

HPV: Here, There, Everywhere

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Learning Objectives

At the conclusion of the session participants should be able to:

- Understand current knowledge of HPV epidemiology, including cervical, anogenital, and oropharyngeal
- Describe sociocultural dynamics of HPV infection
- Identify current prevention, testing, and treatment strategies
- List future challenges and directions

The History of HPV Viruses as Emerging Cause of Cancer

- 1842 association between sexual activity and cervical cancer
- 1940's Cervical pap smears begin
- 1980's gay men have increased rates of anal cancer
 - 1990's people living with HIV survive long enough to develop anal cancer
- 1983 HPV identified in 6 out of 8 oral squamous cell carcinoma

HPV Types

**High Risk
(oncogenic)**

16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82

**Low Risk
(wart-causing)**

6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 81

**Cutaneous
(non-genital)**

1, 2, 3, 4, 7, 10, 27, 28, 41, 57, 65, 88, 95

Most sexually active people
who are not vaccinated
get HPV infection
at some point in their lives,
even if they only have
one sexual partner.

What is the most common symptom of HPV infection

- A. Oral lesions
- ★ B. Most HPV infections are asymptomatic
- C. Anal itch
- D. Cervicovaginal discharge

HPV & the Pelvis

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HPV & the Pelvis

External HPV

- Condyloma Acuminatum- "Genital Warts"

Cervical HPV

- Microscopic Changes- Pap smears, Colposcopy/Biopsy, Pathology
- Macroscopic Changes- Visible lesions and changes
- No changes

Vaginal HPV

Genital Warts- HPV 6 & 11

- How do you know when to intervene?
- Evaluate the following: look, feel, partner, difficult placement, how many or clustering, patient concerns, physical look/disfiguring, does fixing it make it worse?

- How best to treat?
- Imiquimod (Aldara)- 2 x per week, 16 weeks. Apply at night, wash in the morning
- Freezing, Lance, Laser (*wear a mask for aerosol risks*)
- Monitor without treatment

- Not sure what you are looking at?
- Skin tags and Squamous Cell Cancers can look similar
- Biopsy- bleeding, cracked, scabbed, odd placement, irregular in appearance

Genital Warts- HPV 6 & 11 continued...

Clinical to Notes for Practice

- Evaluate for change over time and continue pap smears with HPV co-test as per guidelines
- Incidence of other anogenital cancer, head and neck cancers elevated (study noting Male risk > Women)
- Gardasil covers HPV 6 and 11- Vaccinate when you can!

HPV & the Cervix

Then	Now
Pap smears start when ready to see GYN/First Sexually Active	No Screening Under 21
Occur Annually	Every 3-5 years, dependent on HPV cotest
No HPV Cotest	HPV Reflex and HPV Cotest
Colposcopy every 3 Months	Colposcopy every 6 months
Cone Biopsy, Freezing, LEEP more common	Less Frequent LEEP and Cone Biopsy (no longer “freezing”)

Consensus Guidelines For PAP Smear

ORIGINAL RESEARCH ARTICLE: CERVIX AND HPV

OPEN

Risk Estimates Supporting the 2019 ASCCP Risk-Based Management Consensus Guidelines

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Screening PAP Smear VS Reason PAP Smear

- New Reason for a PAP smear
- New Bleeding- intermenstrual bleeding, bleeding with intercourse
- Notable Friability of the Cervix (can be normal with OCP use)
- Undiagnosed Visible Lesion

Pap in Practice

Clinical notes:

- *Endometrial Cells on a PAP smear over age 45 needs a work-up: Rule out Endometrial Cancer/Hyperplasia*
- *Always document LMP!*

SPECIMEN ADEQUACY:

Comment

Comment: Satisfactory for evaluation. Endocervical and/or squamous metaplastic cells (endocervical component) are present.

