CDC

STD Prevention

Ready-to-Use

STD Curriculum for Clinical Educators

Genital Human Papillomavirus (HPV) Module

Target Audience - Faculty in clinical education programs, including those programs that train advanced practice nurses, physician assistants, and physicians

Contents - The following resources are provided in this module:

- **Faculty Notes** (Microsoft Word and Adobe Acrobat formats) - Includes notes that correspond to the slide presentation, a case study with discussion points, and test questions with answers
- **Slide Presentation** (Microsoft PowerPoint and Adobe Acrobat formats)
- **Student Handouts**
  - **Case Study** (Microsoft Word format)
  - **Test Questions** (Microsoft Word format)
  - **Slides Handout** (Adobe Acrobat format)
  - **Resources** (Microsoft Word format)

Suggested Time Allowance - The approximate time needed to present this module is 60-90 minutes.

These materials were developed by the Training and Health Communication Branch, Division of STD Prevention, CDC. They are based on the curriculum developed by the National Network of STD/HIV Prevention Training Centers (NNPTC) which includes recommendations from the 2002 CDC STD Treatment Guidelines.

Information on the NNPTC can be accessed at:
http://www.stdhivpreventiontraining.org

The 2002 CDC STD Treatment Guidelines can be accessed or ordered online at:
http://www.cdc.gov/std/treatment/default.htm

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Genital Human Papillomavirus (HPV) Infection

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Learning Objectives

1. Upon completion of this content, the learner will be able to:
2. Describe the epidemiology of genital HPV infection in the U.S.
3. Describe the pathology of genital HPV.
4. Discuss the clinical manifestations of genital HPV infection.
5. Identify methods used to diagnose genital warts and cervical cellular abnormalities.
6. Discuss the CDC-recommended treatment regimens for genital warts.
7. Summarize appropriate prevention counseling messages for genital HPV infection.
8. Describe public health measures for the prevention of genital HPV infection.

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Lessons

I. Epidemiology of genital HPV infection in the U.S.
II. Pathogenesis
III. Clinical manifestations and sequelae
IV. Diagnosis of genital warts and cervical cellular abnormalities
V. Patient management
VI. Patient counseling and education
VII. Partner management and public health measures

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I. Epidemiology of Genital HPV Infection in the U.S.

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A. Introduction
    1. Genital HPV infection is one of the most common STDs.
    2. More than 30 types of HPV are sexually transmitted and can infect the genital tract.

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    3. Genital HPV types are divided into two groups, based on their association with cervical cancer.
        a) Infections with low-risk types can cause genital warts and benign or low-grade cervical cell changes (mild Pap test abnormalities) but are not associated with cervical cancer.
        b) Infections with high-risk types can cause low-grade cervical cell changes, high-grade cervical cell changes that are precursors to cancer (moderate to severe Pap test abnormalities), and, in rare cases, cancers of the cervix, vulva, anus, and penis.
    4. Most genital HPV infections, whether caused by low-risk or high-risk types, are transient (go away on their own), asymptomatic, and have no clinical consequences.
    5. Incidence and prevalence information on genital HPV infection is incomplete

because:

a) It is not a reportable infection in any state (genital warts are reportable in a few states).
b) Most infections are not diagnosed because they are brief, asymptomatic, or subclinical (have no visible clinical manifestations) and have no clinical consequences.
c) Most studies estimating incidence and prevalence have been performed in women, with little data about men.

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B. Incidence in the U.S.
   1. The estimated annual incidence of sexually transmitted HPV infection is 6.2 million cases.
   2. An estimated $1.6 billion spent annually in direct medical costs to treat consequences of genital HPV infection.
   3. An estimated 20 million people (15% of the population) currently have a detectable genital HPV infection.

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C. Prevalence in the U.S.
   1. It is estimated that at least 50% of sexually active men and women acquire genital HPV infection at some point in their lives.
   2. A recent estimate suggests that 80% of women will have acquired genital HPV infection by age 50.
   3. An estimated 9.2 million sexually active youth 15-24 years of age are currently infected with genital HPV.

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D. Incidence and prevalence of genital HPV-associated diseases
   1. Genital warts
      a) Prevalence estimates for genital warts are relatively imprecise.
      b) Limited data suggest that annual incidence may be as high as 100 per 100,000 population.
      c) An estimated 1.4 million (1% of the sexually active U.S. population) is affected at any one time.
   2. Cervical cancer
      a) Rates of cervical cancer have fallen by approximately 75% since the introduction of Pap screening programs.
      b) Cervical cancer incidence in the U.S. is currently estimated to be 8.3 per 100,000 women.
         1) Approximately 10,520 new cases annually
         2) Approximately 3,900 deaths annually

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c) Graph: Delay Adjusted Incidence and U.S. Death Rates of Cervical Cancer by Year of Diagnosis and Race: 1973-2001. Although cervical cancer rates continue to decline for both white and black women in the U.S., the burden of disease continues to be on black women.

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E. Transmission of genital HPV infection
   1. Predominantly associated with sexual activity
   2. Likely requires contact with viable HPV and microtrauma to skin or mucous membranes
   3. Can occur from asymptomatic and subclinical patients
   4. Infectivity after treatment of genital warts or cervical cell abnormalities is unknown.
   5. Transmission by fomites (inanimate objects such as environmental surfaces and clothing) has never been documented.
   6. Rarely, genital HPV infection with low-risk types is transmitted from mother to baby during delivery and causes respiratory tract warts in the baby, known as recurrent respiratory papillomatosis (RRP).
      a) Estimates of the incidence rate of RRP are imprecise; they range from 0.4-1.2 cases per 100,000 children.
      b) The preventive value of cesarean delivery is unknown and, thus, should not be performed solely to prevent transmission of genital HPV to the newborn.

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F. Risk factors consistently associated with genital HPV infection in women
   1. Young age
   2. Sexual behavior
      a) Risk increases with increasing lifetime number of male sex partners
      b) Early age of first sexual intercourse
   3. Sexual behavior of male sex partners
      a) Risk increases for women whose sex partners have had multiple sex partners.
   4. Immune status
      a) HPV is more likely to be detected in immune-suppressed women (e.g., HIV-infected persons, women on dialysis, and after kidney transplant).

