Guidelines for Cervical Cancer Screening and Prevention
Management of Abnormal Results
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Medical College of Wisconsin
May 6, 2016
Cervical Cancer

• In US about 12,000 cases resulting in 4,000 deaths per year
  – 50% never screened
  – 10% not screened in last 5 years
  – Mean age 48 years old
• Who are rarely or never screened?
  – Minorities
  – Low socioeconomic status
  – Foreign born
    • Living in the US < 10 years
  – No usual source of healthcare
Cervical Cancer

• Worldwide a major health problem
  – 528,000 cases and 265,000 deaths per year
  – Mortality 52%
• Being rarely or never screened is the major contributing risk factor to most cervical cancer deaths today
• High grade dysplasia takes on average 3-7 years to progress to invasive cervical cancer
  – Cervical cancer screening is effective
Cervical Cancer in the U.S.

Incidence and mortality has decreased 50% over the past 30 years because of widespread screening. Incidence has decreased from 14.8/100,000 in 1975 to 6.7/100,000 in 2011. Death rate decreased from 5.55/100,000 in 1975 to 2.3/100,000 in 2011.
Cervical Cancer and HPV

• Key to getting cancer: **persistent** HPV
• Oncogenic HPV causes cervical cancer
  – 40 types of genital HPV, 15 are oncogenic
• HPV Infection
  – 80% of sexually active adults will acquire HPV
    • Most common in teens and women in early 20’s
  – Smoking, immunosuppression, HIV infection increase likelihood of persistent infection
The graph illustrates the incidence of genital HPV infection over age. The y-axis represents incidence, and the x-axis represents age in years. There are three stages highlighted:

1. **Genital HPV Infection**
   - Peaks at around 15 years of age.

2. **Pre-Cancer**
   - Begins to rise in the late 20s and peaks around 35 years of age.

3. **Cancer**
   - Begins to rise in the late 30s and peaks around 45 years of age.

The graph shows a clear trend of infection peaking early in life and persisting to later stages, indicating a potential risk of developing pre-cancerous and cancerous conditions with age.
HPV Usually a Transient Infection

• 608 college aged women
  – 70% resolved infection at one year
  – 91% resolved infection at 2 years
  – Average duration of infection 8 months

• Manifestation of disease determined by
  – HPV subtype
  – Viral load
  – Patient factors
Natural History of HPV Infection

- Skin to skin transmission
- Enters cell via microtrauma
- Moves to nucleus of infected cell
- Infected cell exhibits koilocytosis
  - Perinuclear halo
  - Enlarged nucleus with clumped chromatin
Activation of oncogenes

- E6 and E7 mRNA cause oncogenic transformation by disrupting tumor suppressors
- E6 degrades p53, inhibits DNA repair and regulation of apoptosis
- E7 inactivates Rb cell cycle regulation
- E7 activates synthesis of the intracellular protein p16
- Excess p16 deregulates and stimulates the cell cycle
Cervical Cancer and HPV

• HPV genotype most important determinant of persistence and progression
• HPV 16 highest carcinogenic potential
  – 55-60% of all cases of cervical cancer
• HPV 18 next most carcinogenic
  • causes 10-15% of cervical CA
• 13 other genotypes cause the remainder
  • 31,33,35,39,45,51,52,56,58,59,68,73
Progression of Cervical Neoplasia
HPV Related Cancers

• 99% cervical cancers
• 90% anal cancers
• 65% vulvar and vaginal cancers
• 35% penile cancers
• 70% head and neck cancers
Primary Prevention
Vaccines

• 2006 Quadrivalent vaccine HPV 6,11,16,18
  – 90% genital warts and 70% of HPV related cancers
• 2009 Bivalent vaccine HPV 16, 18
  – Different adjuvant conferring higher antibody response
• 12/2014 Nonavalent vaccine HPV 6,11,16, 18,31,33,45,52,58
  – 90% genital warts and 90% of HPV related cancers
Vaccination rates in the US

