HPV Human Papillomavirus

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HPV Epidemiology

- Worldwide
  - HPV is the most common STD
  - Est. at least 50% of sexually active (SA) people are infected at least once in their life time with HPV
- U.S.
  - 79 million currently infected with HPV.
  - 14 million new infections each year
  - Highest rates in adults 18-28 years old

HPV Natural History

- Most HPV infection is transient- median duration of 12 months
- Prevalence declines with increasing age
  - Peak prevalence 20-24 years
  - Gradual decline to about 40-45, but may increase slowly again
- Multiple infections
  - 15-14% (more than one HPV type)
  - 52% in immunocompromised patients
- HIV positive- increased persistence/recurrence

HPV Prevalence

- Ho, NEJM 1998;338:423
  - 608 College women followed over 3 years
  - 14% became infected each year
  - Cumulative incidence of 43%
  - Persistence > older age, high risk HPV, multiple types
  - 91% cleared with 2 years of infection
- Typical prevalence of HPV for women under 25 is between 28% and 45%
- Prevalence for men not well studied but probably similar
HPV

- Apx. 150 HPV sub-types identified; subdivided into 2 major branches: cutaneous or mucosal
- 40 mucosal or urogenital types
  - Transmissible through sexual contact
  - Infects the ano-genital and other mucosal tissue
  - Most classified as high risk (HR) oncogenic or low risk

HPV and cancer

- Oncogenic HPV types have been linked to oropharyngeal cancer and cancers of the anogenital tract:
  - Vagina
  - Vulva
  - Cervix
  - Anus
  - Penis
- Non-oncogenic HPV types
  - Anogenital warts men and women
  - Recurrent respiratory papillomatosis

HPV

- HR HPV (types 16,18)
  - Anogenital cancers
    - Vagina: 66%
    - Vaginal: 53%
    - Anus: 79%
  - Oro-pharyngeal: 62%
- HPV 16 linked with oro-pharyngeal cancer
- Each year 26,000 new cancers are attributable to HPV
  - 17,000 women and 9000 men

- HPV cervical cancer disproportionately higher among minorities than whites including:
  - Hispanics
  - Blacks
  - American Indians
  - Alaskan natives
- HPV vaginal cancer rates higher in blacks
- HPV vulva cancer rates higher in whites
- HPV oropharyngeal increasing frequency males > females in all racial groups except blacks
HPV and Cervical Cancer

CIN and Invasive Risk Co-factors in the development of Cervical Cancer

- Epidemiologic
  - Early Sexual Experience
  - # of sexual partners
  - Male partner factors (# sex partners, hx/o STI’s)
  - Smoking
  - Nutritional
  - Carotenoids, vitamin A, retinoids
  - Vitamins C, E, and folate

Prevention - HPV Vaccine

- Two licensed prophylactic vaccines are available
  - Quadrivalent (Gardasil) and bivalent (cervarix)
  - Protects against HPV 6,11,16,18 and 16,18 respect.
    - Prevents 70% of cervical cancers and 90% of genital warts
- Routine HPV vaccination is recommended for all females 11 to 12 years, but can be used as young as 9 years*
- Women 11-26 years (if not previously adm.) and men 9-21(quadrvirulent)
  - Optimal if given before sexual activity
  - ACIP: recommends MSM/Bisexual men be vaccinated through age 26 years.

Challenges of HPV Prevention

- Coverage among Adolescent females 13-17 is lagging behind other vaccines for that age group
- Well below the Healthy People target for 2020 at current rate of vaccination
- Adverse events
  - 56 million doses in US 2006-13 of which 21,000 adverse events reported
    - 92.1% classified as non-serious- ie. Site reactions, hives, headache, fever, etc.
HPV Vaccine – Future Considerations

- Development of a prophylactic pan HPV vaccine
- Potential to eliminate need for screening tests
- Reduce the number of Vaccine doses
  - Evaluation of women in the Costa Rica Vaccine Trial who missed one or more of the three doses of bivalent vaccine evaluated up to 4.2 years
    - Three dose efficacy: 80.9% [95%CI= 71.1-87.7%]
    - Two dose efficacy: 84.1% [95%CI= 50.2-96.3%]
    - However no cross protection against HPV 31, 33 and 45 after two dose regimen
  - Important public health implications for adherence with reduced dosing
- Development of a therapeutic vaccine

HPV Transmission

- Most frequent sites are those susceptible to micro trauma during intercourse
  - Introitus
  - peri-anal and intra-anal membranes
- Increased risk of transmission
  - Hormonal contraception
  - Pregnancy
  - Impaired cell mediated immunity