Order the Right Test:

HPV order, age-based, past history

- Always Cotest: HPV – 16, 18, 45
- HPV HR- all other HPV subtypes can vary by lab
- Know when to ask for reflex testing (eg if ASCUS, then HPV testing)
- Adding any further STD screening to pap smear

Ordering the Right Cytology

IGP, HPV, rfx 16/18,45

IGP, HPV 16/18

IGP, CtNg, HPV 16/18

IGP, CtNg, rfx HPV ASCU

IGP, CtNgTv, HPV 16/18

IGP, rfx HPV ASCU

IGP, rfx HPV 16/18 ASCU

IGP, CtNg, HPV rfx 16/18,45

IGP, CtNgTv, HPV rfx 16/18, 45

IGP, CtNgTv, HPV rfx ASCU

IGP, HPV all pth

IGP, CtNgTv, rfx HPV all

IGP, CtNg, HPV HR

Screening Age

<21 No Screening

21-29 Cytology ONLY, HPV ASCUS is OK every 3 years

30-65 Cytology every 3 years, with HPV Cotest at 5 years

>65 Case by Case basis, but general rule is to end PAPs

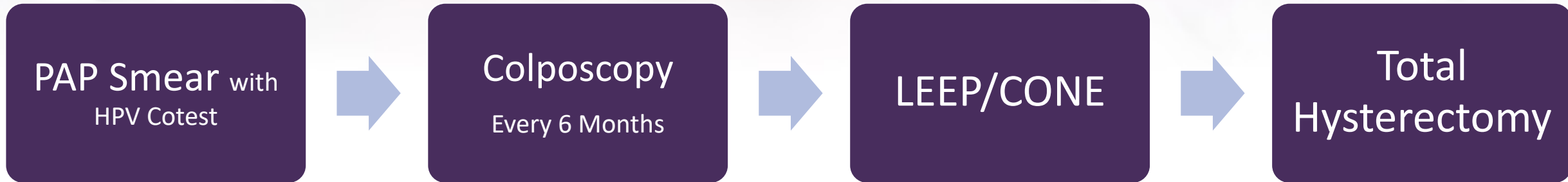
Clinical Notes:

- Know where you are: ordering is unique per practice, EMR and lab
- Usually Ordering HPV will order 16/18 and 45 as break out, but will have all High Risk HPV strains as well

What about Pap Smears over age 65?

- No screening after adequate Negative History
- Continue if immunocompromised or with past HPV history
- Use your judgement
- Patient continues sexual activity- have honest conversations about sexual contacts/partners
- Pap always if unknown source of bleeding or visible lesion
- *At this time Medicare reimburses PAP smears – don't let this be a barrier to completing*

Interventions- Cervical HPV



Follow ASCCP Guidelines

- ASCUS with HPV (*16/18)
- LGSIL (CIN 1, 2)
- Atypical Glandular Cells
- Add Endocervical Curretage (ECC) on First Colposcopy
- Can be Diagnostic or Treatment

- HGSIL (CIN 2-3)
- Persistent LGSIL (3+Colposcopy)
- Rule out HGSIL or Incongruent Pathology
- Endocervical Findings (Cone)
- Carcinoma in Situ (CIS)
- Treatment of lesion
- *Avoid repeated LEEP in childbearing age*

- Pathology HGSIL/CIS/Cancer

*VAIN- Vaginal Intraepithelial Neoplasia

After a LEEP/Cone:

- If clear margins, return to pap smear at 6 months (NOT EARLIER!)
- If margins not clear or further pathology with HSGIL, CIS, Cancer- Refer to GYN ONC for monitoring or Total Hysterectomy +/- associated BSO/Lymph
- Continue Education- *lesion may be gone, but HPV can be present.* Important to continue screening

HPV & the Vagina?