- 40% girls and 20% boys completed full series
- 60% girls and 40% boys have received one or more doses
- In US among girls age 14-19 vaccine type HPV prevalence decreased from 11.5% in 2003-2006 to 5.1% in 2007-2010
  - 56% decline despite 3 dose vaccine coverage of only 32% in this age group
Bivalent Vaccine

Prevents infection with HPV 16 and 18
Approved for **females** age 9-26
3 dose regimen recommended for all females ages 11-12 as 3 dose series at 0,2, and 6 months
Anaphylaxis to latex is a contraindication
Different adjuvant higher antibody response
  • Likely confers longer lasting immunity
  • Likely offer increased cross protection against other related HPV types
Nonavalent vaccine (9vHPV)

• **Females and males** age 9-26 as a 3 dose series at 0,2, and 6 months

• Recommended as a routine vaccination at age 11-12

• Recommended for immunocompromised persons including those with HIV
Goals of Cervical Cancer Screening

- Prevent morbidity and mortality from cervical cancer
  - Not find abnormal cytology
  - Not find HPV infection
  - Not find lesions
    - We don’t know which lesions will progress

- Prevent overzealous management of precursor lesions that most likely will regress or disappear for which harms of management outweigh the benefits
Cervical Screening Guidelines

• Fall 2011
  – USPSTF declined to recommend HPV and Pap co-testing

• Spring 2012
  – ACS, ASCCP, ASCP recommend co-testing for screening women age 30-65

• March 2013
  – Management guidelines devised for every abnormal co-test and biopsy

• April 2014
  – FDA approves one assay for primary HPV testing for women ≥ 25
Current Recommended Cervical Cancer Screening

• < 21: None
• 21-29: Pap every 3 years
• 30-65 Pap and HRHPV every 5 years preferred (or Pap every 3 years acceptable)
• >65: None (following adequate negative prior screening*)
• After hysterectomy: None (without cervix and without history of CIN 2 or greater)

*3 consecutive negative cytology results or 2 consecutive co-tests within 10 years
Prior to cessation of screening, with the most recent within 5 years
Start screening at age 21

• 0.1% of cervical cancer cases
• 1-2 cases/1 million females age 15-19
• US and UK studies showed that earlier screening did not decrease cervical cancer rates in this population
• If <21 and screened, and abnormality detected, follow guidelines of 21-24
Screening 21-29

• Every 3 years with cytology alone
• High prevalence of HPV Co-testing with HPV should NOT be performed
• Annual screening should NOT be performed
Screening women age 30-65

**Age 30-65.** Testing with cytology alone every 3 years or co-testing with cytology and testing for high-risk HPV types every 5 years.

- Co-testing “preferred” and cytology “acceptable” by all but USPSTF.
- USPSTF says either acceptable
Screening age 30-65

- In women ≥ 30 co-testing detects 17-31% more CIN3 (precancer)
- HPV testing is superior to cytology for detecting cervical adenocarcinoma
  - Poorer prognosis and incidence is increasing
When to stop screening

• Age 65 and not at high risk for cervical cancer
• Discontinuation assumes adequate prior negative screening
• Three consecutive negative cytology results or 2 negative co-test results within the previous 10 years, with the most recent within 5 years
• No prior history of cervical cancer, CIN 2/3 in the prior 20 years
When to stop screening

• After total hysterectomy if no CIN2/3 or cervical cancer
• If CIN2+ and cervix removed, after initial post treatment surveillance, continue screening of vaginal cuff with cytology every 3 years for 20 years, even if >65
• Screening should not resume for any reason even if a woman reports having a new sexual partner
Screening young women with HIV

- Begin screening at age of initiation of sexual activity, regardless of mode of HIV transmission, but no later than age 21.
- If < age 30, screen with cytology at time of diagnosis and then annually. If 3 consecutive annual cytology screens normal, then cytology screening can done every 3 years.

