GENITAL HUMAN PAPILLOMAVIRUS (HPV)

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Biology of HPV

• Ubiquitous virus
• 100+ different types
• Trophic to human epithelium
• Most cause no disease
Virology: Human Papillomavirus

- Non-enveloped, double-stranded, circular DNA viruses
- Sexually transmitted HPVs:
  - Low-risk HPVs, which do not cause cancer but can cause skin warts (technically known as condyloma acuminata) on or around the genitals or anus. HPV types 6 and 11 cause 90 percent of all genital warts.
  - Oncogenic HPVs can cause cancer. At least a dozen high-risk HPV types have been identified. Types 16 and 18 are responsible for the majority of HPV-caused cancers.

From family Papovaviridae

Hung et al, 2008

Natural History of HPV Infection

CDC, 2012

Working Model of Cervical Carcinogenesis: Risk Factors for Progression to Neoplasia

Gravitt, 2011.
Prevalence in the U.S.

- It is estimated that at least 50% of sexually active men and women acquire genital HPV at some point in their lives.
- A recent estimate suggests 80% of women will have acquired genital HPV by the age of 50.

HPV and oral pharyngeal and anal cancers

- HPV recognized as a cause of oropharyngeal cancers (back of throat, base of tongue and tonsils)
- In US, about 40-80% of oropharyngeal cancers are caused by HPV
- Increasing incidence noted primarily in white men and at young ages.
- Epidemiology of oral HPV infection is not well understood
- There is good evidence that HPV causes many anal squamous cell carcinomas


Trends: HPV prevalence in U.S. women

Wheeler et al., 2012
CLINICAL MANIFESTATIONS
Clinical Manifestations and Sequelae

- In most cases, genital HPV infection is transient and has no clinical manifestations or sequelae.
- Clinical manifestations of genital HPV infection include:
  - Genital warts
  - Cervical cell abnormalities
  - Anogenital squamous cell cancers
  - Recurrent respiratory papillomatosis
- Most common clinically significant HPV infection manifestations:
  - Genital warts
  - Cervical cell abnormalities

Genital Warts: Appearance

- Condyloma acuminata
  - Cauliflower-like appearance
  - Skin-colored, pink, or hyperpigmented
  - May be keratotic on skin; generally non-keratinized on mucosal surfaces
- Smooth papules
  - Usually dome-shaped and skin-colored
- Flat papules
  - Macular to slightly raised
  - Flesh-colored, with smooth surface
  - More commonly found on internal structures (i.e., cervix), but also occur on external genitalia
- Keratotic warts
  - Thick horny layer that can resemble common warts or seborrheic keratosis

Genital Warts: Location

- Warts commonly occur in areas of coital friction.
- Perianal warts do not necessarily imply anal intercourse.
  - May be secondary to autoinoculation, sexual activity other than intercourse, or spread from nearby genital wart site.
- Intra-anal warts are seen predominantly in patients who have had receptive anal intercourse.
- Patients with visible warts can be simultaneously infected with multiple HPV types.
Genital Warts: Symptoms

- Genital warts usually cause no symptoms other than the warts themselves.
- Vulvar warts—dyspareunia, pruritis, burning discomfort
- Penile warts—occasional itching
- Urethral meatal warts—occasional hematuria or impairment of urinary stream
- Vaginal warts—usually asymptomatic; occasional discharge/bleeding, obstruction of birth canal (secondary to increased wart growth during pregnancy)
- Perianal warts—usually asymptomatic; pain, bleeding on defecation, itching
- Most patients have fewer than 10 genital warts, with total wart area of 0.5-1.0 cm²

Genital Warts: Duration

- May regress spontaneously or persist with or without proliferation.
- Frequency of spontaneous regression is unclear.
- Persistence of infection occurs, but frequency and duration are unknown.
- Recurrences after treatment are common.

Genital Warts and High-Risk HPV

- 90% are caused by HPV 6 or 11
- High-risk HPV types occasionally found in visible genital warts
- Associated with external genital (i.e., vulvar, penile, and anal) squamous intraepithelial lesions
Is biopsy necessary?

