Male HPV Infection - A Challenge For Diagnosis & Treatment
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Outline
Overview of HPV
Differential diagnosis
Special cases
HPV screening in males
Treatment and follow up for HPV in males
Prevention of HPV in males
Conclusions

HPV Facts
- Until recently, HPV prevalence was the least known STD among college students
- HPV research has focused on women and cervical cancer
- By comparison, few efforts have been made in male HPV research
- Little concrete data is available on the natural history of HPV infection in males
- Data on male HPV prevalence varies among studies

Reasons for the lack of knowledge regarding HPV infection in males:
- HPV infection has fewer serious consequences for men than for women
- Adequate screening methods have been established for women
- No practical or universally accepted method has been developed for men

HPV Facts
- Cutaneous HPV types account for two-thirds of all infection: common & plantar warts
- Mucosal HPV types account for the remaining one-third in the form of condyloma (anogenital warts) and/or neoplasia
- Low-Risk HPV: 6, 11, 42, 43, 44, 54, 61, 70, 72 & 81 (84 also under study)
- High-Risk HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 & 82

HPV Facts
- Low-Risk HPV Types:
  - Non-oncogenic (rarely isolated from neoplastic lesions)
  - Types 6 & 11 account for > 90% of all condyloma
- High-Risk HPV Types:
  - Oncogenic - responsible for 99.7% of all cervical cancer (16 & 18 account for 70% of cervical neoplasms)
  - Oncogenic possibilities exist for males in the form of penile, anal, urethral and bladder cancer

HPV Transmission
- Direct Contact with Infected Skin Surfaces
- Fomite Transmission has not been ruled out (Stevens-Simon, et al, 2000)
- Vertical Transmission rate has been determined at < 1% (Smith, et al, 2004)
  - ~2,000 of 4,000,000 infants neonates are infected with Respiratory Papillomatosis via vertical transmission
Transmission: starting point

Latent Period/Incubation: -Lasts several weeks to several years (average 1 – 12 months)
   -Subclinical phase
   -Many HPV infections are self-limiting and resolve without symptoms

Host Cell-Mediated Immune Response:
   -begins ~ 3 months post infection
   -most HPV infections clear without symptoms
   -HPV infection that is not contained can enter a latent phase and reappear as condyloma or intraepithelial neoplasia at a later date

HPV Clearance vs. Persistent Infection:
Clearance:
   -Eradication
   -Levels too low to be detectable
Persistence:
   -Clinical evidence of infection
     Condyloma (genital warts)
     Squamous Intraepithelial Lesions (abnormal proliferation of cells)
     Cause = Low or High Risk HPV

Clearance vs. Persistent HPV Infection:
   -even with active gene expression, as many as 90% of HPV infections will either clear or become latent
   -10% - 20% of HPV infections will persist due to host, viral or environmental factors:
     -immune compromise
     -infection with high-risk types
     -smoking
     -infection with > one type of HPV
### HPV Facts: Male vs. Female

<table>
<thead>
<tr>
<th>Research</th>
<th>Male HPV</th>
<th>Female HPV</th>
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<tbody>
<tr>
<td>Literature</td>
<td>Beginning in 21st Century</td>
<td>Studies since 1920</td>
</tr>
<tr>
<td>Screening Method</td>
<td>No approved method</td>
<td>Pap Test since 1943</td>
</tr>
<tr>
<td>Testing Method</td>
<td>No approved method</td>
<td>Hybrid Capture, PCR</td>
</tr>
<tr>
<td>Visible Symptoms</td>
<td>Not easily detected</td>
<td>Often self detected</td>
</tr>
<tr>
<td>Health Ed. Efforts</td>
<td>Males overlooked</td>
<td>Favor females</td>
</tr>
<tr>
<td>Treatment</td>
<td>Only with symptoms</td>
<td>Symptoms &amp; Pap F/U</td>
</tr>
<tr>
<td>Prevention</td>
<td>Condoms</td>
<td>Approved Vaccine</td>
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<thead>
<tr>
<th>Role in Transmission</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>Viewed as a vector for female infection</td>
<td>Viewed as a victim of HPV infection</td>
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<table>
<thead>
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<th>Morbidity</th>
<th>Male</th>
<th>Female</th>
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<tr>
<td>Condyloma and neoplasms (Anus, Penis, Urethra &amp; Bladder)</td>
<td>Condyloma and neoplasms of the cervix</td>
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<tr>
<th>Mortality</th>
<th>Male</th>
<th>Female</th>
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<tr>
<td>Anal, Penile and Bladder carcinomas</td>
<td>Predominantly Cervical Carcinoma</td>
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### Prevalence

