1/24/24 bb/njm

ANMC Cervical Cancer Prevention Guideline

Our system for the prevention and elimination of cervical cancer in Alaska Native people requires four elements working together.

1. Maximize uptake of HPV vaccine.
2. Regular cervical cancer screening of people at risk for the disease.
3. Medical evaluation and management of abnormal screening results.
4. Tracking of cervical cancer screening results and treatments with customer owner notification.

Facilities and providers involved in cervical cancer screening and prevention will need to continue to work together to maintain the integrity of data to provide quality care.

TIER 1: PREVENTION

HPV Vaccination Recommendations:
Human papilloma virus (HPV) infections, specifically 15 high risk subtypes, are associated with cervical cancer. About 70% of cervical cancers are associated with HPV genotypes 16 and 18 worldwide. ANMC currently offers the 9-valent HPV vaccine, Gardasil 9. Gardasil 9 protects against oncogenic genotypes16, 18, 31, 33, 45, 52, and 58, as well as 6 and 11 which are associated with condyloma. A review of ANMC colposcopy specimens showed that 95% of CIN 3 involved the Gardasil 9 genotypes.

Ideally, HPV vaccination should be given in early adolescence because vaccination is most effective before exposure to HPV through sexual activity. For adults aged 27 through 45 years who are not completely vaccinated, clinicians can consider discussing HPV vaccination with persons who are most likely to benefit.

• HPV is a very common sexually transmitted infection. Most HPV infections are transient and asymptomatic and cause no clinical problems.
• Although new HPV infections are most commonly acquired in adolescence and young adulthood, some adults are at risk for acquiring new HPV infections. At any age, having a new sex partner is a risk factor for acquiring a new HPV infection.
• 80-90% of adults have been exposed to HPV types, although most are not covered by the vaccine and are not considered to be linked to cervical dysplasia and cancer.
• No clinical antibody test can determine whether a person is already immune or still susceptible to any given HPV type.
• HPV vaccine efficacy is high among persons who have not been exposed to vaccine-type HPV before vaccination.
• Vaccine effectiveness might be low among persons with risk factors for HPV infection or disease (e.g., adults with multiple lifetime sex partners and likely previous infection with vaccine-type HPV), as well as among persons with certain immunocompromising conditions.

CDC Advisory Committee on Immunization Practices

Children and adults aged 9 through 26 years. HPV vaccination is recommended between 9 and 12 years of age; Catch-up HPV vaccination is recommended for all persons through age 26 years who have not begun or completed the vaccine series.

Adults aged >26 years. Catch-up HPV vaccination can be considered for all adults aged >26 years. Shared decision-making regarding HPV vaccination is recommended for adults aged 27 through 45 years who are not vaccinated. HPV vaccines are not licensed for use in adults aged >45 years.

Administration. Dosing schedules, intervals, and definitions of persons considered adequately vaccinated have not changed. No prevaccination testing (e.g., Pap or HPV testing) is recommended to establish the appropriateness of HPV vaccination.

Special populations and medical conditions. These recommendations for children and adults aged 9 through 26 years and for adults aged >26 years apply to all persons, regardless of behavioral or medical risk factors for HPV infection or disease. For persons who are pregnant, HPV vaccination should be delayed until after pregnancy; however, pregnancy testing is not needed before vaccination. Persons who are breastfeeding or lactating can receive HPV vaccine.

Two dose Schedule:
For non-immunosuppressed people starting the vaccination series before the 15th birthday, the recommended schedule is 2 doses of HPV vaccine. The second dose should be given 6–12 months after the first dose (0, 6–12-month schedule).

Three dose Schedule:
CDC continues to recommend a 3-dose schedule for persons starting the HPV vaccination series on or after the 15th birthday, and for persons with certain immunocompromising conditions. The second dose should be given 1–2 months after the first dose, and the third dose should be given 6 months after the first dose (0, 1–2, 6-month schedule).

> CDC recommends 3 doses of HPV vaccine (0, 1–2, 6 months) for immunocompromised people age 9 through 26 years. People whose immune responses might be lower, for example due to HIV infection, cancer, autoimmune disease, or taking immunosuppressant medications, should receive 3 doses to make sure they get the most benefit.

Please see the CDC website for further vaccination details.
https://www.cdc.gov/vaccines/vpd/hpv/public/index.html#:~:text=The%20first%20dose%20is%20routinely,given%20before%2015th%20birthday.