G. Risk factors less consistently associated with genital HPV infection in women
   1. Smoking
   2. Oral contraceptive use
   3. Nutritional factors (poor nutrition)
   4. Lack of circumcision of male partners

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H. Risk factors associated with genital HPV infection in men
   1. Greater lifetime number of sex partners

2. Greater number of recent sex partners
3. Being uncircumcised

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II. Pathogenesis

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A. Virology
   1. Key features of HPV
      a) Double-stranded DNA virus that belongs to the Papovaviridae family
      b) Small and non-enveloped virions
      c) Over 100 characterized types
      d) Number of recognized HPV types is gradually increasing as more types are identified and genetically characterized.
      e) Genital types have specific tropism (affinity) for genital skin and mucosa.
      f) Very limited animal models and no widely available system for in vitro cultivation
      g) Infection is identified by the detection of HPV DNA or capsid protein.

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   2. HPV genotyping system
      a) Types are distinguished by different DNA sequences (>10% difference) at L1 capsid (surface) protein.
      b) Genital HPV types are generally characterized in terms of their oncogenic potential (ability to cause cervical cancer).
         1) Low-risk types
            i) Associated with genital warts and benign or low-grade cervical cell changes (mild Pap test abnormalities).
            ii) Most visible genital warts are caused by HPV types 6 and 11.
            iii) Recurrent respiratory papillomatosis, a rare condition, is usually associated with HPV types 6 and 11.
         2) High-risk types
            i) Associated with low grade cervical cell changes, high-grade cervical cell changes that are precursors to cancer (moderate to severe Pap test abnormalities), and, in rare cases, anogenital (i.e., cervix, vulva, anus, and penis) cancers.
            ii) HPV types 16 and 18 account for more than half of HPV types found in anogenital cancers.
            iii) Most women infected with high-risk HPV types have normal Pap test results and never develop precancerous (high-grade) cervical cell changes or cervical cancer.

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B. Pathology
   1. Genital HPV infects squamous epithelium and stimulates cellular proliferation.
   2. Affected cells display a broad spectrum of changes ranging from benign hyperplasia to dysplasia to invasive carcinoma.

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C. Natural history of genital HPV infection
    1. Most infections are transient, asymptomatic or subclinical, and have no clinical consequences in immunocompetent individuals.
    2. The incubation period is unclear.
        a) Probably 3 weeks to months for genital warts
        b) Probably several months to years for cervical cellular abnormalities
    3. The median duration of new cervical infections (measured by detection of HPV DNA) is 8 months but varies by HPV type.
        a) 70% of new infections clear within 1 year.
        b) 90% of new infections clear within 2 years.
        c) The gradual development of an effective immune response is thought to be the likely mechanism for HPV DNA clearance.

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    4. Persistent infection is infection that is not cleared by the immune system and is characterized by persistently detectable HPV DNA.
        a) HPV infection that persists is the most important risk factor for precancerous (high-grade) cervical cell changes and cervical cancer.
        b) Factors associated with persistent infection include:
            1) Older age
            2) High-risk HPV types
            3) Immune suppression
        c) Most women with persistent HPV infection do not develop cervical cancer precursors or cervical cancer.
    5. It is unclear whether HPV infection that becomes non-detectable at mucosal surfaces has completely cleared or remains latent in basal cells with potential for later reactivation.

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III. Clinical Manifestations and Sequelae

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A. In most cases genital HPV infection is transient and has no clinical manifestations or sequelae.
B. Clinical manifestations of genital HPV infection include:
    1. Genital warts
    2. Cervical cell abnormalities
    3. Anogenital squamous cell cancers
    4. Recurrent respiratory papillomatosis
C. The two most common clinically significant manifestations of genital HPV infection are:
    1. Genital warts that are visualized without magnification
    2. Cervical cell abnormalities that are detected by Pap test screening (with or without HPV DNA testing) or colposcopy

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D. Genital warts
    1. Genital warts have 4 morphologic types:
        a) Condylomata acuminata
            1) Cauliflower-like appearance
            2) Skin-colored, pink, or hyperpigmented
            3) May be keratotic on skin; generally non-keratinized on mucosal surfaces
        b) Smooth papules: usually dome-shaped and skin-colored
        c) Flat papules
            1) Macular to slightly raised
            2) Flesh-colored, with smooth surface
            3) More commonly found on internal structures (i.e., cervix), but also occur on external genitalia
        d) Keratotic warts: thick horny layer resembling common warts or seborrheic keratosis

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    2. Location
        a) Genital warts appear most commonly in areas of coital friction.
            1) Men–penis, scrotum, urethral meatus, and perianal area
            2) Women--introitus, vulva, perineum, and perianal area
        b) Less common genital warts sites:
            1) Cervix and vaginal walls in women
            2) Pubic area, upper thighs, or crural folds in men and women
        c) Perianal warts do not necessarily imply anal intercourse, but may be secondary to autoinoculation, sexual activity other than intercourse, or spread from a nearby genital wart site.
        d) Intra-anal warts are seen predominantly in patients who have had receptive anal intercourse.
        e) HPV types causing genital warts can occasionally cause lesions on oral, upper respiratory, upper GI, and ocular locations.
        f) Patients with visible warts can be infected simultaneously with multiple HPV types.

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    3. Symptoms
        a) Genital warts usually cause no symptoms other than the warts themselves.
        b) Vulvar warts can cause dyspareunia, pruritis, and burning discomfort.
        c) Penile warts occasionally cause pruritis.
        d) Urethral meatal warts occasionally cause hematuria or impairment of urinary stream.
        e) Vaginal warts occasionally cause discharge, bleeding, or obstruction of birth canal (due to increased wart growth in pregnancy).

f) Perianal warts occasionally cause pain, bleeding on defecation, or pruritis.
g) Most patients have fewer than 10 genital warts, with total wart area of 0.5-1.0 cm^2.

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4. Duration
   a) Genital warts may regress spontaneously or persist with or without proliferation.
   b) Frequency of spontaneous regression is unclear. A few studies indicate a regression rate of 10%-30% within 3 months.
   c) Persistence of infection occurs, but frequency and duration is unknown.
   d) Recurrences after treatment are common (20%-50% recurrence rate at 3-6 months).

