancy

- Integrated DNA found in
  - CIN 3%
  - Cancer 81%
- Integrated DNA found in HPV infection
  - 6/11 0%
  - 16 72%
  - 18 100%

## Mechanism of Malignant Transformation by HPV

1. Integration occurs at E<sub>2</sub> with loss of suppression of E<sub>6</sub> and E<sub>7</sub>
2. Transformation, immortalization
3. The product of E<sub>6</sub> combines with p53  
The product of E<sub>7</sub> combines with p105 RB  
p53 and p105RB are oncogene suppressors
4. Loss of suppression of the *ras* oncogene leads to cancer

## Is HPV Infection Lifelong?

## Three Things You Can't Get Rid Of

- HIV
- HSV
- A condominium in Newark, N.J.

Please note that HPV is not on this list

## Cervical HPV Infection is Self-Limited

Among ~600 Planned Parenthood and Student Health women with HPV at entry

- 60% - 70% lost HPV infection within 30 months based on 3 - 4 consecutive, negative DNA probes
- Estimated median persistence is about 10 months

Moscicki, et al: J Pediatr 1998;132:277-84

## Cervical HPV Infection is Self-Limited

Among college women positive for cervical HPV at enrollment and followed for a median of 7.3 months:

- 59/84 (70%) lost their original HPV type
- 27/59 (46%) subsequently acquired a different HPV type

Kotloff, et al: Sex Transm Dis 1998;25:243-50

## Cervical HPV Infection is Self-Limited

Among urban women with oncogenic HPV followed for about 13 months:

- 33/37 (89%) of HIV-negative women lost their HPV
- 23/51 (45%) of HIV-positive women lost their HPV

Minkoff, et al: Am J Obstet Gynecol 1998;178:982-6

## Cervical HPV Infection is Self-Limited

Among 608 college women followed for up to 3 years after acquiring HPV

- Median duration of infection = 8 months
- 31% no longer infected at 6 months
- 70% no longer infected at 12 months
- 91% no longer infected at 24 months

Ho, et al: N Engl J Med 1998;338:423-8

## Persistence of Cervical HPV

- 177 women positive at enrollment
- 61% (54%-69%) positive at 6 months
- 35% (27%-42%) positive at 1 year

J Infect Dis 1999;180:1415-23

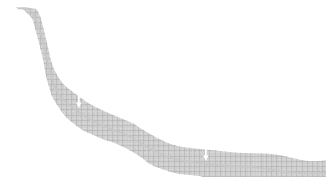
## Persistence of Cervical HPV (Months)

	<u>Oncogenic</u>	<u>Nononcogenic</u>
Mean duration		
Observed	8.9	7.0
Calculated	13.5	8.2
Median time to clearance	8.1	4.8

J Infect Dis 1999;180:1415-23

## Estimated Likelihood of Time to LSIL Regression in Adolescents

- In a study of women 13–22 years of age, there was a 91% probability of regression of LSIL cases within 36 months.
- The probability of progression to HSIL within this same time frame was 3%.



## Things to note about these studies

- One is always concerned about the sensitivity of these tests, but we do know that patients certainly rid themselves of clinical manifestations of HPV as well.
- None of this applies to AIDS patients.
- It does apply to oncogenic as well as nononcogenic HPV types. **But maintenance of infection predisposes to cancer.**

## Things to note about these studies

- Many patients were reinfected after clearing initial infection (i.e. different HPV type)
- Multiple infections were common.
- No matter what, women with a history of HPV infection must be religious about getting yearly cervical cytology

## Risk of SIL as a function of Persistence of HPV

HPV Type	0 & 4 months	8 months	O.R. (95% CI)
None	-	-	1.0 (Reference)
Nononcogenic	+	-	3.55 (0.4-28.5)
	+	+	3.25 (0.7-14.5)
Oncogenic	+	-	3.29 (0.4-26.5)
	+	+	22.02 (8.1-60.2)
16/18	+	-	10.71 (1.1-101.2)
	+	+	12.27 (3.2-47.6)

