Genital Human Papillomavirus (HPV)

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http://www2a.cdc.gov/stdtraining/ready-to-use/

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 fall into two categories: low risk and high risk (oncogenic)

From family Papovaviridae
Hung et al. 2008
VIROLOGY

- Low-risk HPVs:
  - Causes skin warts (condylomata acuminata)
  - HPV 6 and 11
  - Responsible for 90 percent of all genital warts.

- High-risk HPVs:
  - Can cause cancer.
  - HPV types 16 and 18 responsible for the majority of HPV-caused cancers.

Natural History of HPV Infection

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

Prevalence-United States

- 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

- A primary cause of oropharyngeal cancers (back of throat: base of tongue and tonsils)
- In the 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

HPV prevalence in women worldwide

Clinical manifestations

(Wheeler et al., 2012)

(Bosch et al., 2008)
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

- Condylomata 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 keratoses
Penile Warts

Source: Cincinnati STD/HIV Prevention Training Center

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.
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

Cervical Cell Abnormalities

- Usually subclinical
- Detected by Pap test, 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

Diagnosis

- 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

- 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

Condylomata lata

Clinical Manifestations

Vulvar Warts

Diagnosis

- 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 - Cervical Cell, Anal Cell Abnormalities**

- Cytology (Pap test)
  - Useful screening test to detect cervical dysplasia (not HPV per se)
  - Detects squamous epithelial cell changes due to HPV
  - HPV testing for high-risk women >30yo.
- Anal cytology for adults with HIV infection
  - No national recommendations
  - Some HIV specialists offer testing

*(Darrah et al, 2011; Dunne et al, 2011)*

**General Treatment**

- 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.

**Management**

- 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 STDs (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

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.
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 (Aldara)

- 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
Complications

- Complications are rare
- Depressed or hypertrophic scars are uncommon but can occur
- Rarely, chronic pain at treatment site.
- Patients should be warned that persistent hypopigmentation or hyperpigmentation are common with ablative modalities.

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 to:
  - Monitor or treat complications of therapy
  - Document the absence of warts
  - Reinforce patient education and counseling messages
  - 3 month follow-up

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.

Immunodeficient Patients

- More pronounced clinical manifestations, atypical lesions
- More resistant to conventional therapy
- Frequent recurrences after treatment
- Role of warts (or irritated treatment sites) in HIV transmission is unknown.
- Treat only if the patient is symptomatic.
- Because HSIL and invasive cancer can occur in wart-like lesions, especially in the perianal area, lesions which are hyperpigmented or which persist despite treatment should be evaluated by biopsy.
Screening 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.

Prevention

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.

HPV vaccine uptake in young adult women

Laz et al., 2013.
Patient Counseling

- 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.

Partner Notification

- Not indicated, but 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

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