ACOG Practice Bulletin Number 157, January 2016
Women with HIV age 30 and older

• Once has 3 consecutive annual cytology results can be screened with cytology alone every 3 years

• Once has had one negative co-test can be screened with co-testing every 3 years
Screening immunocompromised women

• No studies or major recommendation exists
• Traditionally annual cytology has been done
• Per ACOG it is reasonable to extrapolate recommendations for women with HIV infection to this group with screening beginning at age 21

ACOG Practice Bulletin Number 157, January 2016
Screening DES exposed women

• Used in the US from 1940 to 1971
• Women exposed to DES in utero at increased risk for clear cell adenocarcinoma
• Advise cervical and 4 quadrant vaginal cytology annually and digital exam of vagina annually
• No recommendations from major groups for upper age limit of screening
Primary Screening with HPV Only
FDA Approved April 2014

- US FDA approved a **single** HPV assay for primary screening among women age 25-65 following 3 year 47,000 woman registration trial ATHENA
- In the ATHENA trial 28% of all cases of CIN3+ found in women age 25-29
- Cytology was read as negative in over half of women 25-29 with CIN3+
- Prevalence of HPV 21.9% but prevalence of HPV 16 is 5.3% and HPV 18 1.6%
Prevalence of CIN3+ by Age

ATHENA trial

More CIN3+ disease in women aged 25-29 years than in women aged ≥ 40 years

Wright TC Jr, et al AJOG 2012;206:e1-46e11
Invasive Cervical Cancer in the US SEER Tumor Registry (1975-2010)
## Comparison of Strategies in Women 25-29 Years

*Trade-offs between CIN3+ detected & colposcopy*

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Screening Tests</th>
<th>CIN3+ detected</th>
<th>CIN3+ Missed</th>
<th>Colpos</th>
<th>Colpos to detect 1x CIN3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology with reflex HPV</td>
<td>7,854</td>
<td>51</td>
<td>68</td>
<td>640</td>
<td>12.6</td>
</tr>
<tr>
<td>for ASCUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV Primary</td>
<td>10,226</td>
<td>102</td>
<td>17</td>
<td>1,247</td>
<td>12.2</td>
</tr>
</tbody>
</table>

Wright et al. Presented at the 2019 National Conference on Cervical Cancer.
Primary HPV Screening Algorithm
Age ≥25 every 3 years

Recommended Primary HPV Screening Algorithm

- **Primary HPV Screening**
  - Type 16/18 Positive → Colposcopy
  - 12 other hrHPV + → Cytology
    - ≥ASC-US
    - NILM
      - Follow up in 12 months
  - Negative → Routine Screening
• In women ≥ 25 the FDA approved primary HPV screening test can be considered an alternative to current cytology based screening. **Cytology alone and co-testing remain the options specifically recommended in current major society guidelines.** If used, should be performed as per ASCCP and SGO interim guidance.
## Summary of Cervical Cancer Screening Guidelines

<table>
<thead>
<tr>
<th>Pap test only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative</strong></td>
</tr>
<tr>
<td><strong>ASCUS</strong></td>
</tr>
<tr>
<td>Higher-grade abnormality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pap/HPV cotest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pap−/HPV−</strong></td>
</tr>
<tr>
<td><strong>Pap ASCUS or LSIL/HPV−/Pap−/HPV+</strong></td>
</tr>
<tr>
<td><strong>LSIL/HPV+ or any high-grade lesion regardless of HPV result</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary HPV test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Negative</strong></td>
</tr>
<tr>
<td><strong>HPV+ (not 16/18)</strong></td>
</tr>
<tr>
<td><strong>HPV 16/18+</strong></td>
</tr>
<tr>
<td><strong>≥ASCUS</strong></td>
</tr>
<tr>
<td><strong>Pap/HPV cotesting at 12 mo</strong></td>
</tr>
</tbody>
</table>

*Repeated cotests at shorter interval is recommended for women who are at increased risk for cervical cancer due to underlying medical conditions, immunosuppression, or other factors.
Principles of Management Guidelines