Schoenicht et al: JAMA 2001;286:3106-14

## HPV - 16 Vaccine

- Double-blind, placebo-controlled
- 16 US Sites
- 2392 women
- 3 doses of placebo or vaccine at 0,2,6 months
- Primary endpoint: persistent HPV 16 infection
- 17.4 months followup
- HPV DNA at enrollment, 1 month after 3rd dose of vaccine, and every 6 months thereafter

NEJM 2002

## HPV-16 Vaccine: Results

### Persistent HPV-16 infection

- Placebo: 3.8 infections/100 woman-years
- Vaccine: 0.0 infections/100 woman-years

### Transient HPV-16 Infection

- Placebo: 6.3 infections/100 woman-years
- Vaccine: 0.6 infections/100 woman-years

## Quadrivalent HPV Vaccine

- Protein L1 grown in yeast
  - Types 6,11 (90% of genital warts)
  - Types 16,18 (70% of cervical, anal, penile cancers)
- Vaccinate at times 0, 2 months, 6 months
- Combined endpoint
  - Persistent HPV DNA
  - Cervical or external HPV

Villa et al: Lancet Oncol 2005;6:271-8

## Quadrivalent HPV Vaccine

### Incidence per 100 woman/years

	Vaccine (276)	Placebo (275)
Combined Infection	0.7	6.7
Disease	0.0	1.1
CIN	0.0	0.5

Villa et al: Lancet Oncol 2005;6:271-8

## Quadrivalent HPV Vaccine

### Incidence per 100 woman/years

	Vaccine (276)	Placebo (275)
Type 6	0.0	2.6
Type 11	0.0	0.6
Type 16	0.6	4.5
Type 18	0.2	1.7

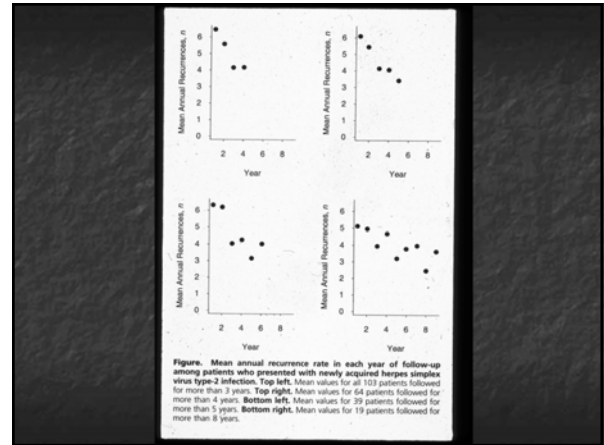
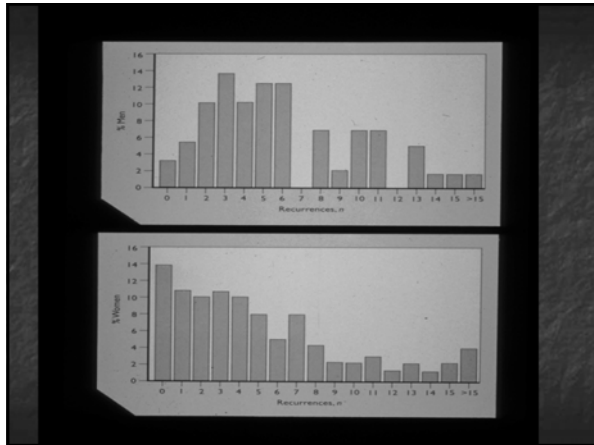
Villa et al: Lancet Oncol 2005;6:271-8

Goal of therapy is destruction of visible lesions and induction of immune response to the warts

There is no therapy that can eliminate latent virus, although laser burns off subclinically infected skin

## 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



## 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)

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

## 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

## 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

## Prospective study of newly acquired genital herpes

- 37% had genital lesions or other genital symptoms (63% asymptomatic)
- Other symptoms (13%): radicular pain, meningitis, NGU, cervicitis
- HSV-1 antibodies increased the percentage of asymptomatic seroconversions
- 15% of asymptomatic seroconverters developed lesions within 45 days