- Anogenital HPV infections are highest among college-age men & women (estimates from 50% to 80% among the 18 - 25 year age group)
- Overall prevalence rate of HPV in women is 22% to 35%
- HPV prevalence in men is 2% to 35%
- HPV prevalence in men relates to sexual practices and the ability to diagnose infection (Gearhart, Peter A., MD, ACOG, Jan., 2007)

### Incidence rates for male HPV infection are difficult to assess due to:

- tendency for infection to be asymptomatic
- lack of approved screening methods

Studies in male HPV infection yield widely ranging prevalence estimates (5.5 – 76%) depending on the population, site tested, sampling method and procedure used. (Weaver et al, Journal of Infectious Disease, 2004:189, February 15)

### Factors in Statistical Variations:

**Population:** HPV prevalence is greater in certain locations, e.g., Mexico

**Site Tested:** HPV detection varies by male genital or anal site

**Sampling Method:** wet vs. dry, swab vs. cytobrush, with/without abrasion, dermis vs. urine vs. blood

**Procedure:** serology, HPV DNA detection (hybrid capture or PCR), cytology


- Visible Genital Warts: 1%
- Subclinical Papillomavirus Infection, Colposcopy or Cytology: 4%
- Subclinical Papillomavirus Infection, DNA or RNA Probes: 10%
- Prior Infection: 60%
- No Prior or Current Infection: 25%
HPV Prevalence in Healthy Men vs. Men with Urethritis

- 75 “healthy” volunteers (18-35yrs) & 130 men with urethritis (17-49yrs)
- Specimen collection via moist cotton swab → Hybrid Capture II
- Sites = glans, coronal sulcus & inner surface of the prepuce

RESULTS:

<table>
<thead>
<tr>
<th></th>
<th>“healthy” men</th>
<th>men w/ urethritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-</td>
<td>74 (98.7%)</td>
<td>106 (81.5%)</td>
</tr>
<tr>
<td>HPV+</td>
<td>1 (1.3%)</td>
<td>24 (18.5%)</td>
</tr>
<tr>
<td>low-risk</td>
<td>0</td>
<td>4 (16.7%)</td>
</tr>
<tr>
<td>high-risk</td>
<td>1 (100%)</td>
<td>12 (50%)</td>
</tr>
<tr>
<td>both types</td>
<td>0</td>
<td>8 (33.3%)</td>
</tr>
</tbody>
</table>

Variables:

- men with urethritis had coitus more frequently and had more partners
- samples among those w/ urethritis were collected by physicians – samples among the “healthy” men were self-collected

CONCLUSION: frequency of sexual activity and number of sexual partners increase the probability of HPV infection - collection process may influence outcome (Takahashi, S. et al. DOI:10; August, 2003)


- “HPV prevalence varied on the basis of sampling, processing methods, anatomic sites or specimens…”
- “Serologic testing for IgG antibodies may be a better measurement of cumulative exposure…but likely underestimates the cumulative incidence of HPV…”
- “…using a saline-wetted sterile Dacron swab after ..rubbing the sample site with..emery paper was superior for specimen adequacy…”
- “…best anatomic sites for….detection of HPV DNA appear to be the glans, corona, prepuce and shaft of the penis”
- “The prepuce is possibly the best single site for HPV DNA detection” however, sampling multiple sites increases adequacy
- “overall viral loads were much lower in penile-scrape specimens than in cervical scrape specimens”
- “…semen, urine and urethral swabs”….are less useful as specimens

- Male HPV prevalence proved “as high as 72.9% and usually >20%”
- “Eight of 9 studies that compared seroprevalence in men & women reported a higher seroprevalence in women than in men”
- “High-risk and low-risk types were less likely to be detected in circumcised men”
- “.76% of male partners of women with HPV were HPV DNA positive”
- “HPV types detected in men…were similar to types commonly detected in women…type 16 was consistently most common…” with 6,11 & 18

(Dunne et al, JOI, October, 2006)