TIER 2: SCREENING AND DETECTION

A. Background

Cervical Cancer Screening Recommendations:
The Alaska Native Medical Center has adopted the recommendations from the 2019 American Society for Colposcopy and Cervical Pathology (ASCCP) Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. By linking our guidelines to the ASCCP, we hope to remain current and to present our process in a familiar format. We will continue to track our age-specific cervix cancer rates and periodically review our guidelines to be sure that no deviation from the national recommendations is warranted.

For screening and management recommendations, the ASCCP App will be used to help determine an individual's risk for CIN3 and recommended plan of care. The full ASCCP Risk Based Management Consensus can be found at:
https://journals.lww.com/jlgtd/Fulltext/2020/04000/2019_ASCCP_Risk_Based_Management_Co nsensus.3.aspx

HPV infections and Cervical Cancer
Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN).(1-3) The presence of HPV has been implicated in >99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high risk (HR) for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers.

Although persistent infection with HR-HPV is necessary for the development of most cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Infection with HPV is extremely common, with estimates of up to 85% of all people being exposed to HPV at some point. However, almost all infected people will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN although this ~~also~~ usually resolves once the HPV infection has been cleared.

B. Screening

1. Primary HPV Screening for ≥ 25 years of age

Cervical cancer screening strategies are shifting from cytology to human papillomavirus (HPV) testing. HPV testing is more sensitive and, when negative, offers greater reassurance against cancer. At ANMC, cervical cancer screening samples will be collected in the ThinPrep vial in the usual fashion, and processed in the lab using the cobas® Primary HPV test.

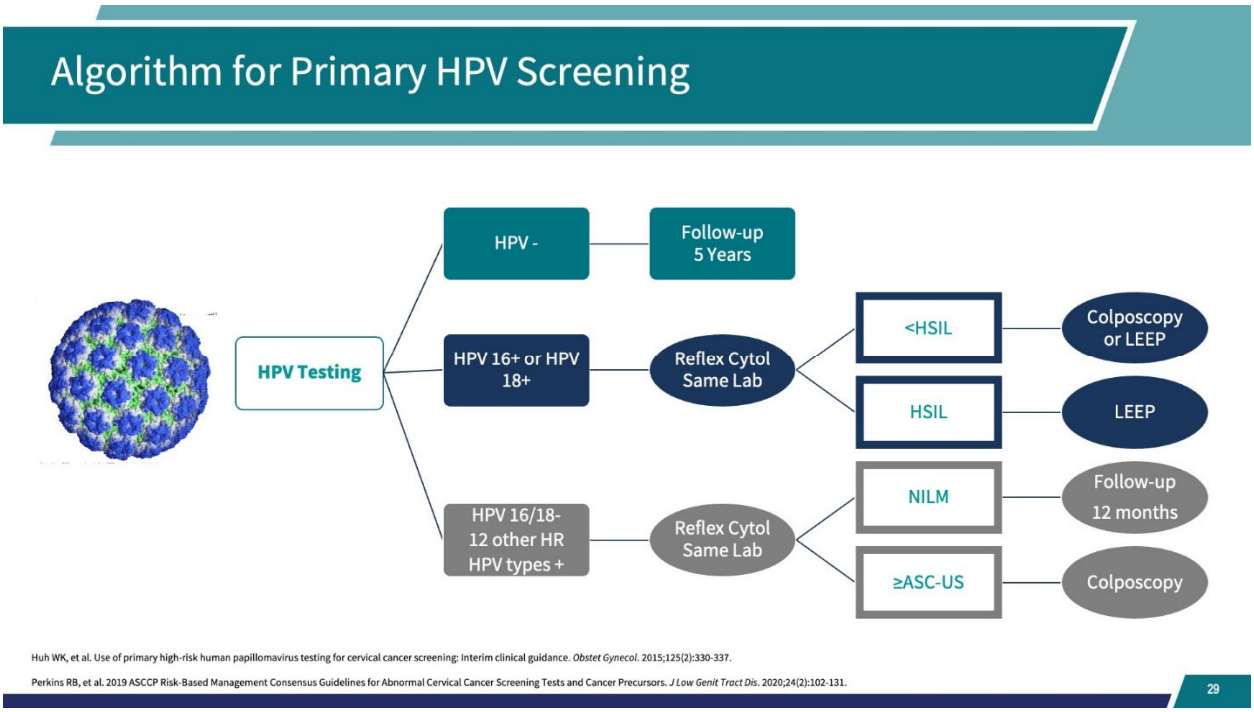
2. HPV Genotyping

Additional risk stratification with partial genotyping, is another useful tool that can determine an individual's risk estimate and help guide management of positive HPV results. The cobas® instrument will result the genotype as 16-positive, 18-positive, or other which groups the non 16/18 high risk HPV genotypes. Genotype results 16 or 18 can go directly to colposcopy, but cytology/morphology testing is helpful to offer expedited treatment with LEEP (see below).

