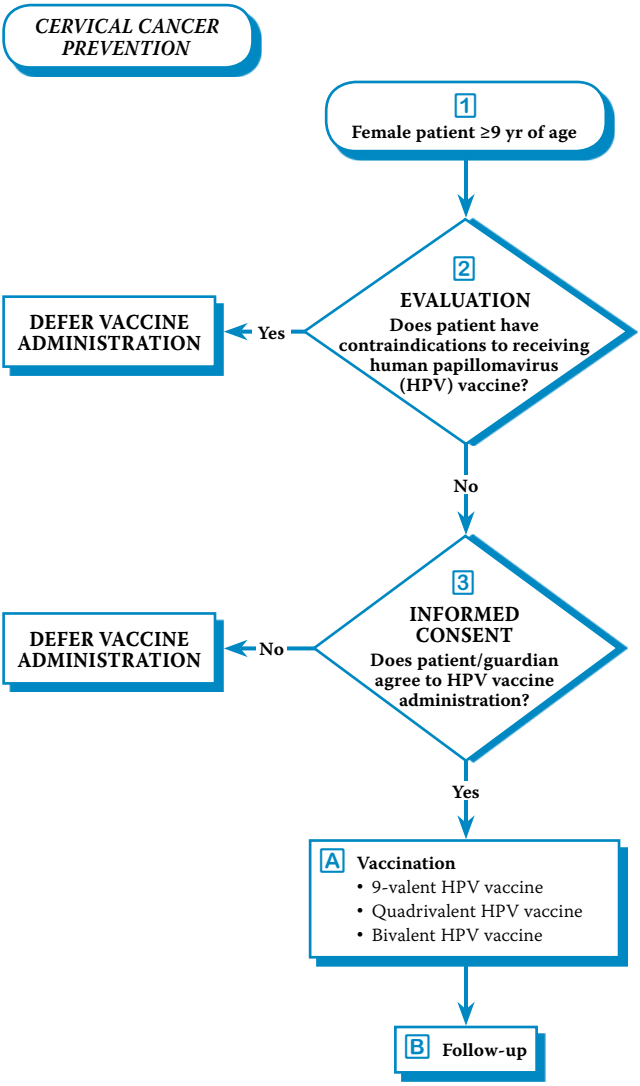
# Cervical Cancer - Prevention & Screening (1 of 11)

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*Specific prescribing information may be found in the latest MIMS.*

## 1 RECOMMENDED RECIPIENTS OF HPV VACCINE

**Routine Vaccination**
- Females, 11-12 yrs of age, are recommended to receive 3 doses of inactivated HPV vaccine
  - Vaccination may be started as early as 9 yrs old
- WHO recommends a 2-dose vaccination schedule with a minimum interval of 6 mth between doses for females <15 yrs old
  - For females ≥15 yrs old and immunocompromised individuals, the 3-dose vaccination schedule is recommended

**Catch-Up Dose**
- Females, 13-26 yrs of age, who have not been previously vaccinated or those who have not completed the doses
- HPV exposure risks should be discussed w/ females 18-45 yrs old
  - Vaccination would provide full benefit to sexually active females who have not been infected by HPV
  - Less benefit is provided to sexually active females who have been infected by one or more HPV types

## 2 EVALUATION

**Contraindications to Use of HPV Vaccine**
- Pregnancy
- Moderate or severe acute illness
  - Vaccination should be deferred until illness subsides
  - Vaccination may be administered to patients w/ minor acute illnesses based on clinical judgement
- Patients w/ history of immediate sensitivity reaction to yeast or to any vaccine component should not receive quadrivalent or 9-valent HPV vaccine
- Patients w/ anaphylactic latex allergy should not receive bivalent HPV vaccine in prefilled syringes

## 3 INFORMED CONSENT

- Vaccination is anticipated to reduce the lifetime risk of cervical cancer by 70-83% as long as Papanicolaou (Pap) screening is continued
- Patients & guardians should be informed regarding:
  - Benefits of the HPV vaccine
  - The risk of cervical cancer associated w/ HPV
  - The sexual transmission of HPV

## A VACCINATION

**Goal of Prophylactic Vaccination**
- Vaccination may reduce the incidence of HPV-related disease (eg cervical, penile, vulvar, vaginal, anal & oropharyngeal cancer & precancerous lesions)
  - It is recommended to vaccinate girls before the start of sexual activity because vaccines do not treat existing HPV infection or HPV-related disease
- HPV vaccines are composed of virus-like particles made up of L1 major capsid proteins & are identical to HPV capsids
- These virus-like particles pose no infectious or oncologic risk because they do not have any viral DNA
  - They also do not have RNA, mercury or egg products
- Clinical trials have shown high efficacy rates for the HPV vaccines

**9-valent HPV Vaccine**
- Contains HPV types 6, 11, 16, & 18 similar to the quadrivalent HPV vaccine but also targets 5 additional cancer causing types 31, 33, 45, 52, & 58
- Protects against genital warts & premalignant lesions & cancers of the cervix, vulva, vagina, & anus
  - Epidemiology studies show that 9-valent HPV vaccine is expected to protect against HPV types that cause about 90% of cervical cancers, >95% of adenocarcinoma in situ, & 75-85% of high-grade cervical intraepithelial neoplasia (CIN 2/3)
- A randomized trial showed noninferior immunogenicity for the HPV types common among the quadrivalent & 9-valent vaccines & high efficacy for the 5 additional HPV types
  - An active comparator-controlled, double-blind, randomized clinical study showed efficacy in preventing HPV 31, 33, 45, 52 & 58-related persistent infection & disease & reduction in the incidence of related Pap test abnormalities, cervical & external genital procedures & cervical definitive therapy procedures
- Individuals who previously received a 3-dose quadrivalent vaccination series may receive 3 doses of 9-valent HPV vaccination; however, there is no Advisory Committee on Immunization Practices (ACIP) recommendation for routine additional 9-valent HPV vaccination of individuals who had completed a bivalent or quadrivalent vaccination series

