Cervical Cytology and Pathology: Past, Present, and Future

Krysta Hood, DNP, RN, CRNP
Nurse Practitioner Senior
Alabama Department of Public Health

Objectives
- Review the history of the Bethesda System
- Provide an overview of Lower Anogenital Squamous Terminology
- Discuss evidence-based research studies
- Give a summary of QA findings
- Examine the relationship between HPV and cervical dysplasia
- Present the New ASCCP Risk Based-Management Guidelines

History of “the Bethesda system” (TBS)
- Bethesda, Maryland, December 1988
- Standardization of terminology
  - Relevant information communicated from the lab to the provider
  - Uniform and reasonably reproducible
  - Reflective of current understanding of cervical neoplasia

Evolution of Nomenclature

Bethesda: Cytology Report Example
Format of the Report: Sample Type/Statement of Adequacy

- Specimen Adequacy - Satisfactory/Unsatisfactory, Presence/Absence of TZ, Quality Indicators - blood, inflammation

Format of the Report: General Categorization

- Negative for Squamous Intraepithelial Lesion or Malignancy (NIL)
- Epithelial cell abnormalities
  - Squamous
  - Glandular
- Other - Endometrial cells > 45 yo

Format of the Report: Interpretation/Results

Squamous Cell Abnormalities
- LSIL
- HSIL
- Squamous cell carcinoma

Glandular Cell Abnormalities
- Atypical
  - Endocervical
  - Endometrial
  - Glandular

Atypical
  - Endocervical cells, favor neoplastic
  - Glandular cells, favor neoplastic
Format of the Report: Interpretation/Results

- Glandular Cell Abnormalities
  - Adenocarcinoma
    - Endocervical
    - Endometrial
    - Extrauterine
    - NOS

Other Malignant Neoplasms (specify)

- Educational Notes and Suggestions

Lower Anogenital Squamous Terminology (LAST)

- Two tiered terminology
  - Low grade squamous intraepithelial lesions
  - High grade squamous intraepithelial lesions

- Terms used for all sites in male and female LGT

LAST Standardization Project

- CIN/VAIN/VIN/AIN- Grade 2 lesions are poorly reproducible among pathologists
- Variable behavior
  - Some progress to HSIL
  - Some regress to LSIL

Use old terminology with the new
- LSIL (CIN 1)
- HSIL (CIN 2)
- HSIL (CIN 3)
Terminology

<table>
<thead>
<tr>
<th>National history model</th>
<th>Histology</th>
<th>Cytology</th>
<th>Pap smear classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>I</td>
<td>NILW</td>
</tr>
<tr>
<td>Infection</td>
<td>Squamous</td>
<td>II</td>
<td>ASC-US</td>
</tr>
<tr>
<td>Metaplasia</td>
<td>CIN1</td>
<td>III</td>
<td>LSIL</td>
</tr>
<tr>
<td>Neoplastic atypia</td>
<td>CIN2</td>
<td>IV</td>
<td>HSIL</td>
</tr>
<tr>
<td>Cancer</td>
<td>Carcinoma</td>
<td>V</td>
<td>Carcinoma</td>
</tr>
<tr>
<td>Severe dysplasia, Carcinoma in situ</td>
<td>CIN3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The ASCUS/LSIL Triage Study for Cervical Cancer (ALTS)

• ASCUS/LSIL = 3 Million results per year
• 5,000 Study Participants from 1996-2000
• Funded by National Cancer Institute

ALTS Management Strategies
1. Immediate Colposcopy of all women
2. Repeat cytology with colposcopy only if high grade lesion
3. Co-testing with referral for colpo if HPV is positive or cytology show high grade lesion

ALTS Study Findings
- HPV testing is sensitive in detecting underlying precancerous lesions
- HPV testing is not useful with diagnosis of LSIL
- Expert interpretations of Paps vary
Kaiser Permanente Northern California (KPNC)

- 1.5 Million women ages 25-65 years
  - 591 cancers, 8473 CIN3+, 21395 CIN2+
- Cotesting and HPV genotyping data
- Vaccination status
- Comparison CDC NBCCEDP data

Cytology ASCUS/HPV Negative

Post Colposcopy Follow-Up

Screening Won’t Protect Your Patients from Most HPV Cancers

- Cervical Cancer
- Cervical Precancer
- Oropharyngeal Cancer
- Anal Cancer
- Vulvar & Vagina Cancer
- Penile Cancer
High-risk HPV and Cervical Cancer

- HPV is the necessary (but not sufficient) agent in the pathogenesis of cervical cancer
- Present in 99.7% of cervical cancers worldwide
- HPV positive detection in cancers of the oropharyngeal, tonsillar, base of tongue, oral cavity, larynx
- Vaccination females and males

HPV Infection: 3 Courses

1) Sustained Remission
   - Immune response contains infection
2) Productive Infection
   - Co-factors present, HPV replicates
     - Cigarette smoking, Chlamydia, OCs, Nutrition, Immunosuppression
3) Neoplastic Transformation
   - Persistent infection

Addressing THE Need for Advanced HPV Diagnostics-ATHENA Study

- 47,000 women, >21 yo
- 1st screening trial for HPV genotyping
  - 16, 18, and 12 additional hrHPV types
- FDA Approved for Primary Screening
- Can be considered an alternative to traditional screening
- Primary hrHPV only every 5 years

Pathology Report
**p16 Immunostain**
- Tumor suppressor gene/biomarker for transforming HPV infection
- Positive results of block staining with p16 indicative of high grade disease
- Improves accuracy of interpretation and prediction of risk for high grade disease
- Clarify discrepancies between cytology and pathology, biopsies/curettage

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**Case Example**
- 23 yo G1P1 with pap history including:
  - 2019- ASCUS
  - 2018- LSIL/HPV positive (outside provider), age 22
  - 2017- LSIL, age 21

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**Case Example**
- Colposcopy findings:
  - External genitalia normal, no gross lesions
  - SCJ not fully visualized
  - Ectocervix unremarkable
  - No mosaicism or punctations noted
  - ECC obtained

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**EVA Image**
Future Guidelines

5-year Risk of CIN 3 by Age and Pap Result

<table>
<thead>
<tr>
<th>Baseline Pap and HPV test result</th>
<th>25-29</th>
<th>30-39</th>
<th>40-44</th>
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<tbody>
<tr>
<td>HSIL</td>
<td>20</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>ASC-H†</td>
<td>10</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>AGC</td>
<td>5.0</td>
<td>14</td>
<td>5.5</td>
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<tr>
<td>ASC-US</td>
<td>3.0</td>
<td>5.5</td>
<td>5.0</td>
</tr>
<tr>
<td>ASC-US/LS</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>HPV positive or HSIL</td>
<td>4.4</td>
<td>7.1</td>
<td>4.4</td>
</tr>
<tr>
<td>HPV-negative or HSIL</td>
<td>0.31</td>
<td>0.18</td>
<td>0.42</td>
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<tr>
<td>Pap-negative</td>
<td>0.2</td>
<td>0.36</td>
<td>0.26</td>
</tr>
</tbody>
</table>

What is the patient’s risk?

- Guideline Committees
- Research based
- Clinical action and reassurance
- Treatment

What is the patient’s risk?

- Colpo
- Short interval surveillance (1 or 3 years)
- 5 year screening
New Guidelines

- HPV Status
- Cytology
- Past History
- New Screening Technology
  - HPV typing
- Vaccination Status
- Patient Characteristics
  - Age, prior negative HPV, etc.