• Preventing all cervical cancer is unrealistic
• Attempts to eliminate all risk result in unanticipated harm from excessive evaluation and treatment
• **Management by risk** – similar risk means similar management
• Immediate risk determines immediate management
• Risk over time determines follow-up interval
<table>
<thead>
<tr>
<th>Current return based on Pap only</th>
<th>Pap-only 5-year CIN3+ risks (implicit risk thresholds)</th>
<th>Cotest 5-year CIN3+ risks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pap result</td>
<td>Frequency</td>
</tr>
<tr>
<td>Immediate colposcopy (high-grade Pap abnormalities)</td>
<td>SCC</td>
<td>&lt;0.01%</td>
</tr>
<tr>
<td></td>
<td>HSIL</td>
<td>0.21%</td>
</tr>
<tr>
<td></td>
<td>ASC-H</td>
<td>0.17%</td>
</tr>
<tr>
<td></td>
<td>AGC</td>
<td>0.21%</td>
</tr>
<tr>
<td>Immediate Colposcopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LSIL</td>
<td>0.97%</td>
</tr>
<tr>
<td>6-12 month return</td>
<td>ASC-US</td>
<td>2.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-year return</td>
<td>Pap-</td>
<td>95.6%</td>
</tr>
<tr>
<td>5-year return</td>
<td></td>
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</tr>
</tbody>
</table>
2013 ASCCP management guidelines
Does anyone understand them?

• How to manage abnormals that did not exist before co-testing
• Define what combination of test results after an abnormal permit safe return to routine screening
• Reflect new data on management of specific results
ASCCP Algorithms Mobile App

- The ASCCP App is a historic step forward for teaching and communicating guidelines

- Can the App improve
  - Understanding of the evidence underlying a guideline?
  - Acceptance of guidelines?

- Could presenting the logic of “Similar Management of Similar Risks” help?
A “Risk Bar” for the App

- “Similar Management of Similar Risks” logic must be obviously and immediately apparent

- The risk calculation underlying the recommendation is displayed on the continuum

- “Why is the recommendation for HPV-negative/ASC-US a 3-year return?”
  - “Oh, the data say it’s just like a negative Pap. I get it.”

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</thead>
<tbody>
<tr>
<td>Management</td>
<td>HPV-/Pap-5-year return</td>
<td>Pap-3-year return</td>
<td>ASC-US1-year return</td>
<td>LSILColposcopy</td>
<td>AGC/ASC-H/HSILColposcopy</td>
</tr>
<tr>
<td>5-year CIN3+ risk:</td>
<td>0.08%</td>
<td>0.26%</td>
<td>2.6%</td>
<td>5.2%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Risk for this result: 0.43%
Cervical Cancer Screening Targets

• CIN 3 is a true precancer, 30-50% progress to cancer over 30 years
  – Must treat since it cannot be predicted which CIN3 lesions will progress to invasion

• CIN 2 is a collection of CIN 3 and CIN1
  – 50% regression rate, low risk of invasion
  – Observation acceptable, especially in younger women

• CIN 1 is a transient or stable HPV infection with minimal cancer risk – DO NOT TREAT!
34 yo G2P2 has a NIL Pap and a positive hrHPV test. She was previously screened with Paps only but has had no screening in 5 years. What is the next step?

1. Immediate colposcopy
2. Co-testing in 3 years
3. Co-testing in 1 year
4. Order HPV DNA genotyping
5. Download the ASCCP mobile app
HPV Genotyping

• Both DNA and mRNA tests available
• 5 year risk of CIN2+ if HPV 16+ is 10%
• Risk of CIN2+ is lower if HPV 18, but there is an association with adenocarcinoma

ASCCP guidelines state HPV genotyping is acceptable without recommending for or against.
Role of HPV 16/18 Genotyping

[Graph showing cumulative incidence of CIN 3+ over follow-up time in months for different HPV test results.]