HPV Transmission

- Transmission can occur by auto- and hetero-inoculation from common skin warts
- Only fully formed virion known to be infectious

HPV Diagnosis

- Presumptive
  - Typical warts on skin
  - Detection of lesion by colposcopy
  - Detection of subclinical lesion by application of 5% acetic acid
- Suggestive
  - Demonstration of typical cytologic changes on pap smear
HPV Diagnosis
- Definitive
  - Identification of characteristic change on biopsy (koilocytosis)
  - Detection of HPV in smear material
- Co-testing

HPV Testing
- Four FDA approved tests in the US
  - Available for women >30 years undergoing cervical cancer screening
  - Should not be used to
    - Screen men for HPV
    - In women <20 years
    - As a general STI screening test

HPV Spectrum of disease
- Condyloma accuminata (genital warts)
- Subclinical disease (cytologic changes)
- Latent/asymptomatic infection
  - No evidence of disease
  - Viral shedding and transmission possible

Differential Diagnosis
Genital Warts
- Normal anatomic structures
  - Pearly penile papules
  - Sebaceous Tyson’s glands
  - Micropapillomatosis or vestibular papillae
    (exaggerated version of physiologic vulvar skin)
**Micropapillary Condylomata vs. Micropapillomatosis**

- Micropapillary condylomata - multiple papillae converge toward a single base
- Micropapillomatosis - each papillae have a single individual base and are exaggerated variant of physiologic vulvar skin

**Genital Warts**

**Differential Diagnosis (Acquired conditions)**

- Bowenoid papules
- Bushke-Lowenstein tumor (*Verrucous Carcinoma*)
- Lichen planus
- Lichen nitidus
- Melanocytic nevi
- Pseudoverrucous papules
- Molluscum contagiosum
- Seborrheic keratosis
- Condyloma lata
- Crohn’s disease
- Skin tags
- **VIN**

**Verrocous Carcinoma**

- Confluent cauliflower like tumor
- Slow growing
- Locally invasive
- Rarely produces metastasis
Paget's Disease
Molluscum contagiosum
Lichen simplex chronicus
VIN 3
Condyloma Accuminata (Genital Warts)

- Incubation period 3 weeks to 8 months
- Usually asymptomatic but occasionally itching, burning, pain, or bleeding
- Spontaneous regression and recurrence common
- No increased prevalence HSIL
- HPV type 6, 11-10% contain HPV 16

Condyloma Accuminata

- Typically raised lesions with a warty granular appearance
- May be flat or hyper-pigmented*
  *Most suspicious for VIN
- Most often multifocal
- Women located
  - introitus, labia minora, majora and perianal skin
- Men located
  - distal half of the penis and the urethral meatus
**HPV – Indications for biopsy anogenital lesions**

- Diagnosis uncertain
- Lesions do not respond to therapy
- Diagnosis worsens during therapy
- Lesion atypical, indurated, pigmented, fixed, bleeding or ulcerated
- Patient with compromised immunity (more likely to have anogenital dysplasia)
HPV Treatment of External Genital Warts

- Cytotoxic agents and keratolytic agents:
  - 5% podophlox (self treatment)
  - Liquid nitrogen
  - 50-80% bichloroacetic or trichloroacetic acid
  - Podophyllin

- Cytodestructive techniques
  - CO2 laser vaporization
  - Electroexcision/fulguration (LEEP)
  - Cryotherapy
  - Sinecatechin ointment (green tea extract)
    - Self applied TID up to 16 weeks

HPV Treatment of genital warts

- Surgical excision
- Immune-modulating agents
  - Imiquimod (Aldara)- interferon and cytokine inducer
  - 5-Fluorouracil
- Alpha-interferon- recalcitrant lesions
  - can be used in combination with laser or electro surgery
  - 80% complete or partial response vs. placebo

HPV-(subclinical manifestations) Lower Anogenital Tract Neoplasias

- More common than genital warts
- Lower anogenital tract neoplasia- AIN, VIN, VAIN, CIN
- Represents 60% & 90% of all HPV infections of the external anogenital tract and cervix respectively
- Best seen with 5% acetic acid solution and colposcopic / anoscopic examination

Role of Cervical Cancer Screening (Pap smear)