3. Reflex Triage Testing for Primary HPV positive results

When the primary HPV screen is positive, an additional reflex triage test is needed to determine management. Current cytology methods available for triage are the traditional Papanicolaou cytology test and the Dual Stain cytology test, CINtec® PLUS. At ANMC, all positive HPV results, regardless of genotype, will be triaged with the Dual Stain to determine the need for colposcopy for the other HR HPV genotypes and the option of expedited treatment with LEEP for the 16/18 genotypes.

Dual Stain (DS): p16/Ki-67 Dual Stain (DS) is a cytology-based test for detection of cervical precancer that has been approved by the FDA for triage of positive test results in HPV screening and HPV-cytology co-testing. DS detects a marker of HPV-related oncogene activity (p16) and a marker of cell proliferation (Ki-67) which, when detected in the same cell, are associated with precancerous cellular changes (CIN3+). Compared to cytology, dual stain requires fewer colposcopies and detects CIN3 earlier.



4. Cytology Screening (traditional Papanicolaou) for 21 to 24 years of age

Young people are at low risk for developing cervical cancer and have a very high incidence of transient HPV infection that presents as an abnormal Pap. People who are 21-24 will be screened for cervical cancer with cytology testing alone consistent recommendations from ASCCP.

According to ASCCP the term “young person” can indicate those who need to be counseled concerning the risk of excisional procedures to pregnancy outcomes, and therefore, no specific age threshold has to be placed on individuals considering future pregnancies. Any deviation from recommended guidelines should be documented under the provider’s **colposcopy** note and a detailed surveillance plan should be included.

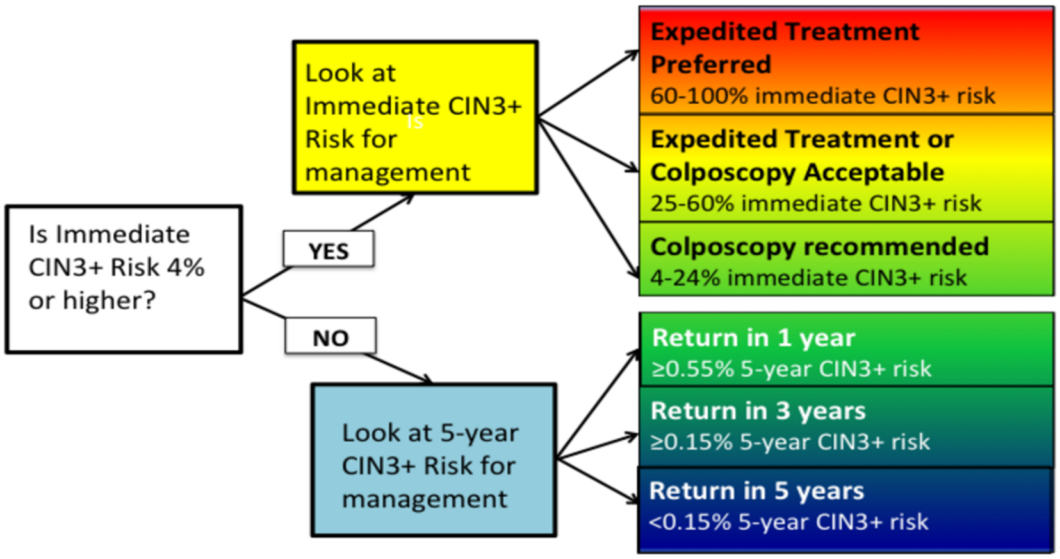
Aggressive management with colposcopy and possible excision or ablative therapy is unlikely to have any benefit and can cause significant harm. Dysplasia when found in a young person is both less likely to progress and more likely to regress than similar lesions found in an adult.

Any preventative visit with a young person should include a review of vaccination history and an offer to start or complete the HPV vaccine series.