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5. High-risk HPV types occasionally are found in visible genital warts and have been associated with external genital (i.e., vulvar, penile, and anal) squamous intraepithelial lesions (i.e., squamous cell carcinoma in situ, bowenoid papulosis, Erythroplasia of Queyrat, or Bowen's disease of the genitalia).
   a) The most commonly recognized clinical manifestation of external genital squamous intraepithelial lesions (SIL) is bowenoid papulosis, dome-shaped or flat papules that are often hyperpigmented.
   b) These lesions can sometimes be clinically indistinguishable from genital warts, but on biopsy demonstrate high-grade SIL.
   c) They occur in what is usually macroscopically normal epithelium and mucosal tissue.

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6. Genital warts in preadolescent children
   a) May be due to sexual abuse and should prompt an evaluation for such.
   b) May also result from vertical transmission, transmission of non-genital HPV types to genital surface, and possibly fomite transmission, although fomite transmission has never been documented.

[Slide 28]
Image: Perianal warts

[Slide 29]
Image: Vulvar warts

[Slide 30]
Image: Penile warts

[Slide 31]
Image: Intrameatal wart

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E. Cervical cell abnormalities
    1. Cervical cell abnormalities are usually subclinical.
        a) They are detected by Pap test, colposcopy, or biopsy.
        b) Magnification by colposcopy can enhance detection of cervical cell abnormalities; histology is used to confirm and stage cervical cell abnormalities.
    2. Cervical cell abnormalities are usually caused by high-risk HPV types.
        a) Most of the time high-risk HPV types do not cause any abnormalities.
        b) Most women infected with high-risk HPV types have normal Pap test results.
    3. Cervical cell abnormalities attributed to HPV often regress spontaneously without treatment.
    4. Cervical cell abnormalities are classified based on whether the abnormality is likely to be a cervical cancer precursor.

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    5. The 2001 Bethesda System classifies cervical cellular abnormalities into one of several categories:
        a) Atypical squamous cells (ASC) are cells that do not appear to be completely normal.
            1) ASC–US—atypical squamous cells of undetermined significance. Sometimes the changes are related to HPV infection. ASC–US changes are usually mild abnormalities.
            2) ASC–H—atypical squamous cells cannot exclude a high-grade squamous intraepithelial lesion. ASC–H changes are more likely to be precancerous abnormalities.
        b) Low-grade squamous intraepithelial lesion (LSIL)--generally a transient infection with a high-risk HPV type.
        c) High-grade squamous intraepithelial lesion (HSIL)--generally a persistent infection with a high-risk HPV type with a higher risk for progression to cervical cancer.
        d) See the American Society for Colposcopy and Cervical Pathology Consensus Guidelines on Management of Women with Cytological Abnormalities for more information on the Bethesda Classification System. http://www.asccp.org/consensus/cytological.shtml

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F. Anogenital squamous cell cancers
    1. HPV infection is causally associated with cervical cancer and probably other anogenital squamous cell cancers (e.g., anal, penile, vulvar, vaginal).
    2. Over 99% of cervical cancers have HPV DNA detected within the tumor.
    3. Persistent infection with a high-risk HPV type (e.g., infection which is not cleared by the immune system and which is characterized by persistently detectable HPV DNA) is necessary but not sufficient for the development of cervical cancer.

a) Other risk factors that increase risk of developing cervical cancer precursors and cervical cancers include:
    1) Early age of first intercourse (16 years or younger)
    2) History of multiple sex partners
    3) Active or passive smoking
    4) Long-term use of oral contraceptive
    5) High number of pregnancies
    6) Immune suppression
    7) Co-infection with *Chlamydia trachomatis* or herpes simplex virus type-2

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

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IV. Diagnosis of Genital Warts and Cervical Cellular Abnormalities

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A. Diagnosis of genital warts
    1. Diagnosis is usually made by visual inspection with bright light.
    2. Diagnosis can be confirmed by biopsy.
        a) Confirmation of diagnosis is needed when:
            1) Diagnosis is uncertain.
            2) Patient is immunocompromised.
            3) Warts are pigmented, indurated, or fixed.
            4) Lesions do not respond or worsen with standard treatment.
            5) There is persistent ulceration or bleeding.
    3. Use of type-specific HPV DNA tests for routine diagnosis and management of genital warts is not recommended.
    4. Acetic acid evaluation (acetowhitening) of external genitalia is not recommended.
        a) Low specificity (many false positives)
        b) Acetowhitening will occur at sites of prior trauma or inflammation.
    5. 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).

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    6. Differential diagnosis of genital warts include:
        a) Other infections
            1) Condylomata lata–tend to be smoother, moist, more rounded, and darkfield-positive for *Treponema pallidum*. This is a manifestation of

secondary syphilis and serologic tests for syphilis are positive.
2) Molluscum contagiosum–papules with central dimple, caused by a pox virus; rarely involves mucosal surfaces.

b) Acquired dermatologic conditions
1) Seborrheic keratosis
2) Lichen planus
3) Fibroepithelial polyp, adenoma
4) Melanocytic nevus
5) Neoplastic lesions

c) Normal anatomic variants
1) "Pink pearly penile papules"
2) Vestibular papillae (micropapillomatosis labialis)
3) Skin tags (acrochordons)

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B. Diagnosis of cervical cell abnormalities

1. Cytology (Pap test)
a) A useful screening test to detect cervical dysplasia (not HPV per se)
b) Provides indirect evidence of HPV because it detects squamous epithelial cell changes that are almost always due to HPV
c) No need for more frequent Pap test screening if external genital warts are present (assuming patient is receiving screening at intervals recommended by her health care provider).
d) The role of anal Pap test for cytologic screening is under investigation, especially among HIV-infected persons.
e) Limitations of Pap tests
1) Specimen adequacy–Pap test occasionally must be repeated when the laboratory judges the specimen unsatisfactory for evaluation.
2) Variable sensitivity (A review of the literature estimated that the sensitivity of a single Pap test was 60%-80% for high-grade lesions, and even lower for low-grade lesions).
3) Technologies using liquid collection media (ThinPrep® Pap Test™, Autocyte Prep™) and computer-assisted reading may enhance sensitivity, but possibly reduce specificity.