NEJM 1999;341:1432-8

## "Asymptomatic" Patients with Genital Herpes

- After training of 53 patients:
  - 33 (62%) reported lesions
  - 12 (25%) reported neurological symptoms
- Therefore: 87% could now recognize symptoms of reactivation

Wald, et al: NEJM 2000;342:844-50

## Among women with a history of symptomatic genital herpes

- 25 % of recurrences are asymptomatic
- Symptomatic recurrences and asymptomatic shedding are both reduced with chronic suppression
- *Symptomatic patients cannot be assured that they are not shedding virus when they are asymptomatic*

## HLA Type May Influence Tendency to Symptomatic HSV-2 Genital Infection

HLA-B27 is associated with symptomatic disease (P=.08)

HLA-Cw2 is associated with asymptomatic disease (P=.06)

Lekstrom-Himes, et al: J Infect Dis 1999;179:1077

## Herpes: Prevalence of asymptomatic shedding in women

- Culture: 1%
- Antigen detection 3%-7%
- Ligase chain reaction 28%

Which of these is the best measure of infectivity?

### 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

### How contagious is genital herpes?

A small prospective study:

- Transmission from symptomatic to uninfected partners
- 1-24 months (median 16 mo) contact
- Sex *primarily* when asymptomatic
- Results:
  - Infection: 6/21 (29%)
  - Rate: 12%/year (95%CI = 2-22%)

### How contagious is genital herpes?

Vaccine Study: Discordant pairs

Transmission from symptomatic to uninfected partners

Subjects advised not to have unprotected sex when infected partner symptomatic

- N = 82 vaccine, 79 placebo
- Days followup: 29138 vaccine; 23174 placebo
- Results: % acquiring HSV/year

Vaccine:	11.3%
Placebo:	7.9%

### 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. (That's the reason that dating services for people with herpes didn't last very long.

If, however, one of you gave herpes to the other, it is very unlikely that you will superinfect each other.

### 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

## 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 probably tell the patient to inform sexual partners of the diagnosis and document in the medical record that one has done so!

## HSV-1 probably protects against HSV-2

1171 Discordant monogamous couples, 19 months followup:

271 HSV-1 negative 39/271 (14.4%) acquisition/yr

678 HSV-1 positive 39/678 (5.9%) acquisition/yr

Sprauce et al: Abstract 39th IDSA, October 2001

## % 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%  $\rightarrow$  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

Age	N	% Genital type 1
15-24	132	72.7%
25-44	140	62.0%
$\geq 43$	54	46.0%

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

## Possible reasons for the relative increase in genital HSV-1

- Increase in orogenital contact
  - 75% of college students
  - 33%-59% of high school students
- Decreased rate of nonvenereal acquisition of HSV-1 in childhood?
- Increased use of condoms with penile-vaginal intercourse (decreased HSV-2)?

## 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

## Suppression of HSV reduces 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

## Suppression of HSV reduces transmission

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

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

## The relationship between condom use and herpes simplex virus acquisition

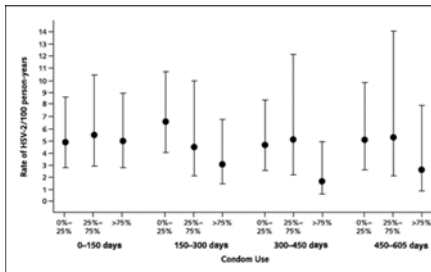
Wald A, Langenberg AGM, Krantz E, et al.

Ann Intern Med 2005;143:707-13

## Study Design

- Prospective, vaccine trial
  - 18 months followup
  - 11 study visits
  - Not adjusted for vaccine status (NS)
- Self reported condom use (probably overestimates)
- Acquisition: seroconversion or viral culture
- Acquisition: N = 118 (6.4%)

Frequency of herpes simplex virus (HSV)-2 acquisition in each study interval stratified by condom use



Wald, A. et. al. Ann Intern Med 2005;143:707-713

Annals of Internal Medicine

Decrease in transmission rate over time

- Nonserologically identifiable immunity (e.g. CMI)???
- Weeding out the susceptibles

Interaction between gender and condom use

- Condom use decreases the rate of HSV-2 acquisition in both men and women
- Hazard Ratios
  - Men: 0.69 [0.51, 0.93]
  - Women: 0.87 [0.58, 1.30]
  - P = 0.39
- Data on women “inconclusive”
  - Earlier study suggested effect for women but maybe not for men.