- Diagnosis usually made by visual inspection
- Biopsy if:
  - Uncertain re: the lesion
  - Lesions do not respond to or worsen during therapy
  - Lesion looks atypical or is bleeding, pedunculated, fixed, indurated or ulcerated
  - Immunocompromise

Source: CDC, 2010

Perianal Warts

Source: Seattle STD/HIV Prevention Training Center at the University of Washington/ UW HSCER Slide Bank

Vulvar Warts

Source: Reprinted with permission of Gordon D. Davis, MD.
Penile Warts

Co-infection with other STDs

- Very common in sexually active adults
  - HPV+ or warts may mean need to screen for STDs
  - More severe disease in immunocompromised individuals

Cervical Cell Abnormalities

- Usually subclinical
- Detected by Pap, colposcopy, or biopsy
- Usually caused by high-risk HPV types
  - Most of the time high-risk HPV types do not cause any abnormalities.
  - Most women infected with high-risk HPV types have normal Pap test results.
- Often regress spontaneously without treatment
Recurrent Respiratory Papillomatosis

- HPV infections in infants and children may present as laryngeal papillomatosis, also known as juvenile onset recurrent respiratory papillomatosis (JORRP).
- Respiratory papillomatosis is a rare condition, usually associated with HPV types 6 and 11.

**Clinical Manifestations**

**DIAGNOSIS**

Diagnosis of Genital Warts

- Diagnosis is usually made by visual inspection with bright light.
- Diagnosis can be confirmed by biopsy when:
  - Diagnosis is uncertain
  - Patient is immunocompromised
  - Warts are pigmented, indurated, or fixed
  - Lesions do not respond or worsen with standard treatment
  - There is persistent ulceration or bleeding
Diagnosis of Genital Warts (continued)

- Use of type-specific HPV DNA tests for routine diagnosis and management of genital warts is not recommended.
- Acetic acid evaluation (acetowhitening) of external genitalia is not recommended.
- External genital warts are not an indication for cervical colposcopy or increased frequency of Pap test screening (assuming patient is receiving screening at intervals recommended by her health care provider).

Differential Diagnosis of Genital Warts

- Other infections
  - Condylomata lata—tend to be smoother, moist, more rounded, and darkfield-positive for Treponema pallidum
  - Molluscum contagiosum—papules with central dimple, caused by a pox virus; rarely involves mucosal surfaces

Differential Diagnosis of Genital Warts (continued)

- Acquired dermatologic conditions
  - Seborrheic keratosis
  - Lichen planus
  - Fibroepithelial polyp, adenoma
  - Melanocytic nevus
  - Neoplastic lesions
- Normal anatomic variants
  - “Pink pearly penile papules”
  - Vestibular papillae (micropapillomatosis labialis)
  - Skin tags (acrochordons)
Diagnosis of Cervical Cell Abnormalities

- Cytology (Pap test)
  - Useful screening test to detect cervical dysplasia (not HPV per se)
  - Provides indirect evidence of HPV because it detects squamous epithelial cell changes that are almost always due to HPV

Diagnosis

- High-risk (oncogenic) HPV testing reserved for:
  - Women over 30 with Pap testing
  - NOT for men
  - Should not be used for general STD testing or for women < 21
- Low-risk HPV testing not indicated

| Table 1 | Recommendations for Cervical Cancer Screening | American College of Obstetricians and Gynecologists | American College of Obstetricians and Gynecologists
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<tr>
<td>Age (y)</td>
<td>Do not screen.</td>
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<td>Age 21-29</td>
<td>Screen 1 screening in 3 years BPV or testing not recommended.</td>
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<td>Age 30-45</td>
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<td>Age 45+</td>
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<td>Other</td>
<td>No screening if negative prior screen.</td>
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<td>History</td>
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<td>Residual HPV</td>
<td>No change in screening recommendation.</td>
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*Source: Saikumar et al.*
*American College of Obstetricians and Gynecologists, 2008.*
*American College of Obstetricians and Gynecologists, 2010.*
*Pap smear test or liquid-based cytology.*
Anal cancer screening

- For adults with HIV infection
  - Modeled on cervical cancer screening: cytology, high-resolution anoscopy, biopsy
  - Many HIV specialists are performing biennial or annual
  - No national recommendations

(Darragh et al, 2011; Dunne et al, 2011)

TREATMENT

General Treatment of Genital Warts

- Primary goal is removal of symptomatic warts.
- If left untreated, genital warts may regress spontaneously or persist with or without proliferation.
- In most patients, treatment can induce wart-free periods.
- Currently available therapies may reduce, but probably do not eradicate infectivity.
- Effect of current treatment on future transmission is unclear.
### General Treatment of Genital Warts (continued)

- No evidence that presence of genital warts or their treatment is associated with development of cervical cancer.
- Some patients may choose to forgo treatment and await spontaneous resolution.
- Consider screening persons with newly diagnosed genital warts for other STD (e.g., chlamydia, gonorrhea, HIV, syphilis).