2. Nucleic acid testing
a) A definitive diagnosis of HPV is based on detection of viral nucleic acid (DNA or RNA) or capsid protein.
b) A test that detects high-risk types of HPV DNA in cells scraped from the cervix is commercially available. The FDA has approved this test for two optional uses:
1) To triage women with atypical cells of undetermined significance (ASC-US) Pap test results, and
2) As an adjunct to the Pap test to screen for cervical cancer in women 30 years or older.
c) Use of HPV DNA testing for women with SIL Pap test results is unnecessary because the vast majority of women with SIL are infected

with HPV.
    1) Diagnosis of SIL requires additional techniques (e.g. cytology, colposcopy, and histopathology).
    2) External genital warts are not an indication for HPV DNA testing.
3. Colposcopy
    a) Indication for colposcopy is guided by physical exam and Pap test findings with or without HPV DNA test findings.
    b) External genital warts are not an indication for cervical colposcopy.
4. Histology (biopsy)
    a) Indications for cervical biopsy include:
        1) Visible exophytic lesions on the cervix
        2) Pap test with HSIL
        3) Pap test with ASC-H or LSIL with colposcopic abnormalities
    b) Indications for biopsy of external genitalia include:
        1) Suspected bowenoid papulosis
        2) Other atypical lesions where diagnosis is uncertain
5. For more information on guidelines for managing women with cervical cytologic abnormalities, refer to the 2001 Consensus Guidelines for the Management of Women with Cervical Cytologic Abnormalities. http://www.asccp.org/consensus/cytological.shtml

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V. Patient Management/Treatment

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A. General treatment of genital warts
    1. Primary goal is removal of symptomatic warts.
    2. If left untreated, visible genital warts may regress spontaneously or persist with or without proliferation.
    3. In most patients, treatment can induce wart-free periods.
    4. Currently available therapies may reduce, but probably do not eradicate, infectivity.
    5. Effect of current treatment on future transmission is unclear.
    6. No evidence that presence of genital warts or their treatment is associated with development of cervical cancer.
    7. Because of uncertainty regarding the effect of treatment on future transmission and the possibility for spontaneous resolution, some patients may choose to forgo treatment and await spontaneous resolution.
    8. Consider screening persons with newly diagnosed genital warts for other STDs (e.g., chlamydia, gonorrhea, HIV, syphilis).

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B. Treatment regimens
    1. Patient-applied and provider-administered treatment regimens are available.
    2. Providers should be knowledgeable about and have available at least one patient-applied and one provider-administered treatment.

C. Choice of treatment should be guided by:
    1. The preference of the patient
    2. The available resources
    3. The experience of the healthcare provider
D. Factors that may influence selection of treatment include:
    1. Wart size
    2. Number of warts
    3. Anatomic site of wart
    4. Wart morphology
    5. Patient preference
    6. Cost of treatment
    7. Convenience
    8. Adverse effects

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E. Treatment response
    1. Affected by:
        a) Number, size, duration, and location of warts
        b) Immune status (pregnancy, HIV infection)
        c) In general, warts located on moist surfaces and in intertriginous areas respond better to topical treatment than do warts on drier surfaces.
    2. Many patients require a course of therapy rather than a single treatment.
        a) Non-surgical, locally destructive techniques may require multiple treatments.
        b) Evaluate the risk-benefit ratio of treatment throughout the course of therapy to avoid over-treatment.
    3. There is no evidence that any specific treatment is superior to any of the others.
        a) No treatment is ideal for all patients or for all warts.
        b) The use of locally developed and monitored treatment algorithms has been associated with improved clinical outcomes.

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F. Recurrence after treatment
    1. Up to 2/3 of patients will experience recurrences of warts within 6-12 weeks of therapy; after 6 months most patients have clearance.
        a) 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.
        b) 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.

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G. Complications
    1. Complications rarely occur if treatments for warts are employed properly.

a) Depressed or hypertrophic scars are uncommon but can occur, especially if the patient has had insufficient time to heal between treatments.
b) Rarely, treatment can result in disabling chronic pain syndromes (e.g., vulvodynia or hyperesthesia of the treatment site).

2. Patients should be warned that persistent hypopigmentation or hyperpigmentation are common with ablative modalities.

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H. CDC-recommended regimens for external genital warts (patient applied)
1. Podofilox 0.5% solution or gel (Condylox™)
a) Patients should apply podofilox solution with a cotton swab, or podofilox gel with a finger, to visible genital warts twice daily for 3 days, followed by 4 days of no therapy.
b) This cycle may be repeated as necessary for up to 4 cycles.
c) Total wart area treated should not exceed $10cm^2$, and a total volume of podofilox should be limited to 0.5mL per day.
d) If possible, the health care provider should apply the initial treatment to demonstrate the proper application technique and identify which warts should be treated.
e) *The safety of podofilox during pregnancy has not been established*.

-OR-

2. Imiquimod 5% cream (Aldara™)
a) Patients should apply imiquimod cream with a finger once daily at bedtime, 3 times a week for up to 16 weeks.
b) The treatment area should be washed with mild soap and water 6-10 hours after the application.
c) *The safety of imiquimod during pregnancy has not been established.*
3. Using patient-applied treatments
a) Provider should identify warts for treatment and teach patients how to apply substance.
b) Patient must be able to identify and reach warts to be treated.
c) Podofilox 0.5% solution or gel, an antimitotic drug that destroys warts, is relatively inexpensive, easy to use, and safe.
d) Most patients experience mild or moderate pain or local irritation after treatment with podofilox.
e) Imiquimod is a topically active immune enhancer that stimulates production of interferon and other cytokines.
f) Local inflammatory reactions are common with use of imiquimod; these reactions are usually mild to moderate.
g) Follow-up is not required, but may be useful several weeks into therapy to determine appropriateness of medication use and response to treatment.

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I. CDC-recommended regimens for external genital warts (provider-administered)
1. Cryotherapy with liquid nitrogen or cryoprobe
a) Repeat applications every 1 to 2 weeks.

b) May be used on internal or external warts and during pregnancy.