- Positive HPV 16 test
- Positive HPV 18 test
- Negative HPV 16/18 and positive for other high-risk HPV
- Negative for all high-risk HPV types
Management of Women ≥ Age 30, who are Cytology Negative, but HPV Positive

- **Repeat Cotesting**
  - @ 1 year
  - Acceptable
  - Cytology Negative and HPV Negative
  - Repeat cotesting

- **HPV DNA Typing**
  - Acceptable
  - ≥ASC or HPV positive
  - HPV 16 or 18 Positive
  - Repeat cotesting @ 1 year
  - Manage per ASCCP Guideline

  - HPV 16 and 18 Negative
  - Manage per ASCCP Guideline
She returns in one year. Co-testing shows Pap NIL and HPV negative. What is the next step?

1. Pap only in 3 years
1. Repeat co-testing in one year
2. Repeat co-testing in 3 years
3. Repeat co-testing in 5 years
Cytology Negative, HPV Positive

Management of Women ≥ Age 30, who are Cytology Negative, but HPV Positive

- **Repeat Cotesting**
  - @ 1 year
  - Acceptable
  - Cytology Negative and HPV Negative
    - Repeat cotesting @ 3 years
- **HPV DNA Typing**
  - Acceptable
  - HPV 16 or 18 Positive
  - HPV 16 and 18 Negative
    - Repeat Cotesting @ 1 year
- **Colposcopy**
  - Manage per ASCCP Guideline

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She returns in 3 years and her co-testing Pap is NIL and HPV positive. What do you do now?

• 1. Co-testing in one year
• 2. Immediate colposcopy
• 3. HPV genotyping
Management of Women ≥ Age 30, who are Cytology Negative, but HPV Positive

- **Repeat Cotesting**
  - @ 1 year
  - Acceptable

- **HPV DNA Typing**
  - Acceptable
  - HPV 16 or 18 Positive
  - HPV 16 and 18 Negative

- **Cytology Negative and HPV Negative**
  - Repeat Cotesting @ 3 years

- **≥ASC or HPV positive**
  - Colposcopy

- **NO**

- **Manage per ASCCP Guideline**

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21 year old has first Pap which shows ASC-US. You get reflex HPV testing and she is HPV +. What is next step?

1. Refer for colposcopy
2. Repeat Pap in one year
3. Repeat Pap and HPV test in one year
4. Repeat HPV test alone in one year
Management of Women Ages 21-24 years with either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)

Women ages 21-24 years with ASC-US or LSIL

Repeat Cytology @ 12 months Preferred

HPV Positive

Reflex HPV Testing Acceptable for ASC-US only

HPV Negative

Routine Screening

Negative, ASC-US or LSIL

ASC-H, AGC, HSIL

Repeat Cytology @ 12 months

Negative x 2

≥ ASC

Colposcopy

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Managing Women Ages 21-24

• HPV infection incidence peaks in this age group
• 5 year risk of CIN3+ after ASC-US or LSIL is 3%
• Treatment can have adverse consequences on future pregnancy
• Be conservative in your management
22 year old has a Pap showing HSIL. Her previous Pap last year was ASC-H. She did not follow up until now. What is the next step?

- 1. Repeat Pap in one year
- 2. See and treat with LEEP
- 3. Ask for HPV testing
- 4. Colposcopy
Management of Women Ages 21-24 yrs with Atypical Squamous Cells, Cannot Rule Out High Grade SIL (ASC-H) and High-grade Squamous Intraepithelial Lesion (HSIL)

Colposcopy
(Immediate loop electrosurgical excision is unacceptable)

No CIN2,3

CIN2,3

Two Consecutive Cytology Negative Results and No High-grade Colposcopic Abnormality

Observation with colposcopy & cytology*
@ 6 month intervals for up to 2 years

Other results

High-grade colposcopic lesion or HSIL
Persists for 1 year

HSIL
Persists for 24 months with no CIN2,3 identified

Biopsy

CIN2,3
(if no CIN2,3, continue observation)

Manage per ASCCP Guideline

Diagnostic Excisional Procedure*

Manage per ASCCP Guideline for young women with CIN2,3

Routine Screening

Manage per ASCCP Guideline

*If colposcopy is adequate and endocervical sampling is negative. Otherwise a diagnostic excisional procedure is indicated.
*Not if patient is pregnant

© Copyright, 2013, American Society for Colposcopy and Cervical Pathology. All rights reserved.
Her colposcopic directed biopsies show HSIL (favor CIN 2). What is the next step?