### Treatment Regimens

- Patient-applied and provider-administered therapies are available.
- Providers should be knowledgeable about and have available at least 1 patient-applied and 1 provider-administered treatment.
- Choice of treatment should be guided by:
  - The preference of the patient
  - The available resources
  - The experience of the healthcare provider

### Treatment Regimens (continued)

- Factors influencing treatment selection:
  - Wart size
  - Number of warts
  - Anatomic site of wart
  - Wart morphology
  - Patient preference
  - Cost of treatment
  - Convenience
  - Adverse effects
Treatment Response

- Affected by:
  - Number, size, duration, and location of warts, and immune status
  - In general, warts located on moist surfaces and in intertriginous areas respond better to topical treatment than do warts on drier surfaces.
- Many patients require a course of therapy rather than a single treatment.
  - Evaluate the risk-benefit ratio of treatment throughout the course of therapy to avoid over-treatment.
- No evidence that any specific treatment is superior to any of the others.
  - The use of locally developed and monitored treatment algorithms has been associated with improved clinical outcomes.

Recurrence

- Up to 2/3 of patients will experience recurrences of warts within 6-12 weeks of therapy; after 6 months most patients have clearance.
  - If persistent after 3 months, or if there is poor response to treatment, consider biopsy to exclude a premalignant or neoplastic condition, especially in an immunocompromised person.
- Treatment modality should be changed if patient has not improved substantially after 3 provider-administered treatments or if warts do not completely clear after 6 treatments.

Complications

- Complications rarely occur if treatments for warts are employed properly.
  - Depressed or hypertrophic scars are uncommon but can occur, especially if the patient has had insufficient time to heal between treatments.
  - Rarely, treatment can result in disabling chronic pain syndromes (e.g., vulvodynia or hyperesthesia of the treatment site).
  - Patients should be warned that persistent hypopigmentation or hyperpigmentation are common with ablative modalities.
CDC-Recommended Regimens for External Genital Warts (Patient-Applied)

• Podofilox 0.5% solution or gel (Condylox™)
  • Patients should apply solution with cotton swab or gel with a finger to visible warts twice a day for 3 days, followed by 4 days of no therapy.
  • Cycle may be repeated as needed up to 4 cycles.

OR

• Imiquimod 5% cream (Aldara™)
  • Patients should apply cream once daily at bedtime, 3 times a week for up to 16 weeks.
  • Treatment area should be washed with soap and water 6-10 hours after application.

OR

• Sinecatechins 15% ointment
  • Patients should apply 3 times daily for not more than 16 weeks. The medication should not be washed off after use.

Patient-applied treatments

• Podofilox
• Anti-mitotic
• Apply BID x 3D then no tx for 4D
• Up to 4 cycles
• Total wart area should not exceed 10 sq cm

Imiquimod

• Stimulates interferon
• Apply at HS 3x/week x 16 weeks
• Wash area 6-10 hrs later
• May weaken condoms
Sinechatetin ointment

- Green tea extract
- TID x 16 weeks only

CDC-Recommended Regimens For External Genital Warts (Provider-Administered)

- Cryotherapy with liquid nitrogen or cryoprobe
  - Repeat applications every 1-2 weeks, OR
- Podophyllin resin 10%-25% in compound tincture of benzoin
  - Apply a small amount to each wart and allow to air dry
  - Treatment may be repeated weekly if needed, OR
- Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%-90%
  - Apply small amount only to warts and allow to dry
  - Treatment may be repeated weekly if needed, OR
- Surgical removal—tangential scissor excision, tangential shave excision, curettage, or electrosurgery

Cryotherapy, surgery

- Cryoprobe or liquid nitrogen
- Need special training
- GYN or URO referral
### Provider-administered: Podophyllin

- Podophyllin resin 10-25%
- Applied to wart and air dried before dressing
- No open lesions
- Not larger area than 10 sq cm
- Wash off 1-4 hours later

### TCA/BCA

- Caustic agent
- Apply small amount and let dry
- White frosting develops
- If needed neutralize with sodium bicarb
- Repeat weekly

### Treatment of Exophytic Cervical Warts

- High-grade squamous intraepithelial lesions (SIL) must be excluded before treatment is initiated.
- Management should include consultation with a specialist.
Management of Genital Warts in Immunodeficient Patients

- More frequent, more pronounced clinical manifestations and occurrence of atypical lesions
- More resistant to conventional therapy, recurrence common
- Role of warts (or irritated treatment sites) in HIV transmission is unknown.
- Treat only if the patient is symptomatic.
- HSIL and invasive cancer can occur in wart-like lesions, especially in the perianal area
- So, lesions which are hyperpigmented or which persist despite treatment should be biopsied.