-OR-

2. Podophyllin resin 10%-25% in compound tincture of benzoin
   a) Apply a small amount to each external wart and allow to air dry.
   b) To avoid the possibility of problems with systemic absorption and toxicity, some experts recommend that application be limited to < 0.5mL of podophyllin or < 10cm^2 of warts per session.
   c) Some specialists suggest that the preparation area be thoroughly washed off 1 to 4 hours after application to reduce local irritation. Local irritation is common.
   d) Repeat weekly if needed.
   e) Potency, components, and contaminants in podophyllin are not standardized, and the shelf life is uncertain.
   f) *The safety of podophyllin during pregnancy has not been established.*

   -OR-
3. Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%-90%
   a) Apply a small amount only to warts and allow to air dry (white "frosting" develops).
   b) If excess amount of acid is applied, powder the treated area with talc or sodium bicarbonate (i.e., baking soda), or with liquid soap preparations to remove unreacted acid.
   c) Can be painful after application and may be caustic to unprotected skin around the warts (which can be protected by the application of Vaseline).
   d) Repeat weekly if necessary.
   e) Can be used on vaginal and anal warts as well as on external warts and during pregnancy.

   -OR-
4. Surgical removal–tangential scissor excision, tangential shave excision, curettage, or electrosurgery
   a) Surgical therapy is most beneficial for patients who have large numbers or areas of genital warts.
   b) Can be used on accessible internal warts and during pregnancy.

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J. CDC-recommended alternative treatment regimens
   1. Intralesional interferon
      a) Systemic interferon is not effective.
      b) Intralesional interferon has efficacy because of antiviral and/or immunostimulating effects.
      c) Efficacy and recurrence rates of intralesional interferon are comparable to other treatment modalities.
      d) Not recommended for routine use because of inconvenient routes of administration, frequent visits, and the association between its use and a high frequency of systemic adverse effects.
   2. Laser surgery–costly, but may be useful in management of extensive warts or intraurethral warts, particularly for those patients who have not responded to

other treatment regimens.
3. 5FU currently is not recommended because of side effects.

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K. Treatment of exophytic cervical warts
   1. High-grade squamous intraepithelial lesions must be excluded before treatment is initiated.
   2. Management should include consultation with a specialist.

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L. CDC-recommended regimens for vaginal warts

Treat only if symptomatic, since most treatments also affect normal tissue and could cause scarring and pain.

   1. Cryotherapy with liquid nitrogen
      a) The use of a cryoprobe in the vagina is not recommended because of risk for vaginal perforation and fistula formation.

   -OR-

   2. TCA or BCA 80%-90% applied to warts
      a) Apply small amount only to warts and allow to air dry (white “frosting” develops).
      b) If an excess amount of acid is applied, powder the treated area with talc, sodium bicarbonate (i.e., baking soda), or with liquid soap preparations to remove unreacted acid.
      c) Repeat weekly if needed.

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M. CDC-recommended regimens for urethral meatus warts
   1. Cryotherapy with liquid nitrogen

   -OR-

   2. Podophyllin 10%-25%–in compound tincture of benzoin
      a) Treatment area must be dry before contact with normal mucosa.
      b) Repeat weekly if needed.
   3. Although data evaluating the use of podofilox and imiquimod for the treatment of distal meatal warts are limited, some specialists recommend their use in certain patients.

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N. Treatment of anal warts
   1. Cryotherapy with liquid nitrogen

   -OR-

   2. TCA or BCA 80%-90% applied to warts
      a) Apply small amount only to warts and allow to dry (white “frosting” develops).
      b) If an excess amount of acid is applied, powder the treated area with talc, sodium bicarbonate (i.e., baking soda), or with liquid soap preparations to remove unreacted acid.

c) Repeat weekly if needed.
-OR-

3. Surgical removal
4. Warts on the rectal mucosa should be managed in consultation with a specialist.

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O. CDC-recommended regimens for oral warts
   1. Cryotherapy with liquid nitrogen
   -OR-
   2. Surgical removal

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P. Management of genital warts during pregnancy
   1. Genital warts can proliferate and become more friable during pregnancy.
   2. Cytotoxic agents (podophyllin, podofilox, imiquimod) should not be used.
   3. Cryotherapy, TCA, BCA, and surgical removal may be used.
   4. HPV types 6 and 11 can cause recurrent respiratory papillomatosis in infants and children. The route of transmission (i.e., transplacental, perinatal, or postnatal) is not completely understood.
   5. The prevention value of cesarean delivery is unknown; thus, C-section should not be performed solely to prevent transmission to neonate.
      a) Cesarean delivery may be indicated for women with genital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding.
      b) In rare instances, C-section may be necessary if extensive warts obstruct the birth canal or the risk of extensive bleeding during vaginal delivery is thought to be high.

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Q. Management of genital warts in immunodeficient patients
   1. General considerations
      a) Occur more frequently
      b) More pronounced clinical manifestations and occurrence of atypical lesions such as oral warts
      c) More resistant to conventional therapy
      d) Recurrence of lesions after treatment more common
      e) High-grade squamous intraepithelial lesions (HSIL) and invasive cancer arising in or resembling genital warts are more frequent in immunodeficient patients.
      f) Role of warts (or irritated treatment sites) in HIV transmission unknown
   2. Treatment considerations
      a) Treatment unlikely to be effective due to high recurrence rate; therefore treat only if the patient is symptomatic.
      b) 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.

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R. Pap test screening in immunodeficient patients
   1. Immunodeficiency appears to accelerate intraepithelial neoplasia and invasive cancer.
   2. Provide cervical Pap test screening every 6 months for 1 year, then annually for all HIV-infected women with or without genital warts.
   3. The value of anal Pap tests and anoscopy in the absence of symptoms has not beem established, but is under investigation.
      a) Because of the increased incidence of anal cancer in HIV-infected homosexual men, screening for anal cancer by cytology in this population is advocated by some specialists.
      b) However, until more data about the natural history of anal SIL and treatment efficacy are available, such a screening approach is not recommended.

[Slide 64]

S. Genital wart follow-up
   1. Counsel patients to:
      a) Watch for recurrences (most frequent in first 3 months after treatment)
      b) Get regular Pap screening at intervals as recommended for women WITHOUT genital warts. The presence of genital warts is not an indication for increase in frequency of Pap test screening (assuming patient is receiving screening at intervals recommended by her health care provider) or for cervical colposcopy.
   2. Follow-up evaluation is not mandatory after wart clearance, but provides an opportunity to:
      a) Monitor or treat complications of therapy
      b) Document the absence of warts
      c) Reinforce patient education and counseling messages
   3. Patients concerned about recurrences should be offered a follow-up evaluation 3 months after treatment.