<table>
<thead>
<tr>
<th>ACHA/NCHA HPV Data (2003 – 2006)</th>
<th>Total: Not all ID’d gender</th>
<th>Female n</th>
<th>Female %</th>
<th>Male n</th>
<th>Male %</th>
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<tbody>
<tr>
<td>2003</td>
<td>302</td>
<td>228</td>
<td>75%</td>
<td>60</td>
<td>20%</td>
</tr>
<tr>
<td>2004</td>
<td>845</td>
<td>649</td>
<td>77%</td>
<td>152</td>
<td>18%</td>
</tr>
<tr>
<td>2005</td>
<td>1155</td>
<td>885</td>
<td>77%</td>
<td>234</td>
<td>20%</td>
</tr>
<tr>
<td>2006</td>
<td>2060</td>
<td>1594</td>
<td>77%</td>
<td>421</td>
<td>20%</td>
</tr>
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</table>

- Study included 136 males 18yrs – 63yrs – mean 28.5
- 5.2% (7/136) had visible condyloma – 3.7% (5/136) had “lesions”
- Findings:
  - Asymptomatic HPV is common in men
  - Male HPV appears to be multifocal
  - Male HPV prevalence varies between studies (41 – 43%)
  - Predominant oncogenic types: HPV-16, HPV-51 &HPV-59
  - Predominant nononcogenic type in all genital sites: HPV-84
  - HPV-84 was one of the most prominent on hand swabs suggesting the possibility of hand-to-genital transmission
  - HPV genotype distribution is inconsistent between men & women suggesting selective transmission
  - An ideal & consistent sampling method would facilitate repeated measurements of HPV in men over time

Male-Specific HPV Issues (presenting at College Health Services):
- My girlfriend was diagnosed with genital warts….
- My ex-girlfriend received an abnormal Pap result….
- I’ve seen the Ad on TV and want to be tested for HPV……..
- I have had this bump all my life – is it a genital wart??
- I have a male partner and receive anal penetration – what tests should I have?

Differential diagnosis for popular urogenital lesions in males*

- Genital warts
- Pearly penile papules
- Molluscum contagiosum
- Milia
- Sebaceous cyst
- Herpes
- Other

Genital warts (Condyloma accuminata)
- Usually soft, moist, pink polyp
- Usually cluster
- May become pendunculated
- Classic “cauliflower” appearance
- Can appear on lower abdomen and other areas not typically covered by a condom
- Often not classic-appearing

Pearly penile papules
- The classic misdiagnosis
- Relatively common benign tumors
- Histology: angiofibroma
- Seen a regular projections for the edge of the glans at the coronal margin
- Do not contain HPV DNA by polymerase chain reaction
- Should not be “treated” – consider as a variation of normal

Molluscum contagiosum
- Benign viral infection
- Most cases resolve within 6-9 months
- Sometimes lesions are large, pustule-appearing
Potential for autoinoculation
Common for lesions to become inflamed (erythematosus border)
Treatment:
  - Benign neglect
  - Cryotherapy
  - Lesional trauma
  - Others

**Milia**
Ectopic sebaceous glands
Known by some as “Fordyce’s spots”
Uniform appearance and distribution
Commonly seen on the faces of adults or in areas of trauma or inflammation
In adults, milia may persist indefinitely

**Other**
Sebaceous cysts
Herpes
  - Misdiagnosis = missed opportunity for appropriate counseling and treatment
Scabies (usually nodular scabies)
Lichen planus
Condyloma lata
  - Secondary syphilis
    - Usually more flat-topped than condyloma accuminata
    - If ANY doubt, test for syphilis
Folliculitis

**Hints for diagnosis**
Urogenital HPV lesions
  - Generally are not associated with inguinal lymphadenopathy
  - Might itch but do not hurt (unless inflated)
  - Do not wax and wane over a course of days/weeks

**Oropharyngeal HPV infection**
Independent risk factor for oropharyngeal squamous-cell carcinoma
HPV 16 associated with 15-fold increase in risk
Seropositivity for HPV 16 associated with 32-fold increase in risk
Tobacco and alcohol provided no additional risk
Believed to be transmitted by oral sex