- Incidence: 0.2-0.3 cases per 100,000 in the US
- -HPV most common cause of VAIN- HPV 16/18 most prevalent

- Categories: VAIN 1, 2, 3 and CIS
- -Most of what we know with VAIN is extrapolated from HPV and Cervical studies

- **When to PAP vaginally?**
- Monitoring s/p Total Hysterectomy for Cervical Cancer (or high risk pathology)
- History of VAIN
- New Visible Lesions

- Refer to GYN/Onc
- *Vaginal Colposcopy with biopsy is painful , and more vascular than cervix*

*VAIN- Vaginal
Intraepithelial
Neoplasia

The Future

- Pap Smears become confirmatory, not screening
- Screening with HPV **ONLY** as standard of care
- Less and less cervical cancer, and associated anogenital cancers
- More understanding of microbiome and microscopic cervical changes
- Learning more about HPV- where it can live, what it can impact, how long it lasts, recurrence, etc
- Wider uptake of Gardasil in the population
- Development of therapeutic vaccines for HPV

HPV & the Oropharynx

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HPV and Oral Cancer—The stats

- HPV detected in 45% to 90% of head and neck squamous cell carcinomas (HNSCC), most commonly in the lingual and palatine tonsils or base of the tongue
- Incidence rates of HPV-positive oropharyngeal cancer have been increasing among white men and women. Age is usually 10 years younger than that of cancer of the oral cavity; roughly seen as early as age 40. **There has been a recent shift that we are now seeing it older men once again.**
- The age at sexual debut is decreasing with oral sex being performed more by men and women that are currently aged 30 to 49 years compared to older generations.

Which risk factors are MOST associated with Oral HPV16+ Tumors?

- A. Tobacco use, HIV infection
- B. Alcohol, same sex partner
- ★ C. Smoking marijuana, history of oral sex
- D. Multiple sex partners, poor oral hygiene

Risk Factors

- History of sexual activity at a young age
- Having multiple sexual partners
- History of genital warts
- History of oral sex
 - (Speculated to be the main transmission mode of oral HPV infection)
- History of oral and anal sexual contact
- History of marijuana use
- HIV infection
- History of having same sex partner

Researchers conducted a study in which they stratified risk factors according to HPV-16 tumor status and found that HPV-16 positive tumors were associated strongly with specific sexual behaviors and marijuana smoking – not with tobacco smoking, alcohol, or poor oral hygiene.

Signs & Symptoms

- Persistent sore throat
- Non-healing sore in the mouth
- Earaches
- Hoarseness
- Enlarged lymph nodes
- Pain with swallowing
- Unexplained weight loss

***Most patients
may have no
signs or
symptoms!***

Physical Exam Findings

High risk clinical presentations

- Sharply defined, leukoplakic lesions (especially >1 cm)
- Non-homogenous or mixed red-white lesions
- Erythroplakic lesions
- Areas of persistent ulceration and indurated lesions



Is there a test to find out if I have
oral HPV?

Screening for HPV

Oral HPV Testing Pitfalls

- Acetic staining: May become diluted with saliva, detects trauma
- Rinsing: May be positive, but does not indicate where the lesion is
- Swab: Must brush non keratinized surface such as buccal mucosa, the vestibule, the floor of the mouth, the border of the tongue (until the oropharynx), under the surface of the tongue.
**Keratinized surfaces are resistant to collection)
- Biopsy of the lesion is most accurate

Prognosis and Treatment Options

Prognosis depends on:

- The stage and grade of cancer
- Location of tumor
- Association of tumor with HPV

Treatment options depend on:

- Stage and grade of cancer
- Location of tumor
- Maintaining patient speech and swallowing functions
- General health of patient

Prognosis for HPV positive OSCC

- HPV positive OSCC is associated with a significant overall survival rate when compared to patients with HPV negative tumors. Various studies reveal statistics between 40% and 50% increased overall survival rate.

HPV & the Anus

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At Risk Populations

- HIV+
- MSM (men who have sex with men)
- Iatrogenic immunosuppression (ie transplant and biologicals)
- Gynecologic disease (cervical/vaginal/vulvar dysplasia)
- Inflammatory Bowel Disease

Question

Do anal pap smears reduce the risk of anal cancer at the same rate as cervical pap smears for cervical cancer?