- Significant reduction of Cervical ca in U.S.
- 13,000 new cases each year
- Cervical ca mortality- 4,400
- Annual screening for cervical dysplasia
- Counsel patients on the purpose and importance of routine pap smears
- External warts are not an indication for more frequent pap smears
Pap Smear Classification (Bethesda)

- Adequacy of specimen
- Normal
- Benign cellular changes
  - infection
  - inflammation
  - radiation
- Epithelial cell abnormalities
  - ASCUS/AGCUS
  - LSIL
  - HSIL
  - Cancer: SCC vs adenocarcinoma

False Negative Pap Smears

- Sampling Error
- Delayed Fixation
- Bleeding
- Contamination with lubricant
- Inflammation

Liquid-based Collection and Thin-Layer Processing

- Minimal cell loss with immediate fixation
- Decreased unsatisfactory rate 63%
- Decreased ASCUS/AGCUS 3.0 - 26.6%
- SIL detection increased by 52.2 - 65.0%
- Enhanced sensitivity
- No loss in specificity

Lee. Obstet Gynecol 1997; 90:278
Guidos. Diagn Cytopathol 1999; 20:70

Cervical Transformation Zone

- Squamous metaplasia:
  Dynamic zone of cell replication, where columnar cells are replaced by squamous epithelial cells
- The transformation zone (greatest exposure):
  Menarche
  Younger women
  Pregnancy
  OCP use
Cervical Cancer Screening

- Cervical cancer screening should begin at age 21 years.
  - Women under 21 should not be tested
  - Women between 21 and 29
    - HPV testing should not be used for screening in this age group
  - Women between 30 and 65
    - Cervical pap every 3 years
    - With HPV (co-testing) every 5 years (preferred)
  - Women over 65 years
    - If past regular screening tests normal stop screening (ACOG recommendation)
    - If history of serious dysplasia continue for 20 years after the diagnosis regardless of age.

Possible Roles for HPV Testing in Cervical Screening Programs

- Primary screening modality
  - Perform cytology on HPV + patients
  - Establish consistent evidence of high sensitivity
- Adjunct to cytology
  - High sensitivity for high grade CIN
- Triage of borderline and mild dyskaryosis
  - Clearest role
  - + for high risk refer for Colposcopy

Pap evaluation: 21-24 years

- Normal- repeat 3 years
- ASCUS/no HPV- repeat 12 months
  - If negative, ASCUS or LSIL –repeat 12 months
  - two negative Paps in a row- repeat 3 years
  - If Pap at 24 months is ASCUS or greater refer for colposcopy
  - If Pap at 12 months is HSIL or greater proceed to Colposcopy (includes ASC-H)
- ASCUS/negative HPV- repeat 3 years
- ASCUS/Positive HPV- repeat cytology 12 months
  - At 12 month Pap– Follow ASCUS/NoHPV

Cervical Cancer Screening

- History of hysterectomy (with cervix)-
  - no screening if negative history of severe dysplasia or cervical cancer.
- HPV vaccinated
  - Should still follow screening recommendations for her age group
- APP for smart phone: Pap guide
**Pap Evaluation: 25-29 years**
- Normal: repeat cytology (Pap smear) 3 years
- ASCUS/ no HPV testing: repeat 12 months
- 12 month pap normal: repeat 3 years
- If ASCUS or greater: Colposcopy
- ASCUS/ negative HPV: repeat in 3 years
- ASCUS/ positive HPV: proceed to colposcopy
- LSIL/ASC-H or greater: proceed to colposcopy

**Pap Evaluation: 30-65 years**
- Cytology alone: if normal repeat 3 years
  - ASCUS with reflex HPV
    - If negative rescreen with co-testing in 3 years
    - If positive HPV: colposcopy
  - ASCUS with no reflex HPV
    - Obtain sample and test for HPV or
    - Repeat in 12 months, if negative repeat in 3 years, if ASCUS or greater refer for colposcopy

**Pap Evaluation (30-65)**
- LSIL with negative HPV
  - Repeat co-testing in 12 months preferred
  - Colposcopy is acceptable

Results of 12 month repeat co-testing:
- if ASCUS or > proceed to colposcopy (with endometrial biopsy for AGCUS or AIS)
- If HPV positive with any cytology results then proceed to colposcopy
- If both negative repeat Cytology with co-testing 3 years

Note: the risk of CIN 3 with LSIL/neg HPV is similar to ASCUS alone
Pap Evaluation 35-65

- LSIL with Positive HPV (co-testing)
  - Proceed to colposcopy

- HSIL or >
  - Proceed to colposcopy

Pap Evaluation - Greater than 65 years

- No screening following adequate negative prior screens
  - Including cytology alone or both negative cytology and HPV