C. Follow up of abnormal results

1. Risk-Based Framework

Based on the ASCCP guidelines, a risk-based approach will be used to determine clinical actions. Specifically, the immediate and 3-year or 5-year risk of developing CIN3, AIS, or cancer (CIN3+) is estimated using prevalence-incidence mixture models. Resulting clinical actions are based on risk thresholds determined by the 2019 guidelines. Thresholds have been developed for return in 5 years, return in 3 years, return in 1 year, colposcopy, or expedited treatment. Colposcopy is recommended when the immediate risk of CIN3+ is 4-24%. Expedited treatment or colposcopy exam is offered when risk is 25%-59%. For risk over 60%, expedited treatment is preferred.



D. Special Circumstances

1. Ambiguous Results

It is not uncommon to have results where there is no specific guideline or evidence-based resource to direct care ("use clinical judgement" in ASCCP app). In these circumstances, it is best to consult a colposcopist for a plan of care.

2. Menopause/Atrophy

- ASC-US or LSIL in a postmenopausal person is often an effect of estrogen loss on the epithelium (atrophy), rather than HPV infection.
- A diagnosis of atrophic vaginitis should be made by history and exam, including a visual exam of the vagina and a wet mount looking for squamous maturation (parabasal cells). Treatment should be offered, based on symptom relief goals.
- A short course of vaginal estrogen to treat vaginal atrophy prior to follow-up co-testing is a practical option to rule out true dysplasia for patients who have no contraindication to estrogen therapy. Rx: Conjugated estrogen cream (Premarin)1gm vaginally qHS X 3wks then repeat cytology (Pap) in 1wk. If the follow-up cytology co-test doesn't normalize with this treatment, management according to the ASCCP guidelines is recommended.

3. HIV, people who are immunocompromised, DES

- People with HIV infection are managed as per the ASCCP guidelines, "*Managing Patients with Immunosuppression*". Although research is limited, the HIV cervical cancer screening and abnormal result management recommendations can apply to other immunocompromised people (ie: solid organ transplant, stem cell transplant, systemic lupus erythematous, and bowel disease or rheumatologic disease requiring current immunosuppressive treatments).
- People who are younger than 30 living with HIV should have Pap testing (cytology only) at the time of initial diagnosis or with onset of vaginal penetration sex even if under 21 years of age. Co-testing is not recommended for HIV positive people younger than 30. If the initial cytology screening result is normal, the next screening should be in 12

months. If three consecutive annual screenings are normal, follow-up cervical cytology should be every 3 years. If the cytology test is ASCUS with no HPV results, repeat cytology in 6 -12 months, with colposcopy referral for ASC-US or higher. For any result of ASC-US or higher on repeat cytology or if HPV positive, referral to colposcopy is recommended. For all cytology results of LSIL or worse (including ASC-H, AGC, AIS, and HSIL), referral to colposcopy is recommended regardless of HPV test result if done.

- People who are 30 years and older should be screened with co-testing (HPV screen and cytology). People infected with HIV who have one negative co-test result (normal cytology and negative HPV) can have their next cervical cancer screening in 3 years.
- People who have been exposed to diethylstilbestrol should have cervical cancer screening with visual inspection/cytology/HPV screening co-test annually.

4. Pregnancy

- The indications for colposcopy are not changed by pregnancy.
- Cervical biopsies are safe in pregnancy and should be done for lesions suspicious for high-grade disease or invasion. Endocervical sampling or curettage should not be done.
- Since unsatisfactory colposcopy may become satisfactory as the pregnancy progresses, it is recommended that pregnant people with an unsatisfactory colposcopy undergo a repeat exam in 6-12 weeks.
- The increased vascularity of the cervix in pregnancy may accentuate colposcopic findings.
- For positive HPV results with a triage cytology test ASCUS or LSIL, or Dual Stain positive, a single colposcopic exam that does not suggest a high-grade lesion is sufficient evaluation during pregnancy.
- For individuals with HSIL cytology or colposcopic findings of high-grade dysplasia found early in pregnancy, a second evaluation can be done later in pregnancy.
- If the abnormal screening test was not completely evaluated during the pregnancy or high-grade dysplasia was suspected on exam, a colposcopy should be planned for the post-partum visit. Otherwise, the patient can follow up at normal intervals.