**Anal warts**
Consider skin tags and fissures in the differential diagnosis

**Anal cancer**
In the US, anal cancer in MSM is more common than cervical cancer in women
  - Clear association with HPV infection
  - Study of 1218 HIV-negative MSM age 18-89:
    - Correlated with history of:
      - receptive anal intercourse during the proceeding 6 months
      - and with >5 sex partners during the preceding 6 months
      - did not correlate with subject age
  - Rare in general population
    - 70-80 per 100,000 HIV-positive MSM
    - Incidence has gone up in era of HAART
Anal Pap testing
   Evolving protocols
   Consult with reference laboratory for protocol
   Evolving standard of care
      Males and females who practice receptive anal intercourse
   Concept: Dysplasia testing vs. HPV testing
   Most studies involve HIV-positive MSM
      Anal cytology UNDERestimates the degree of anal dysplasia
      ANY abnormality (ASCUS and >) should be referred for
      high-resolution anoscopy and biopsy

**Squamous cell carcinoma of the penis**

HPV infection associated with 15-71% of penile SCC
   Subtypes 16 and 18
      But also 6, 11, and 30
Risk factors
   Smegma retention
   Chronic balanitis
   Ultraviolet light exposure
   Chemical carcinogen exposure
   Cigarette smoking
   HIV infection
   Immunosuppression

*For visual examples, please refer to the links indicated in the reference portion at the end of
the handout*

**HPV screening**

Visual diagnosis
   Many cases asymptomatic
Visible lesions
   Clinical skill
      Acetowhiteness likely adds like to visual screening
Acetowhiteness + peniscopy
   An evolving standard of care?
      Primary care?
      College health?
      Follow-up?
HPV DNA detection
   Multiple studies using penis “scraping” techniques to screen for HPV DNA
      None approved
   Laboratory processing similar to HPV DNA testing of liquid-based Pap samples

**Male HPV Treatment:**

- Goal: eradication or reduction in symptoms
- Treatment may not eliminate HPV
- Selection of modality depends on
   - size of lesion
   - number of lesions
o anatomic site
o patient preference
o provider experience

**ABLATION** (by Provider):
- Bi-Chloroacetic/Tri-Chloroacetic Acid (BCA/TCA): causes chemical destruction of the condyloma epithelium; applied weekly until resolved
- Cryo-Surgery: freezes intracellular fluid; Liquid N2 directly applied to each lesion weekly until resolved; applied with a cotton swab or cyroprobe
- Podophyllin: blocks cell growth by blocking cell division; applied weekly until resolved; patient must completely wash the treated area in one to four hours

**ABLATION** (ordered by provider & self-administered)
- Podofilox: causes tissue necrosis; applied bid x 3 days followed by no treatment for 4 days; may be repeated for a maximum of four cycles
- Aldara 5% Cream (Imiquimod): modifies the immune response; applied qod x 3 of 7 days & removed with soap & water in 6 – 10 hrs; can be repeated weekly up to 16 weeks

**Treatments Requiring a Referral:**
**Surgical Intervention**
- **Electro-cautery:** high-frequency current to cut & coagulate condyloma
- **Laser Surgery:** precisely controlled method targeting a specific area; CO2 Laser useful in persistent HPV infection; used in treatment of urethral and periurethral condyloma
- **Surgical Excision:** removal of condyloma with a scalpel, scissors or curette; allows pathologic analysis

**Medical Intervention**
- **5-Fluorouracil (5-FU):** antimetabolite causing tissue destruction by interfering with DNA/RNA synthesis; self-applied 1 to 3 x weekly; absorbed systemically
- **Interferon:** both immunomodulatory & antiviral activities; given intralesionally at the base of each condyloma 3 x week x 3 weeks

**REFER:**
- Persistent Condyloma
- Urethral Condyloma
- Distal Anal Condyloma

**Non-Prescription HPV Treatments:**

**OTC’s (not recommended for genital warts):**
- **Salicylic Acid** (Compound W)
- **Liquid Nitrogen**

**Homeopathic Remedies:**
- **PHP HPV Super Kit:** series of herbal meds that “teach” the immune system the suppress the virus ([www.biogetica.com](http://www.biogetica.com))
- **Naturasil**: plant extract, topical solution, anti-viral activity, absorbed cutaneously & systemically ([www.naturasil.com](http://www.naturasil.com))
- **OXi-MED**: anti-viral/o2 infusion cream ([www.wartcream.com](http://www.wartcream.com))