[Slide 65]

T. Treatment of cervical cell abnormalities
   1. Detailed discussion of treatment of cervical cell abnormalities is beyond the scope of this educational offering.
   2. For more information on managing women with cervical cell abnormalities, refer to:
      a) CDC National Breast and Cervical Cancer Early Detection Program http://www.cdc.gov/cancer/nbccedp/index.htm
      b) 2001 Consensus Guidelines for the Management of Women with Cervical Cytologic Abnormalities http://www.asccp.org/consensus/cytological.shtml

[Slide 66]

VI. Patient Counseling and Education

[Slide 67]

A. Patient counseling and education should include:
   1. The nature of HPV infection
      a) Genital HPV infection is common in sexually active adults.
      b) Incubation period is variable, and it is often difficult to determine the source of infection.
      c) Natural history of HPV infection is usually benign.
         1) Low-risk genital HPV types are associated with mild Pap test abnormalities and genital warts.
         2) High-risk types are associated with mild to severe Pap test abnormalities and, rarely, cancers of the cervix, vulva, anus, and penis.
         3) Most women infected with high-risk HPV types have no Pap test abnormalities and do not develop cervical cancer.
      d) Genital warts have a high recurrence rate after treatment.

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   2. Transmission issues
      a) Determining source of infection usually difficult; infection is not evidence of infidelity.
      b) Recurrences usually are not re-infection.
      c) Likelihood of transmission and duration of infectivity with or without treatment are unknown.
      d) Abstinence and long-term mutual monogamy with an uninfected partner are the most effective options to prevent transmission.
      e) The value of disclosing a past diagnosis of genital HPV infection to future partners is unclear, although candid discussions about past STD should be encouraged and attempted whenever possible.

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   3. Risk reduction
      a) Assess patient's behavior-change potential.
      b) Develop individualized risk-reduction plans with the patient for lasting results.
      c) Discuss prevention strategies such as abstinence, mutual monogamy with an uninfected partner, condoms, limiting number of sex partners, etc.
      d) Effect of condoms in preventing transmission of genital HPV infection is not known.
         1) HPV infections can occur in male and female genital areas that are not covered by a latex condom, as well as in areas that are covered.
         2) While the effect of condoms in preventing HPV infection is unknown, condom use has been associated with lower rates of genital warts and cervical cancer, both HPV-associated diseases.

[Slide 70]

B. HPV and cervical cancer prevention patient counseling and education resources
   1. American Social Health Association, National HPV and Cervical Cancer Prevention Resource Center. Available at: http://www.ashastd.org/hpvccrc/
   2. CDC Cervical Cancer Screening Fact Sheet http://www.cdc.gov/cancer/nbccedp/cc_basic.htm
   3. National Cancer Institute Cervical Cancer Screening Information For Patients http://www.nci.nih.gov/cancerinfo/pdq/screening/cervical/patient/
   4. American Society of Colposcopy and Cervical Cancer Pathology http://www.asccp.org/pdfs/patient_edu/women_should_know.pdf

[Slide 71]

VII. Partner Management and Public Health Measures

[Slide 72]

A. Partner management for patients with genital warts
   1. Sex partner examination is not necessary for management of genital warts because no data indicate that reinfection plays a role in recurrences.
   2. Providing treatment solely for the purpose of preventing future transmission cannot be recommended because the value of treatment in reducing infectivity is not known.
   3. The counseling of sex partners provides an opportunity for these partners to:
      a) Learn about the implications of having a partner who has genital warts and about the potential for future disease transmission
      b) Receive STD and Pap screening if necessary

[Slide 73]

B. Cervical cancer screening
   1. The key strategy to prevent cervical cancer is regular cervical cancer screening (Pap test screening) for all sexually active women.
   2. New technologies including liquid-based cytology and testing for high-risk HPV types may offer potential advantages over conventional Pap testing.
   3. Several organizations provide guidelines for cervical cancer screening (e.g., age to begin screening, screening intervals, special considerations), including the American Cancer Society (ACS), the American College of Obstetricians and Gynecologists (ACOG), and the U.S. Preventive Services Task Force (USPSTF).
      a) CDC Cervical Cancer and Pap Test Information http://www.cdc.gov/cancer/nbccedp/info-cc.htm
      b) National Cancer Institute Screening for Cervical Cancer Health Professional Information http://www.nci.nih.gov/templates/doc_pdq.aspx?cdrid=62756
      c) American Cancer Society http://www.guideline.gov/summary/summary.aspx?doc_id=3530&nbr=2756&string=Cervical+AND+Cancer+AND+Screening
      d) ACOG http://www.acog.org/from_home/publications/press_releases/nr07-

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e) U.S. Preventive Services Task Force Cervical Cancer Screening Recommendations http://www.ahrq.gov/clinic/uspstf/uspscerv.htm
f) American Society for Colposcopy and Cervical Pathology Consensus Guidelines on Management of Women with Cytological Abnormalities for more information on the Bethesda Classification System and on management of cervical cell abnormalities: http://www.asccp.org/consensus/cytological.shtml

[Slide 74]

C. Reporting requirements
   1. Genital HPV infection is not a reportable infection in any state.
   2. Genital warts are reportable in some states.
   3. Check with state or local health department for reporting requirements in your area.

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D. HPV vaccines
   1. Several potential HPV vaccine approaches are under investigation. The most promising is the use of virus-like particles (VLPs), which preserve native conformations of viral proteins without presence of viral DNA.
      a) In a recent double-blind, multi-center, randomized clinical trial, administration of a HPV type 16 (HPV-16) VLP vaccine reduced the incidence of HPV-16 infection and HPV-16-related cervical intraepithelial neoplasias.
      b) HPV-16 is present in 50% of cervical cancers and high-grade cervical intraepithelial neoplasias and in 25% of low-grade cervical intraepithelial neoplasias.

CASE STUDY

[Slide 77]
Anne Drew is a 34-year-old woman who comes in stating that she wants to get "checked out" because Jonathan, her sex partner, has small solid "bumps" on the skin at the base of his penis. Jonathan told her that he was diagnosed and treated for genital warts about a year ago, and his health care provider told him they could recur.

History

- No history of abnormal Pap tests and no history of STDs
- Last Pap test was performed 4 months ago
- Sexually active since age 16 with men and has had a total of 7 sex partners over her lifetime
- Currently sexually active with 1 partner for the last 8 months
- Uses oral contraceptives for birth control

[Slide 78]
1. What should be included in Ms. Drew's evaluation?