Anal Cytology

- ↑ Sensitivity ↓ Specificity
- Various methods
- 3-10% unsatisfactory

Anal Pap

Equipment

- water-moistened synthetic-fiber swab with non-scored stick
- Liquid media (same as cervical cytology)

1. Evert anal verge.
2. Blindly insert one half of swab through the anal verge.
3. Apply lateral pressure in a circular motion while withdrawing the swab (10+ seconds)
4. Stir into liquid preparation (15+ seconds)

<https://www.youtube.com/watch?v=YyzmLYFc7Yc>

Histologic Grades & Paired Cytology

		Histology			
		Normal	LSIL	HSIL	SCC
Cytology	Normal	58%	37%	5%	0%
	ASCUS	37%	23%	40%	0%
	LSIL	14%	50%	36%	0%
	HSIL	3%	22%	70%	6%

Adapted from: Panther 2004

Management of Anal HSIL

- Observation only
- Topical therapy
- Ablative therapy
- Surgical therapy

*****ALL TREATMENTS OF ANAL HSIL ARE OFF-LABEL**

Anal HSIL Natural Regression & Progression

Regression (HSIL→benign/LSIL)

Around **25%** of HSIL spontaneously regress /year¹⁻⁵

- SPANC: 24% regression of HSIL mostly to LSIL¹
 - 19% HIV+ and 37% HIV-
- Regression ↓ with age^{1,2,5}

Progression (HSIL→Cancer)

Takes several years (~5 yrs?)^{4,5}

- Rate of progression: 1 in 377 HSIL to CA(HIV+ MSM)²
- SPANC: 2 HSIL progressed; 1.2% per year (95% CI 0.31–4.95)¹
- Progression risk ↑ with age^{1,2,5}

Anal HSIL Treatment

156 HIV+ MSM w/ HSIL

Topical
imiquimod

Topical
5FU

Electro-
cautery

Complete Clinical Response

24%

17%

39%

Recurrence

Wk 24

22%

Wk 48

46%

Wk 72

67%

Wk 98

71%

58%

68%

S/E (Grade 3+)

43%

27%

18%

(Pain, bleeding, and itching)

Anal Cancer Morbidity

- Most incident anal cancer is extensive enough to require CT/RT +/- surgery
- Early identified cancers can be excised
- Long term physical, sexual sequelae

The image features a microscopic view of cells, likely from a tissue sample, with a central text overlay. The cells are arranged in a dense, somewhat circular pattern, with a central area that is blurred and out of focus. The text is white and centered horizontally across the middle of the image.

HPV & Psychologic Burden

Addressing Psychological Burden

- HPV might be the patient's first STI
 - May be anxiety or concern surrounding sexual practices
- Sexual practices post diagnosis -- "Am I contagious?"
 - "Do I have to tell my partner?"
- Destigmatize HPV infection
- Patients often don't understand "atypical cells" or "precancer"
- Stress the importance of periodic screening
- Consider partner screening
- Trauma informed care

A microscopic view of skin cells, showing a dense layer of cells with a textured, bumpy surface. The cells are arranged in a regular pattern, and the overall color is a muted purple or lavender. The text "HPV Vaccination" is centered over the image in a white, sans-serif font.

HPV Vaccination

HPV Vaccination

- Vaccination covers: 6,11(warts), 16/18, 31,33,45,52, 586
- 70% of Cervical Cancers caused by HPV 16/18
- 20% of Cervical Cancer caused by HPV 31, 33, 45, 52, 58.6
- Reduced need for frequent screenings invasive procedures
- Well studied, with longevity
- Protects the unknown of HPV

Vaccination After 26

- **Things to think about**
- How old is your patient?
 - Up to about age 30 at this time, likely to have received HPV vaccination
 - Younger patients may not know they had it at earlier age- ask family, past medical providers, vaccine cards
 - Age 35-45 had the option for Gardasil in 20's but may/may not have taken it
 - Over age 45- likely to have not had vaccination
- Did the patient finish the series?
- Did the patient receive Gardasil 4 or 9?

- **Vaccinate when you can**
- Especially if not yet sexually active or never received
 - *Less benefit with increased age due to exposure, but it's not a NO*
- Most insurances reimburse >age 27 vaccination
- Unknown if completed series
- High risk/immunocompromised
- Good history taking on sexual activity

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