• 1. Repeat Pap in one year
• 2. Treat with excisional LEEP
• 3. Treat with cryotherapy ablation
• 4. Repeat Pap and colposcopy in 6 months
Management of Young Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 2,3 (CIN2,3) in Special Circumstances

Young Women with CIN2,3

Either treatment or observation is acceptable, provided colposcopy is adequate. When CIN2 is specified, observation is preferred. When CIN3 is specified, or colposcopy is inadequate, treatment is preferred.

Observation - Colposcopy & Cytology

- @ 6 month intervals for 12 months

- 2x Cytology Negative and Normal Colposcopy
  - Cotest in 1 year
    - Either test abnormal
      - Both tests negative
        - Cotest in 3 years
    - Cotest in 1 year

- Colposcopy worsens or High-grade Cytology or Colposcopy persists for 1 year
  - Repeat Colposcopy/Biopsy Recommended

Treatment using Excision or Ablation of T-zone

- CIN3 or CIN2,3 persists for 24 months
  - Treatment Recommended
ASC-H and HSIL in Women Ages 21-24

• Precancer risk higher than after ASC-US/LSIL
• 5 year risk of CIN3+
  – 16% after ASC-H
  – 28% after HSIL
• Most CIN2 in this group will regress – up to 49%
  – Risk of progression but usually takes time
  – Treat if CIN 2 persists for 2 years – ablation preferred
• Treatment preferred for CIN3
• Cancer unlikely during extended observation
Guidelines for Colposcopy

• Always recommend for
  – HSIL (High Grade Squamous Intraepithelial Lesion)
  – ASC-H (Atypical Squamous Cells, Can’t Exclude HSIL)
  – AGC (Atypical Glandular Cells)
  – Cervical lesion or abnormal appearing cervix
  • Pap and HPV testing can be negative even when invasive cancer is present
Guidelines for Colposcopy

• Sensitivity of colposcopy is poor
  – The experts miss 18-36%
• Biopsies should be done with all colposcopies
  – If no lesions seen random biopsies+/-ECC
  – 20.9% of random biopsies show HSIL
• All visible lesions should be biopsied
• Sensitivity of colposcopy improves with every additional biopsy performed
METHOD OF DIAGNOSING WOMEN WITH CIN 2 OR WORSE (SPOCCS II)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Total/Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colpo biopsy</td>
<td>208/364</td>
<td>57.1%</td>
</tr>
<tr>
<td>Colpo biopsy + 2 o’clock</td>
<td>256/364</td>
<td>70.3%</td>
</tr>
<tr>
<td>Colpo biopsy + 2, 4 o’clock</td>
<td>297/364</td>
<td>81.6%</td>
</tr>
<tr>
<td>Colpo biopsy + 2, 4, 8 o’clock</td>
<td>329/364</td>
<td>90.4%</td>
</tr>
<tr>
<td>Colpo biopsy + 2, 4, 8, 10 o’clock</td>
<td>344/364</td>
<td>94.5%</td>
</tr>
<tr>
<td>Colpo biopsy + 2, 4, 8, 10 + ECC</td>
<td>364/364</td>
<td>100%</td>
</tr>
</tbody>
</table>

57.1% vs. 70.3% vs. 81.6% vs. 90.9% vs. 94.5% vs. 100%, Chi-Square = 326, df=5, P<.001

Pretorius et al, Int J Ca, 2007
The accuracy of colposcopic biopsy: analyses from the placebo arm of the quadrivalent HPV vaccine clinical trials