Ms. Drew's evaluation should include a pelvic exam with a visual inspection of genitalia. Diagnosis of genital warts is usually made by visual inspection with bright light. If the diagnosis is uncertain, it can be confirmed by biopsy.

Acetic acid evaluation of external genitalia is of limited value due to its low specificity (many false positives) and is not recommended. Ms. Drew had a normal Pap test four months ago. There is no need for more frequent Pap tests when external genital warts are present.

HPV DNA testing is not recommended for diagnosis and management of external genital warts.

[Slide 79]
Physical Examination

- Vital signs: blood pressure 96/74, pulse 78, respiration 13, temperature 37.1° C
- Cooperative, good historian
- Chest, heart, musculoskeletal, and abdominal exams within normal limits
- Pelvic exam is normal
- Visual inspection of the genitalia reveals multiple small (<0.5 cm), flesh-colored, papular lesions in the perineal area

[Slide 80]
2. What is the differential diagnosis for the papular genital lesions?

Correct responses include the following:

- Secondary syphilis (Condylomata lata)
- Molluscum contagiosum–caused by a pox virus
- Genital warts–caused by HPV

- Sebaceous glands–acquired dermatologic condition
- Skin tags–acquired dermatologic condition
- Melanocytic nevi–acquired dermatologic condition
- Lichen planus–acquired dermatologic condition

3. What is the **most likely** diagnosis based on history and physical examination?

Genital warts is the most likely diagnosis due to her partner's history of genital warts and the appearance of the lesions.

It is not a high priority to test for this diagnosis. The diagnosis of genital warts is usually based on clinical appearance. No serologic test is commercially available, nor would one be helpful in making the diagnosis of genital warts since the presence of antibodies does not indicate active infection.

If the lesions appear atypical (pigmented, fixed, indurated, or ulcerated), then biopsy is indicated.

Secondary syphilis is not the most likely diagnosis, given the patient's history and the general low incidence of syphilis. It is a high priority to test for this diagnosis because the Condylomata lata of secondary syphilis can mimic genital warts. A serologic test for syphilis should be performed to evaluate for that possibility.

Molluscum contagiosum is not the most likely diagnosis because the lesions are smooth dome-shaped papules with a characteristic central umbilication (dimple). It is not a high priority to test for this diagnosis.

Sebaceous glands is not the most likely diagnosis. Sebaceous glands are normal anatomical structures that are generally smooth and yellowish-white, and are usually not located on the perineum. It is not a high priority to test for this diagnosis.

Skin tags is not the most likely diagnosis. Skin tags are normal structures. While they may be somewhat pedunculated like warts, they have a smooth instead of a rough surface. It is not a high priority to test for this diagnosis.

Melanocytic nevi is not the most likely diagnosis. Melanocytic nevi are hyperpigmented lesions. It is not a high priority to test for this diagnosis.

Lichen planus is not the most likely diagnosis. Lichen planus tend to be hyperpigmented lesions, and are violaceous and polygonal. It is not a high priority to test for this diagnosis.

4. Which laboratory tests should be ordered or performed?

Correct responses include the following:

- Serologic test for syphilis (e.g., RPR – STAT if available)
- Test for *Chlamydia trachomatis*
- Test for *Neisseria gonorrhoeae*
- Counseling and testing for HIV

Screening for other STDs, including HIV, should be considered for all persons newly diagnosed with HPV. A serologic test for syphilis should be performed to rule out secondary syphilis.

[Slide 81]
Patient Management
The following genital warts management options are discussed with Ms. Drew:

Patient-applied therapy
- Podofilox 0.5% solution or gel (Condylox)
- Imiquimod 5% cream (Aldara)

Provider-administered therapy
- Cryotherapy with liquid nitrogen or cryoprobe
- Podophyllin resin 10%-25% in compound tincture of benzoin
- Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%-90%

Surgical removal

No intervention

[Slide 82]
5. What is the effect of treatment on future transmission? What is the possibility of recurrence after treatment?

The effect of treatment on future transmission is unknown. Because of uncertainty about the effect of treatment on future transmission and the possibility for spontaneous resolution, some patients may choose to forgo treatment and await spontaneous resolution.

Recurrence of genital warts within the first several months after treatment is common and usually indicates recurrence rather than reinfection. Many patients require a course of therapy rather than a single treatment. Treatment is labor intensive and non-surgical, locally destructive techniques may require multiple treatments. Complications rarely occur if treatments for warts are properly employed.

6. What are appropriate counseling messages for Ms. Drew about genital warts and HPV infection?

Correct responses include the following:
- Genital HPV is a sexually transmitted viral infection which is common in sexually

active adults.

- The incubation period is variable and it is often difficult to determine the source of infection.
- The 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.
- The majority of women infected with high-risk HPV types do not develop cervical cancer.
- Genital warts have a high recurrence rate after treatment.
- The value of disclosing a past diagnosis of genital HPV infection is unclear, although candid discussions about past STD should be encouraged and attempted whenever possible.
- HPV infections can occur in male and female genital areas that are covered or protected by a latex condom, as well as in areas that are not covered.
- While the effect of condoms in preventing HPV infection is unknown, condom use has been associated with lower rates of genital warts and cervical cancer, both HPV-associated diseases.
- There is no need for her to have more frequent Pap test screenings after being diagnosed with genital warts (assuming she is receiving screening at intervals recommended by her health care provider), since genital warts are associated with low-risk HPV types, not the high-risk types associated with moderate to severe Pap test abnormalities and invasive cancer.

7. What conditions could cause a substantial increase in the number and size of Ms. Drew's genital warts?

Pregnancy and immunodeficiency can cause a substantial increase in the number and size of genital warts.

TEST QUESTIONS

1. It is estimated that at least ___of sexually active adults are infected with genital HPV during their lifetime.
    a. 10%
    b. 25%
    c. 40%
    d. 50%

2. All of the following are true about transmission of genital HPV, **except**:
    a. Transmission is associated with sexual activity.
    b. Transmission via fomites has been documented.
    c. Transmission can occur from asymptomatic and subclinical patients.
    d. Transmission probably requires contact with viable HPV and microtrauma to skin/mucous membranes.