E. Provider Privileges and Responsibilities

Basic colposcopy privileges
Granted to providers recently trained in colposcopy, and not expert in treatment of gynecologic disease. A HPV positive test and ASC-US/CIN I cytology test comprise more than 90% of the patients needing colposcopy. While finding high grade dysplasia in any one of these patients is less likely, most of the significant dysplasia will come from this group because it is so much larger than the remaining groups. The risk of CIN2/3+ for this group is 6-12% and if colposcopy is planned vs excisional procedure, collaboration with an experienced colposcopist is recommended. If a treatment plan is outside the recommended guidelines, consultation with a provider who has full colposcopy privileges is recommended.

Full colposcopy privileges
This is limited to providers with training and at least two years of experience in colposcopy and the management of dysplasia AND with the recommendation of the Medical Director. All colposcopies for positive screening results with cytology results suggesting high grade dysplasia should optimally be with a provider in this group. If the provider recommends a treatment

outside the guidelines, then it is required that the provider document the reasons for the plan in the customer owner's record.

F. Colposcopy Documentation Responsibilities

Evaluate and document the following:

- Indications for colposcopy
- Past history of cervical cytology, colposcopy, treatment
- Parity
- Contraception
- Pregnancy status
- Menopausal status
- Hysterectomy status
- Smoking history
- HIV status
- HPV vaccination status

Obtain informed consent.

Examination

- Examine vulva and vagina grossly.
- Examine the cervix with multiple magnifications after application of 3%–5% acetic acid.
- Examine cervix with both white light and a red-free (blue or green) filter.
- Examine upper vagina with magnification.

Documentation

- Document:
    - cervix visibility (fully/not fully visualized)
    - SCJ visibility (fully/not fully visualized)
    - whether cervical manipulation is needed, to completely visualize the SCJ, e.g., using an applicator stick or endocervical speculum
    - colposcopic findings.
        - Aceto-whitening present (yes/no)
        - Lesion(s) present (yes/no)
        - If lesion(s) present, document extent of lesion(s) visualized (fully/not fully), lesion size and location, description (color, contour, borders, vascular changes).
    - colposcopic impression (benign–normal/LSIL/HSIL/cancer).
    - Location of biopsies if biopsies indicated,
    - Whether ECS performed and method: curettes brush or both

- Post-procedure: Document how customer owner will be notified of results and management plan. Once results are available, the customer owner will be notified and recommendations for plan of care discussed.

- Documentation of notification should be included as an addendum in the **colposcopy** note from that visit. A copy of this note should be forwarded to PCP and Screening and Prevention for coordination of follow up.

References:

Local

- Day GE, Lanier AP, Bulkow L, Kelly JJ, Murphy N. Cancers of the breast, uterus, ovary and cervix among Alaska Native women, 1974–2003. Int J Circumpolar Health 2010; 69(1): 72-86
- Becker TM Regional Differences in Cervical Cancer Incidence Among American Indians and Alaska Natives, 1999–2004. Cancer 2008;113 (5 suppl):1234–43.
- Sebbelov AM et al. Comparison of human papillomavirus genotypes in archival cervical cancer specimens from Alaska natives, Greenland natives and Danish Caucasians. Microbes and Infection 2000, 121-126
- Carmack AM, Schade TL, Sallison I, Provost EM, Kelly JJ. Cancer in Alaska Native People: 1969 – 2013, The 45 Year Report. Anchorage, AK: Alaska Native Tumor Registry, Alaska Native Epidemiology Center, Alaska Native Tribal Health Consortium 2015. 153 p. http://anthctoday.org/epicenter/publications/Cancer45-yearReport/45_Year_Report_FINAL_Online_Version.pdf

National/International:

- U.S. Preventive Services Task Force. Screening for Cervical Cancer: U.S. Preventive Services Task Force Recommendation Statement. https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/cervical-cancer-screening (Accessed 1/11/24)
- Perkins, R, Guido, R, Castle, P, Chelmow, D, Einstein, M, Garcia, F, Huh, Warner K, Kim, JJ, Moscicki, A, Nayar, R; Saraiya, M, Sawaya, GF, Wentzensen, N, Schiffman, M. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. Journal of Lower Genital Tract Disease: April 2020 - Volume 24 - Issue 2 - p 102-131.
- 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors: Erratum Journal of Lower Genital Tract Disease: October 2020 - Volume 24 - Issue 4 - p 427
- Chelmow D, Waxman A, Cain JM, Lawrence HC 3rd. The evolution of cervical
- screening and the specialty of obstetrics and gynecology. Obstet Gynecol. 2012 Apr;119(4):695-9.
- Lagheden C, Eklund C, Lamin H, Kleppe SN, Lei J, Elfström KM, Sundström K, Andrae B, Sparén P, Dillner J. Nationwide comprehensive human papillomavirus (HPV) genotyping of invasive cervical cancer. Br J Cancer. 2018 May;118(10):1377-1381.
- Meites, E, Szilagyi, PG, Chesson, HW, Unger, ER, Romero, JR, Markowitz, LE. Centers for Disease Control and Prevention (CDC). Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices MMWR Morb Mortal Wkly Rep. 2019 Aug 16; 68 (32): 698-302.
- ACOG Practice Advisory. Updated Guidelines for Management of Cervical Cancer Screening Abnormalities. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/10/updated-guidelines-for-management-of-cervical-cancer-screening-abnormalities (accessed 1/11/24).
- Human papillomavirus vaccination. Committee Opinion No. 809. American College of Obstetricians and Gynecologists. Obstet Gynecol Aug 2020. (Re-affirmed 2023)
- Demarco, M, Egemen, D, Raine-Bennett,TR, Cheung, LC, Befano, B, Poitras, NE, Lorey, TS, Chen, X, Gage, JC, Castle, PE, Wentzensen, N, Perkins, RB, Guido, RS, Schiffman, M. Management Consensus Guidelines A Study of Partial Human Papillomavirus Genotyping in Support of the 2019 ASCCP Risk-Based Management

Consensus Guidelines. Journal of Lower Genital Tract Disease: April 2020 - Volume 24 - Issue 2 - p 144-147.

- Waxman, AG, Conageski, C, Silver, M, Tedeschi, C, Stier, EA, Apgar, B, Huh, WK, Wentzensen, N, Massad, LS, Khan, MJ, Mayeaux, EJ, Einstein, MH, Schiffman, M, Guido, RS. ASCCP Colposcopy Standards: How Do We Perform Colposcopy? Implications for Establishing Standards. Journal of Lower Genital Tract Disease: October 2017 - Volume 21 - Issue 4 - p 235-241.

APPENDIX A
Dot Phrase Examples

Colpo Visit History

Here for colposcopy

Screening Hx:

Social Hx:
Tobacco:
Contraception:

Gyn Hx:

HPV Vaccine:

Colposcopy Exam

CONSENTS:
Consented for: exam, colposcopy, biopsies and endocervical curettage.
Discussed risks of discomfort, infection, bleeding and failure to diagnose.
Specific concern for the need for further evaluation/treatment addressed.
Benefits: diagnosis of abnormal cells or cervical cancer in an early stage.

Description of procedure:
A speculum was placed and complete visualization of the cervix and vagina was undertaken without complication. The cervix was visualized completely.
The squamocolumnar junction was _ visualized completely with manipulation. Acetic acid was placed on the cervix as well as the vagina. The green filter was utilized to view any lesions/vessels. Translucent/Dense acetowhite areas with geographic/straight borders were noted at _, _ and _ o'clock. No AV, mosaicism, or punctation noted. Biopsies were taken using the Tischler biopsy forceps at these locations. A vigorous endocervical curetting was performed in the standard manner using a Kevorkian curette, as well as the endocervical cytobrush. Silver Nitrate/Monsels was used to achieve hemostasis and the patient tolerated the procedure well.

IMP:

Colposcopy Plan:
Discussed Impression and HPV infection. Encouraged healthy lifestyle exercise, daily multivitamins and avoiding excessive ETOH, drugs or tobacco.

Will call with pathology results, follow-up to be coordinated at that time.
Post-procedure instructions given. Nothing in vagina for next 2-3 days. Brownish/black discharge is common following the use of Monsel's solution. Call if fever, pelvic pain, or significant bleeding or discharge occurs and will call if any symptoms persist
Patient given opportunity to ask questions and all questions answered. She verbalized understanding and is agreeable to the above plan of care.

Follow up one year
Discussed results with CO who agrees with recommended plan to repeat cotest in one year.

Treatment

Discussed diagnosis with CO with options and recommendations. For HSIL lesions, LEEP is preferred option. Alternatives include expectant management with colpo and cotests q 6 months. Risks and benefits of LEEP reviewed and CO agrees with this plan. Will forward to Screening and Prevention to schedule CO for next available LEEP appt.

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Reviewed 12/6/13 STT
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