**Home Remedies Males May Try:**
- OTC Tagamet – 2 tabs qd until clear
- Raw red potatoes – rub warts with cut end for 5 minutes at hs – wash off in am
- Castor Oil – apply bid until clear
- Banana peel – cut a piece to cover wart with inside surface and secure with a Band-Aid overnight
- Windex – spray warts qd x 10 days
- Cigarette Ashes – rub on warts for 1 – 2 weeks
- Clear Nailpolish – apply to warts am and hs until clear

**Male HPV Prevention:**

A direct correlation exists between anogenital HPV infection and measures of sexual activity including:

- Age at first coitus
- Life-time number of sexual partners
- Frequency of sexual activity
- Type of sexual activity
- Males tend to become sexually active earlier than females

**Education targeting males:**

- **Value of abstinence**: and ultimately a single monogamous relationship with an equally abstinence partner
- **Delay sexual debut**: HPV infection tends to follow the first sexual encounter (ASCCP: June, 2006)
- **Limit number of lifetime sexual partners**: a direct correlation between multiple sexual partners and HPV infection has been demonstrated in numerous studies (Gearhart: January, 2007)
- **Consistent Condom use**: can decrease but not completely eliminate HPV transmission. One study of 82 female college students demonstrated that those 100% compliant with condom use were 70% less apt to contract HPV infection (Winer, et all: NEJM, 2006)

**Circumcision:**

  - “HPV detection was significantly less common among.. participants who were circumcised..(20% vs. 40%)”
  - ”In multivariate analyses.......only circumcision remained ..linked to reduced odds of oncogenic & nononcogenic HPV detection”
  - ”Male circumcision is associated with a reduced risk of penile HPV infection…”

  - ”Circumcised men are less likely than uncircumcised men to have penile HPV”
  - ”Female partners of men who engage in risky sexual behavior have a reduced
likelihood of having cervical cancer if the man is circumcised”
-”...the effect of circumcision status on the prevalence of cervical cancer
suggested that circumcision may reduce the likelihood...in current
partners..however, this result was not statistically significant’

**HPV Vaccine Use in Males:**

- *Cervarix* (Glaxo, FDA approval pending)
  - Covers HPV Types 16 & 18
  - Clinical Trials on Females ONLY
  - No Anal cancer component
  - Marketing will address only females

**HPV Vaccine Use in Males:**

HPV Vaccine Use in Males:

- **Gardasil** (Merck; June, 2006 FDA Approval)
  - Effective for HPV Types 6 & 11, 16 & 18
  - Ongoing trials in males 9 – 15yrs (include an anal cancer component)
  - Trials → substantial immune response in men, but difficult to measure protection
    - Current government study targets the use of Gardasil in HIV-infected preteen boys & girls
    (CHAMP: June, 2006)

**January, 2007 SHS listserve query: “Is your Health Service making Gardasil available to males?”**

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<thead>
<tr>
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<td>31</td>
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<td>Yes</td>
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<tr>
<td>No?*</td>
<td>2</td>
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*Did not offer a specific yes or no answer

**HPV Vaccine use in Males – The Facts:**

- Safe use of *Gardasil* in males has been established
- *Gardasil* is being administered to males in Australia, New Zealand and the European Union
- HPV 16 & 18 cause at least 70% of anal cancer and 70% of precancerous penile lesions
- The incidence of anal cancer in MSM has more than doubled in the last 30 years
- HPV 6 & 11 cause >90% of condyloma in men & women
- *Gardasil* is nearly 100% effective in preventing cervical cancer
  
  JNCI: 2005 97(9)

**HPV Vaccine Use in Males – The Facts:**

- 90% conditions caused by HPV Types 6 & 11 and 16 & 18 could be eliminated if boys and girls were vaccinated before the age of 12
- Girls only vaccination = 75% reduction
- The only debates surrounding male HPV vaccination relate to:
“When you want to reduce disease in a population, you to immunize as many people as you can. If you can immunize a large percentage of men and prevent them from infecting women you can reduce the disease in women.”

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School of Medicine

Male HPV Infection – A Challenge to Diagnosis & Treatment

References

1. 2006 CDC STD Treatment Guidelines: [www.cdc.gov/std/treatment/](http://www.cdc.gov/std/treatment/)


26. UCSF Anal Neoplasia Research and Treatment Group. www.analcancerinfo.ucsf.edu*