Short Course Therapy of Recurrent HSV-2 Genital Herpes

Valacyclovir 500 mg orally bid

	N=362 3 days	N=359 5days
Time to lesion healing	4.4 d	4.7 d
Duration of pain	2.9 d	2.5 d
Length of episode	4.3 d	4.4 d

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)

Cin 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%

Aoki, et al: Clin Infect Dis 2006;42:8-13

## Topical resiquimod for genital herpes

- Patients with  $\geq 6$  recurrences per year
- During recurrence, 0.01% or 0.05% applied 2-3 times/week for 8 hours, for 3 weeks
- Median time to recurrence prolonged from 57 days to 169 days ( $p=0.006$ )
- May not be reproducible: sorry

Sprauance: *J Infect Dis* 2001;184:196

## Experimental Herpes Vaccines

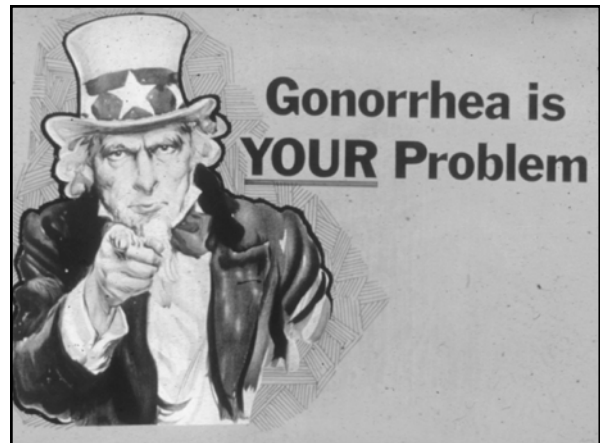
- Glycoprotein D2 + lipid A adjuvant
- Vaccinated at months 0, 1, 6
- Partners of patients with genital HSV followed for 19 months
- Symptomatic infection confirmed by laboratory techniques

Sprauance: 41st ICAAC, 2001

## Experimental Herpes Vaccines: Vaccine efficacy

- Reduction in infection rate:
- HSV 1-/2- women:
  - Study 1: 73% (19-91%)  $p=0.02$
  - Study 2: 74% (9-93%)  $p=0.02$
- No effect in HSV 1+/2- women or in men

Sprauance: 41st ICAAC, 2001



## Quinolone-resistant *N. gonorrhoeae*

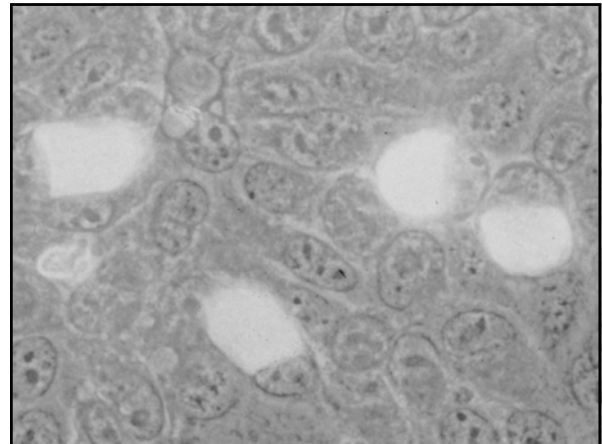
- Originated in Pacific Rim
  - Fluoroquinolones over-the-counter
- First US isolates in Ohio (Ohio?)
- Entire West Coast
- Can no longer use single dose FQ for gonorrhea acquired in Pacific, West Coast
  - Travel history important