Genital Wart Follow-Up

- Counsel patients to:
  - Watch for recurrences
  - Get regular Pap screening at intervals as recommended for women WITHOUT genital warts
- After visible warts have cleared, follow-up evaluation not mandatory, but provides opportunity to:
  - Monitor or treat complications of therapy
  - Document the absence of warts
  - Reinforce patient education and counseling messages
- Offer patients concerned about recurrences a follow-up evaluation 3 months after treatment.

Pap Test Screening in Immunodeficient Patients

- Immunodeficiency appears to accelerate intraepithelial neoplasia and invasive cancer.
- Provide cervical Pap test screening every 6 months for 1 year, then annually for all HIV-infected women with or without genital warts.
- Anal pap tests and anoscopy: value in absence of symptoms not established, but is under investigation
PATIENT EDUCATION

Response to diagnosis

• Upset
• Sexual dysfunction
• Relationship conflict
• Fear of cancer
• Fear of treatments
  • Offer: reassurance re: commonness, dormancy (i.e., HPV does not imply infidelity)
  • Discuss analogies and compare to other infections
  • Allow patients to discuss their understanding of diagnosis
  Dunne et al, 2011

The Nature of HPV Infection

• Genital HPV infection is common in sexually active adults.
• Incubation period is variable, and it is often difficult to determine the source of infection.
• Natural history of HPV infection is usually benign:
  • Low-risk genital HPV types are associated with mild Pap test abnormalities and genital warts.
  • High-risk types are associated with mild to severe Pap test abnormalities and, rarely, cancers of the cervix, vulva, anus, and penis.
  • Most women infected with high-risk HPV types have no Pap test abnormalities and do not develop cervical cancer.
  • Genital warts have a high recurrence rate after treatment.
Transmission Issues

- Determining source of infection is usually difficult.
- Recurrences usually are not re-infection.
- Transmission risk to current and future partners is unclear.
- Abstinence and long-term mutual monogamy with an uninfected partner are the most effective options to prevent transmission.
- Likelihood of transmission and duration of infectivity with or without treatment are unknown.
- Value of disclosing a past diagnosis of genital HPV infection to future partners is unclear, although candid discussions about past STD should be encouraged.

Prevention

- Vaccination
- Do condoms work?
- Oral HPV and oral cancers
- Screening

Vaccine

- HPV vaccine is recommended for girls (Gardasil or Cervarix) and boys (Gardasil) age 11 or 12 of age. It may be given starting at age 9.
- Catch up: females 13 through 26 and males 13 to 21 years of age.
- Recommended for men through age 26 who have sex with men or whose immune system is weakened.
Is partner notification recommended?

- No, not in order for partners to have exam/treatment
- Many do anyway! (Hoover et al, 2009)
- CDC (2010) recommendation:
  - Inform partners because they can get warts
  - Also re: other counseling points
  - Will need to abstain from sex during treatment
  - Both partners would benefit from screening for other STDs

Case study

- MK is a 20 year old woman presenting for a first appointment in the STD clinic. She complains of itchy "bumps" in the vaginal area. She denies vaginal discharge, dyspareunia, and dysuria. She says her partner of one month has no symptoms and she is worried.
- You examine her and diagnose her with genital warts. The patient is very upset. What can you tell her about her condition?

But, she asks, "Did my boyfriend give this to me?" What would you answer?
- Does she need a Pap test?
- An HPV test?
- A biopsy?
- What are her treatment options?
- Which one do you think you would offer first?
- Will I need a c/section if I get pregnant?
- Am I going to give this to other people?
References


Hoover, K., Friedman, A., Montano, D., et al. What about the partners of women with abnormal Pap or positive HPV tests? Sex Trans Dis. March 2009;36(3):141-146. DOI: 10.1097/OLQ.0b013e31818eb765