3. HPV types __ and ___ account for more than half of HPV types found in genital cancers.
    a. 6 and 11
    b. 6 and 18
    c. 16 and 18
    d. 11 and 16

4. Genital HPV types are characterized in terms of their oncogenic potential (ability to cause cervical cancer).
    a. True
    b. False

5. Most women infected with high-risk HPV types:
    a. Develop cervical cancer
    b. Have normal Pap test results
    c. Have abnormal Pap test results
    d. Have genital warts

6. Which of the following is the most important risk factor associated with development of cervical cancer precursors (high-grade cervical cell changes) and cervical cancer?
    a. Older age
    b. High-risk HPV types
    c. Persistence of HPV infection
    d. Immunodeficiency

7. If left untreated, visible warts may:
    a. Resolve on their own
    b. Remain unchanged
    c. Increase in size and number

d. Any of the above

8. Which factor should guide genital wart treatment?
    a. The preference of the patient
    b. The available resources
    c. The experience of the health care provider
    d. All of the above

9. Which of the following is **not** a presentation of genital warts?
    a. Condylomata acuminata
    b. Smooth papules
    c. Flat papules
    d. Keratotic warts
    e. All of the above are presentations of genital warts

10. Acetic acid evaluation of external genital warts is of limited value because:
    a. It has low sensitivity (many false negatives).
    b. It has low specificity (many false positives).
    c. It is not cost effective.
    d. All of the above

11. Manifestations of genital HPV infection include:
    a. Genital warts
    b. Cervical cell abnormalities
    c. Anogenital squamous cell cancers
    d. Respiratory papillomatosis
    e. All of the above

12. Most genital HPV infections are transient and have no clinical manifestations or sequelae.
    a. True
    b. False

13. Which HPV types usually cause cervical cancer?
    a. Low-risk types
    b. High-risk types
    c. Both low-risk and high-risk types
    d. Neither low-risk nor high-risk types

14. Diagnosis of external genital warts is usually made by:
    a. Visual inspection
    b. Biopsy
    c. Acetic acid evaluation
    d. HPV DNA test

15. The FDA has approved the HPV DNA test for use in:
    a. Cervical cancer screening for women under 30 years
    b. Triage of women with ASC-US Pap test results
    c. Triage of women with LSIL Pap test results
    d. External genital wart diagnosis

16. Cervical cellular abnormalities are detected by which of the following?
    a. Serologic test
    b. Pap test
    c. Wet mount
    d. HPV DNA test

17. Which of the following statements is true about the treatment of genital warts?
    a. In most patients treatment does not induce wart-free periods.
    b. Current treatment decreases future transmission.
    c. The primary goal is removal of symptomatic warts.
    d. Available therapies eradicate infectivity.

18. Which of the following is a patient-applied treatment for external genital warts?
    a. Podofilox
    b. Podophyllin
    c. Trichloroacetic acid (TCA)
    d. Bichloroacetic acid (BCA)

19. Which of the following is a provider-administered treatment for external genital warts?
    a. Cryotherapy with liquid nitrogen or cryoprobe
    b. Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%-90%
    c. Podophyllin resin 10%-25% in compound tincture of benzoin
    d. All of the above

20. All of the following external genital wart treatments may be used in pregnancy, **except**:
    a. Surgical removal
    b. Trichloroacetic acid (TCA) or biochloroacetic acid (BCA) 80%-90%
    c. Imiquimod 5% cream (Aldara)
    d. Cryotherapy

21. Which of the following is true of HPV infection in immunodeficient patients?
    a. Genital warts occur more frequently.
    b. Genital warts are more resistant to conventional therapy.
    c. The occurrence of atypical lesions (e.g., oral warts) is more likely.
    d. All of the above

22. Patient counseling and education should cover:
    a. The nature of HPV infection
    b. Transmission issues
    c. Risk reduction
    d. All of the above

23. All of the following are appropriate patient education messages about the nature of HPV infection **except**:
    a. Genital HPV is a viral infection which is one of the most common STDs.
    b. High-risk HPV types are associated with external genital warts.
    c. Genital warts have a high recurrence rate after treatment.
    d. The majority of women with high-risk HPV types do not develop cervical cancer.

24. Which of the following is correct about partner management for patients diagnosed with genital warts?
    a. Sex partner examination is not necessary for management of genital warts because no data indicate that reinfection plays a role in recurrences.
    b. Providing treatment solely for the purpose of preventing future transmission cannot be recommended because the value of treatment in reducing infectivity is not known.
    c. The counseling of sex partners provides an opportunity for these partners to learn about the implications of having a partner who has genital warts and about the potential for future disease transmission and receive STD and Pap screening if necessary.
    d. All of the above

25. The presence of genital warts is an indication for:
    a. Change in Pap test frequency
    b. Cervical colposcopy
    c. Both of the above
    d. Neither of the above

26. Which of the following actions should be considered for patients with newly diagnosed genital warts?
    a. Screening of all current and former sex partners for genital warts
    b. Immediate Pap smear, regardless of when last Pap screening was performed
    c. Screening for other STD (e.g., chlamydia, gonorrhea, HIV, syphilis)
    d. HPV DNA test

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Websites and Other Resources

1. CDC Division of STD Prevention: www.cdc.gov/std
2. National Network of STD/HIV Prevention Training Centers: http://depts.washington.edu/nnptc/
3. 2002 CDC STD Treatment Guidelines (including downloadable version for Palm devices): http://www.cdc.gov/STD/treatment/
4. CDC National STD Hotline: 800-227-8922 or 800-342-2437
    a. En Español: 800-344-7432
    b. TTY for the Deaf and Hard of Hearing: 800-243-7889
5. CDC National Prevention Information Network (NPIN): www.cdcnpin.org
6. American Social Health Association, National HPV and Cervical Cancer Prevention Resource Center: http://www.ashastd.org/hpvccrc/
7. CDC Cervical Cancer and Pap Test Information http://www.cdc.gov/cancer/nbccedp/info-cc.htm
8. National Cancer Institute (NCI): http://www.nci.nih.gov
9. U.S. Preventive Services Task Force Cervical Cancer Screening Recommendations: http://www.ahrq.gov/clinic/uspstf/uspscerv.htm
10. American College of Obstetrics and Gynecology: http://www.acog.org
11. American Society of Colposcopy and Cervical Pathology (ASCCP): http://www.asccp.org