## Quinolone-resistant *N. gonorrhoeae*

- Chromosomal mutation
- Ciprofloxacin MIC
  - $\geq 1 \mu\text{g/ml}$  = resistant
  - $\geq 4 \mu\text{g/ml}$  = 50% failure rate
- Resistant isolates
  - Hawaii 20%
  - Asia 40%
  - California 9%

### Fluoroquinolone resistant *N. gonorrhoeae* among MSM - 2003

- Fraction of gonococcal isolates from MSM which were fluoroquinolone resistant:
  - Massachusetts: 26/249 (10.4%)
  - New York City: 22/643 (3.4%)
    - 2002: 0.3%
    - 2001: 0.1%
- Specific sexual history important



### Is infection with *Chlamydia trachomatis* a risk factor for cervical carcinoma?

- Seroepidemiological survey:
- If antibody to *Chlamydia trachomatis* is present, the adjusted odds ratio (95% CI) for SCC is:
  - Serotype G 6.6 (1.6 - 27)
  - Serotype I 3.8 (1.3 - 11.0)
  - Serotype D 2.7 (1.3 - 5.6)
- Beware of behavioral confounders

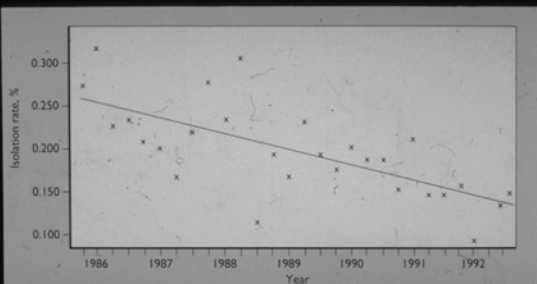
JAMA 2001;285:47-51

### Prior chlamydial infection as predictor of future infection

- Family planning clinic women (73,000)
  - Initial prevalence 5.4%
  - New infection 3.7%
  - Repeat infection 19.7%
- California Health Dept women (203,000)
  - Repeat infection 15.2%

Don't bother with test of cure but might rescreen in 3 months to detect reinfection

2002 STD Conference



### Etiologies of Sexually Transmitted NGU

- *Chlamydia trachomatis* 15%-50%
  - Recent studies ~ 25%
- *Ureaplasma urealyticum* 10%-40%
- *Mycoplasma genitalium* ~30%??
- *Trichomonas vaginalis* 1%-17%
- Herpes simplex virus (1°)

## Support for *Ureaplasma urealyticum* as a cause of NGU

- Inoculation studies
- Isolation rates higher in chlamydia negative NGU
- Differential treatment studies

## Differential treatment studies in NGU

	<u>C+U-</u>	<u>C-U+</u>
Sulfonamides	Cure	-----
Aminocyclitols	-----	Cure
Tetracyclines	Cure	Cure-
Erythromycin	Cure	Cure

## *Mycoplasma genitalium* and NGU

- |                       |                 |
|-----------------------|-----------------|
|                       | <i>Mg</i> (PCR) |
| ■ NGU (121)           | 22%             |
| ■ No urethritis (117) | 4%              |

Totten P: JID 2001;183:269-79

## Epidemiologic Treatment of Nongonococcal Urethritis

- Male NGU may be diagnosed by the presence of urethral inflammation which is independent of etiology.
- A female contact to a man with NGU may be infected with one of the other agents:
  - *Ureaplasma urealyticum*
  - *Mycoplasma genitalium*
  - (*Trichomonas vaginalis*)
- Such female contacts should be treated even if they are negative for *Chlamydia trachomatis*.

## Pelvic Inflammatory Disease

## Clinical Features Suggesting PID Rather than Appendicitis

- History of prior PID
- History of vaginal discharge
- Finding of vaginal discharge
- Urinary symptoms
- Urinary findings
- Tenderness outside the RLQ
- Cervical motion tenderness
  - *Am J Emerg Med* 1993;11:569-72

## PID in 27 HIV-Infected vs 322 Uninfected Women

- More severe initial presentation
  - Higher WBC count (11.3 vs 7.4)
  - More fever (54% vs 28%)
- Similar complication rate
  - Tuboovarian abscess (19% vs 14%)
  - Need for surgery (15% vs 6.2%, P= 0.10)