- History of CIN2 or >
  - Screen for at least 20 years after definitive treatment
  - ACOG 2012 guidelines recommends screening with cytology every 3 years after initial post treatment surveillance

Pap Evaluation

- HIV infection
  - Screen with Pap twice the first year after diagnosis of HIV
  - If negative, annually thereafter
  - Interval may be shorter based on treatment history

- Any abnormal Pap ASCUS or greater should be referred for colposcopy

- ***Current guidelines currently being reviewed***
  - Continue with above until new recommendations released

AGCUS

- 17-34% associated intraepithelial or invasive lesions

- Associated lesions:
  - Cervical adenocarcinoma
  - Endometrial adenocarcinoma
  - Metastatic Ca

- Risk of HGSIL:
  - Premenopausal 30.4%
  - Postmenopausal 7.4%

Kennedy. Gynecol Oncol 1996; 63:14
Korn. JBM 1998; 43:774
Douka. Obstet Gynecol 1998; 91:278
AGCUS or AIS

• > 35 years must be evaluated with endometrial biopsy
• < 35 years
  • Endometrial biopsy should be performed if risk factors for endometrial neoplastic lesions
  • Unexplained vaginal bleeding
  • Chronic conditions suggesting anovulation

HPV

Subclinical Manifestations

• Histologic findings alone have little predicative value of HPV type
• HPV typing determines whether low vs high risk for progression to invasive disease

HPV

Subclinical Manifestations

• Best appreciated with magnification & 5% acetic acid solution (colposcope)
• Slightly elevated, well demarcated focal lesions with or without mosaic patterns or punctations
• Commonly seen on labia minora, perianal, vestibular skin & cervical transformation zone

Cervical Ectopy
CIN 3–CA in situ
(coarse punctuation and coarse mosaic)

Leukoplakia

Numerous cysts in an established transformation

Timing of Intervention for HPV Related Cervical Dysplasia
**HPV Treatment of Cervical Warts**

- Dysplasia must be excluded before treatment is begun
- Management should be carried out in consultation with an expert

**HPV Management of Subclinical Disease**

- Cervical, vaginal, and vulvar intraepithelial lesions (CIN, VAIN, VIN respectively)
- Management usually based on colposcopic directed biopsy results and pap smear
- Cervical lesions- cure rates related to size and distribution of lesions, not morphologic grade or HPV type

**HPV Management of Subclinical Disease**

- Observation
- Excision/ablation
  - LEEP/LLETZ
  - Laser
  - Conization
- Interferon
- 5-FU
- Accutane

- Management determined by the location, severity and number of lesions
- LSIL- Observation, 70% of low grade lesions will regress spontaneously
- HSIL- 80% progression if untreated
  - Ablative or excisional dependent on the size and location of the lesion
  - Endocervical lesions should be managed with excisional therapy
- Cervical, vulvar, vaginal ca- refer gyn oncologist
**HPV Subclinical Management**

**Ablative vs. Excisional Treatment**

Ablative - 80-90% effective but, may be used inadvertently in early invasive disease

Excisional - Best for treatment of CIN, especially high grade endocervical lesions

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**HPV Subclinical Manifestations**

Advantages of LEEP/LLETZ
- Low risk for missing invasive disease
- Diagnosis and therapy in one session
- Office procedure
- Low cost of equipment
- May be used for treatment of condylomata, intraepithelial lesions of the vagina & external anogenital epithelium

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**HPV Management of Sex Partners**

- Evaluation of sex partners is not necessary
- Role of infection is minimal
- No practical screening tests available for subclinical disease

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**HPV, Squamous Intraepithelial Lesions and HIV**

- Increased rate of detection of genital HPV
- Genital warts - more severe, difficult to treat
- Higher incidence of VAIN, VIN
- Multifocal and multicentric SIL is common
- Increased frequency and severity of SIL with declining CD4 counts
- Increased recurrence rate after standard treatment of SIL
Recurrence of LGW after Treatment in HIV

- Recurrence rates after successful treatment is not well characterized in immunocompetent population.
- Study of recurrence rates after complete resolution in 241 HIV+ and 1095 HIV- men and women. (DePanfilis, STD 2002;29:121-125)
  - Patients were followed for one year after resolution.
  - Treatment was dependent on #, size, and location of the lesion.
  - Recurrence 66% HIV+ vs. 26.8% HIV- (p<0.001)