<table>
<thead>
<tr>
<th>Colpo Directed Biopsy</th>
<th>LEEP Histology</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neg</td>
<td>CIN1</td>
<td>CIN2</td>
<td>CIN3/AI S</td>
</tr>
<tr>
<td>Neg</td>
<td>195</td>
<td>82</td>
<td>29</td>
<td>54</td>
</tr>
<tr>
<td>CIN1</td>
<td>12</td>
<td>65</td>
<td>28</td>
<td>17</td>
</tr>
<tr>
<td>CIN2</td>
<td>1</td>
<td>2</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>CIN3/AI S</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>49</td>
</tr>
<tr>
<td>Total</td>
<td>215</td>
<td>153</td>
<td>81</td>
<td>145</td>
</tr>
</tbody>
</table>

CIN2+ called CIN1 or Neg 128/226 (57%)
CIN3/AIS called CIN1 or Neg 71/145 (49%)

Stoler MH et al, Int J Cancer, 2010
Risk of only performing random biopsy complement on women with the worst Paps: PROPORTION OF CIN 2 OR WORSE AS A FUNCTION OF CERVICAL CYTOLOGY

<table>
<thead>
<tr>
<th>CYTOLOGY</th>
<th>CIN 2 OR WORSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-US/HPV POS</td>
<td>44/159 (27.7%)</td>
</tr>
<tr>
<td>ASC-H OR LSIL</td>
<td>72/159 (45.3%)</td>
</tr>
<tr>
<td>HSIL, CANCER, AGUS, ENDO OUT OF PHASE</td>
<td>43/159 (27.0%)</td>
</tr>
</tbody>
</table>

LAST (Lower Anogenital Squamous Terminology)

• Histologic LSIL – CIN 1
• Histologic HSIL – CIN 2, CIN 3
• Goal to create a dichotomous separation of morphologic designations that reflect transient active HPV replication (LSIL) versus persistent HPV associated precancer (HSIL)
LAST (Lower Anogenital Squamous Terminology)

• Accepts CIN3 as a true precancer
• CIN 2 – highest interobserver variability
• Recommends p16 immunostaining to adjudicate equivocal precancers – CIN2
  – Concern for overtreatment of CIN2 if merged into HSIL. Advised that the 2 tier diagnosis be qualified with the relevant –IN category in parentheses
• Advise against using p16 staining in CIN1 cases with result of upgrading and overtreating lesions that represent infections
  – 30% of CIN 1 lesions p16 positive
Managing ASCUS in adult women

• Up to 2/3 are HPV associated
• HPV+ more frequent in younger women
  – 60% age <25 vs 25% ages 45-55
• More frequent among those with multiple partners
• HPV triage of ASCUS is more cost-effective then repeat cytology
Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology*

**Repeat Cytology**
@ 1 year
Acceptable

- **Negative**
  - Routine Screening*
- **> ASC**
  - **Colposcopy**
  Endocervical sampling preferred in women with no lesions, and those with inadequate colposcopy; it is acceptable for others

**HPV Testing**
Preferred

- **HPV Positive**
  - (managed the same as women with LSIL)
- **HPV Negative**
  - Repeat Cotesting
  @ 3 years

**Manage per ASCCP Guideline**

*Management options may vary if the woman is pregnant or ages 21-24.
+Cytology at 3 year intervals

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30 year old has had 3 normal Pap tests. Pap shows LSIL and HPV test is negative. What is the next step?

- Repeat co-testing in 3 years
- Colposcopy
- Repeat co-testing in 1 year
- Repeat Pap in one year
Management of Women with Low-grade Squamous Intraepithelial Lesions (LSIL)*

**LSIL with negative HPV test**
- Preferred
- Repeat Cotesting @ 1 year
  - Cytology Negative and HPV Negative
    - Repeat Cotesting @ 3 years
  - ≥ASC or HPV positive

**LSIL with no HPV test**
- Acceptable
- Colposcopy
  - No CIN2,3
    - Manage per ASCCP Guideline
  - CIN2,3
    - Manage per ASCCP Guideline