Barbosa: Obstet Gynecol 1997;89:65-70

## PID Severity and Probability of Live Birth in 12 Years

Mild	90%
Moderate	82%
Severe	57%

Lepine: Am J Obstet Gynecol 1998;178:997

## Aerobic Organisms Recovered from Upper Tract Specimens in Acute PID

Coagulase negative staphylococci  
Group B streptococci  
 $\alpha$ -hemolytic streptococci  
nonhemolytic streptococci  
*Neisseria gonorrhoeae*  
*Escherichia coli*  
*Gardnerella vaginalis*

From Walker, et al

## Anaerobic Organisms Recovered from Upper Tract Specimens in Acute PID

*Bacteroides fragilis*  
*Prevotella species*  
*Prevotella bivia*  
*Prevotella disiens*  
*Peptostreptococcus anaerobius*  
*Peptostreptococcus asaccharolyticus*  
*Peptostreptococcus species*

From Walker, et al

## Other Organisms Recovered from Upper Tract Specimens in Acute PID

*Mycoplasma hominis*  
*Ureaplasma urealyticum*  
*Chlamydia trachomatis*

From Walker, et al

## Challenges to the Study of PID Treatment

- Many studies used clinical criteria rather than laparoscopic diagnosis
- Often emphasize hospitalized patients
- Many are not randomized

## Challenges to the Study of PID Treatment

- Usual endpoints are acute response, whereas important clinical goals require longer followup:
  - Preservation of reproductive function
  - Prevention of recurrence/chronic pain
  - Prevention of ectopic pregnancy

## Inpatient vs Outpatient Treatment of PID (PEACH Study)

- "Inpatient regimen"
  - Cefoxitin 2gm iv q6h + Doxycycline 100 mg iv bid for at least 48 hours
  - Doxycycline 100 mg p.o. bid to complete 14 days
- "Outpatient regimen"
  - Cefoxitin 2 gm im + probenecid 1 gm po
  - Doxycycline 100 mg bid to complete 14 days
- I would favor ceftriaxone 125-250 mg

## Inpatient vs Outpatient Treatment of PID (PEACH Study)

	<u>Inpatient</u>	<u>Outpatient</u>
Changed regimens	3.3%	2.9%
Continued tenderness	18.0%	21.0%
Persistent endometritis	37.6%	45.9%
PID recurrence	16.6%	12.4%
Infertility (1 yr)	18.4%	17.9%
Chronic pain	33.7%	29.8%
Mean time to pregnancy	21 months	21 months

## Comparison of CDC Recommended Regimens for Inpatient Treatment of PID

	Cure	Improve	Fail
Cefoxitin/doxycycline (N=94)	80%	15%	5%
Cefotetan/doxycycline (N=94)	89%	4%	6%
Clindamycin/gentamicin (N=104)	84%	11%	6%

Hemsell DL, Clin Infect Dis 1994;19:720-7

## Response Rate for Inpatient Treatment of Uncomplicated PID

Regimen (unrandomized)	Response
Cefotetan 2gm iv q 12 h Doxycycline 100 mg iv/po q 12 h	71/73 (97%)
Clindamycin 900 mg iv q 8 h Gentamicin 1.5 mg/kg iv q 8 h	16/18 (89%)
Ampicillin 1 gm iv q 6 h Clindamycin 900 mg iv q 8 h Gentamicin 1.5 mg/kg iv q 8 h	14/14 (100%)

## Response Rate for Inpatient Treatment of PID

Regimen (Randomized)	Response
Meropenem 500 mg iv q8h	185/211 (88%)
Clindamycin 900 mg + Gentamicin 1.5 mg/kg IV q 8 h	166/184 (90%)