**LSIL with positive HPV test**
- Colposcopy

*Management options may vary if the woman is pregnant, postmenopausal, or ages 21-24 years (see text)

Figure 6
Managing ASC-H in adult women

• 60% are HPV+
  – HPV triage is NOT recommended
• CIN 3+ risk when HPV negative is 3.5% at 5 yrs
• CIN3+ risk when HPV positive is 25% at 5 years
Management of Women with Atypical Squamous Cells: Cannot Exclude High-grade SIL (ASC-H)*

Colposcopy
Regardless of HPV status

No CIN2,3

Manage per ASCCP Guideline

CIN2,3

Manage per ASCCP Guideline

*Management options may vary if the woman is pregnant or ages 21-24 years.
HSIL in adult women

- Immediate CIN3+ risk is 36%
- Risk increases to 47% at 5 years
- Colposcopy with endocervical assessment
- Immediate loop electrosurgical excision acceptable especially when future pregnancy not an issue
- 6% of women age 30-64 with HSIL will have cancer
40 year old had a LEEP for CIN 3. LEEP showed CIN 3. Margins negative. What is the next step?

- HPV testing at 12 months
- Pap testing every 6 months
- Colposcopy and cytology at 6 and 12 months
- Co-testing at 12 and 24 months
Cumulative risk of CIN2+ following subsequent negative follow up tests after treatment for CIN2,3, or AIS
Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia - Grade 2 and 3 (CIN2,3) *

*Management options will vary in special circumstances or if the woman is pregnant or ages 21-24
†If CIN2,3 is identified at the margins of an excisional procedure or post-procedure ECC, cytology and ECC at 4-6mo is preferred, but repeat excision is acceptable and hysterectomy is acceptable if re-excision is not feasible.

Adequate Colposcopy

Either Excision† or Ablation of T-zone *

Inadequate Colposcopy or Recurrent CIN2,3 or Endocervical sampling is CIN2,3

Diagnostic Excisional Procedure†

Cotesting at 12 and 24 months

2x Negative Results

Any test abnormal

Colposcopy
With endocervical sampling

Repeat cotesting in 3 years

Routine screening

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28 year old with a BMI of 68 and AUB-O has a Pap showing AGC-NOS. What is your next step?

1. Ask for reflex HPV testing
2. Repeat Pap in 6 months
3. Colposcopy with endocervical sampling
4. Endometrial sampling
5. Both colposcopy with ECC and endometrial sampling
Review of 3,890 AGCUS Paps

-5.2% had a malignancy
  • 57.6% endometrial
  • 23.6% cervical adenocarcinoma
  • 6.9% other
  • 5.4% cervical squamous cell carcinoma
  • 5.4% ovarian
  • 1% fallopian tube

– 23% had a significant finding
  • 11.1% HSIL
  • 8.5% LSIL
  • 2.9% AIS
  • 1.4% endometrial hyperplasia

Obstet Gynecol 2006;107:701-8
Initial Workup of Women with Atypical Glandular Cells (AGC)

All subcategories (except atypical endometrial cells)

Colposcopy (with endocervical sampling) and Endometrial sampling (if ≥ 35 yrs or at risk for endometrial neoplasia *)

Atypical Endometrial Cells

Endometrial and Endocervical Sampling

No Endometrial Pathology

Colposcopy

*Includes unexplained vaginal bleeding or conditions suggesting chronic anovulation.
Subsequent Management of Women with Atypical Glandular Cells (AGC)

Initial Cytology is AGC - NOS

- No CIN2+, AIS or Cancer
  - Cotest At 12 and 24 months
    - Both negative: Cotest 3 years later
    - Any abnormality: Colposcopy

- CIN2+ but no Glandular Neoplasia
  - Manage per ASCCP Guideline

Initial Cytology is AGC (favor neoplasia) or AIS

- No Invasive Disease
  - Diagnostic Excisional Procedure *
  *Should provide an intact specimen with interpretable margins. Concomitant endocervical sampling is preferred.
Questions?

KEEP CALM AND FIGHT CERVICAL CANCER