## Oral Moxifloxacin in the treatment of PID

- Regimens (14 days)
    - Moxifloxacin 400 mg p.o. qd for 14 days
    - Ciprofloxacin 500 mg STAT plus doxycycline 100 mg p.o. bid and metronidazole 400 mg p.o. tid
  - Diagnosis: Clinical + ultrasound + laparoscopic
  - Endpoint: Clinical response at end of therapy
- |       | N   | Cure+Imp | Cure+Imp @ FU |
|-------|-----|----------|---------------|
| Mox   | 232 | 96.6%    | 89.2%         |
| C/D/M | 202 | 98.0%    | 87.8%         |
- *This is not an FDA approved regimen*

## Bacterial Vaginosis

“Sexually associated” rather than “sexually transmitted”

## Mechanisms of Preterm Delivery in Bacterial Infections

- Decidua and fetal membranes produce
  - TNF $\alpha$
  - Interlukins 1 $\alpha$ , 1 $\beta$ , 6, 8
  - GCSF
- Inflammatory mediators stimulate
  - Prostaglandin synthesis and release
  - PMN chemotaxis and infiltration
  - Activation of metalloproteases

## Mechanisms of Preterm Delivery in Bacterial Infections

- Prostaglandins stimulate uterine contractions
- Metalloproteases:
  - Chorioamniotic membrane rupture
  - Remodel collagen, soften cervix

## Bacterial Vaginosis and HIV

- Epidemiology:
  - Cross-sectional and longitudinal studies
  - Prevalence of HIV increased with greater abnormality of vaginal flora
- Mechanism
  - Loss of protection from H<sub>2</sub>O<sub>2</sub>-producing *Lactobacillus*
  - HIV induction by cervicovaginal lavage fluid
  - *G. vaginalis* increases HIV expression in cell culture

## Complications of Bacterial Vaginosis

	Relative Risk
■ <b>Nonpregnant</b>	
■ Endometritis	2.6-12.4
■ Salpingitis	3.0
■ Posthysterectomy vaginal cuff /wound infection	3.2-6.2
■ <b>Pregnant</b>	
■ Chorioamnionitis	1.9-6.8
■ Premature labor and delivery	1.4-6.9
■ Postpartum fever	5.8
■ Postpartum endometritis	5.8
■ Postpartum salpingitis	3.7

### Clindamycin cream fails to prevent gestational complications of G BV

	Preterm Delivery	Puerperal Infection
Clindamycin (177)	4.0%	13%
Placebo (178)	3.4%	19%

Kekki et al: Int J Gynecol Obstet 1999;67:S39-52

### Lesbians and bacterial vaginosis

- Bacterial vaginosis is found in 29%-52% of lesbians (4 studies)
- Rates of other genital infections are lower than in male homosexuals or heterosexual women

### BACTERIAL VAGINOSIS AND UPPER TRACT DISEASE

- BV-associated organisms may infect the upper tract
- BV-associated organisms may facilitate ascent of *N. gonorrhoeae* or *Chlamydia trachomatis* by breaking down cervical mucus or immunoglobulins

### Nonculturable Bacteria in Bacterial Vaginosis

- Identified using broad range bacterial ribosomal PCR, fluorescence *in situ* hybridization microscopy
- BV diagnosed by Amsel criteria

Fredicks DN, et al: *NEJM* 2005;353:1899-911

### Nonculturable Bacteria in Bacterial Vaginosis

- | Number of phylotypes  | Mean (range) |
|-----------------------|--------------|
| ■ Bacterial vaginosis | 12.6 (9-17)  |
| ■ Normal              | 3.3 (1-6)    |
- P < 0.001

Fredicks DN, et al: *NEJM* 2005;353:1899-911

### Nonculturable Bacteria in Bacterial Vaginosis

- Findings of interest in bacterial vaginosis
  - Lactobacillus (*L. crispatus*) absent
    - *L. acidophilus* not found in normals
  - 3 highly sensitive and specific phylotypes related to clostridia
    - BV Associated Bacteria (BVAB) 1,2,3
  - No mycoplasmas
  - *Gardnerella vaginalis* common but nonspecific
  - *Atapobium vaginae* common but less specific
  - Anaerobes common

Fredicks DN, et al: *NEJM* 2005;353:1899-911

**\$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.”

Las Vegas Sun On-line 1/13/00



**Questions & Answers**