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## A VACCINATION (CONT'D)

**9-valent HPV Vaccine (Cont'd)**

- According to ACIP, the 9-valent HPV vaccine may be used to continue or complete the vaccination series began w/ a different HPV vaccine product; however, there is no recommendation for additional doses of 9-valent HPV vaccine for individuals who began the series w/ a bivalent or quadrivalent HPV vaccine & had finished the series w/ the 9-valent HPV vaccine
- Available data demonstrate no serious safety concerns in individuals who, after completing a 3-dose series of quadrivalent HPV vaccine, were vaccinated w/ 9-valent HPV vaccine
  - On receiving the 9-valent vaccine, safety profiles are generally similar between the HPV naive person & a person who had completed a 3-dose series

**Quadrivalent HPV Vaccine**

- Contains HPV capsids of type 6, 11, 16 & 18
- Recommended for prevention of cervical cancers & precancers, & genital warts
- Demonstrated to protect against vulvar, vaginal & anal cancers & precancers
- Amorphous aluminum hydroxyphosphate sulfate is the vaccine adjuvant which helps evoke higher immune response
- Studies show 100% efficacy in preventing type-specific HPV infection & cervical intraepithelial neoplasia or CIN 2/3
  - At least 5 yrs follow-up data is available & strong immune memory has been demonstrated
  - Data show cross-protection efficacy in reducing incidence of CIN 2/3 or adenocarcinoma in situ (AIS) caused by 10 other oncogenic types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 & 59)
  - Results of 3 clinical trials suggest that the vaccine appears to prevent reinfection or reactivation of disease w/ vaccine HPV types among sexually active women
  - Safety & clinical efficacy have been confirmed in women 24-45 yrs of age based on a randomized double-blind trial

**Bivalent HPV Vaccine**

- Contains virus-like particles for HPV types 16 & 18
- Formulated w/ a novel, proprietary ASO4 adjuvant system that consists of aluminum & 3-o-desacyl-4-mono-phosphoryl lipid A (MPL)
  - Adjuvant system boosts antibody level by at least 11-fold higher than those from natural infection
- Data from a clinical trial translated to 95.1% efficacy for prevention of persistent cervical HPV infection & follow-up studies showed 100% efficacy for prevention of CIN lesions associated w/ HPV types 16 & 18
  - At the end of 64 mths follow-up, data revealed that >98% of patients were seropositive for HPV types 16 & 18
  - Vaccine efficacy against CIN2+ after 8.4 yrs follow-up was 100% for lesions associated w/ HPV 16/18; antibody concentrations remained ≥10-fold higher than after natural infection
- Based on a randomized controlled study, data showed cross-protection against CIN2+ caused by 12 non-vaccine oncogenic HPV types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 & 68)
  - Individual cross-protection against HPV types 31, 33 & 45 as supported by virological & lesion endpoints
  - Reduced number of colposcopy referrals of 26.3% & cervical excision procedures of 68.8% among subjects w/ no evidence of previous HPV infection
- Vaccine efficacy against CIN3+ irrespective of HPV DNA in lesions was 93.2% in the total vaccinated cohort (TVC)-naive as showed in the end-of-study results from a double-blind, randomized, efficacy study

## B FOLLOW-UP

- Screening for cervical cancer is still recommended because:
  - Only 70% of the virus types associated w/ invasive cervical cancer consist of HPV 16 & 18 types
  - Women may not be entirely protected if they have been infected w/ other HPV types prior to vaccination
  - Duration of protection has not been established & ongoing studies are still being monitored for HPV vaccines
- Screening services should be tied up w/ treatment & post-treatment follow-up
  - Monitoring & evaluation are significant for cervical cancer prevention
- An alteration in prevalence of disease probably will not be evident for another decade or more after the institution of regular prophylactic vaccine
  - At which time, screening recommendations may change

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## CERVICAL CANCER SCREENING RECOMMENDATIONS

| | U.S.[1] | Hong Kong College of Obstetricians & Gynaecologists[2] | Malaysia Ministry of Health[4] | Philippine Cervical Cancer Screening Program[5] | Cervical Screen Singapore[6] | Taiwan Association of Obstetrics & Gynecology[8] | Himpunan Onkologi Ginekologi Indonesia[9] |
|---|---|---|---|---|---|---|---|
| Start Pap test screening in female patients | At 21 yrs of age | 25 yrs of age or around the 1st vaginal intercourse[3] | 20 yrs of age if sexually active | 25 yrs of age | 25 yrs of age in sexually active women; women who have never had sexual intercourse need not undergo screening | 3 yrs after 1st vaginal intercourse or ≥30 yrs of age; women who have never had sexual intercourse need not undergo screening | 20 yrs of age if sexually active |
| Screening interval for women <30 yrs old | Pap test (conventional & liqd-based): every 3 yrs | Every 3 yrs after 2 consecutive normal annual tests.<br>Annually for women at high risk of developing cervical cancer more rapidly | Every 3 yrs after 2 consecutive normal annual tests | Visual inspection of the cervix aided by acetic acid (VIA) once every 5-7 yrs in areas w/o Pap smear capability; Pap smear in all other areas | Every 3 yrs; may start at an early age & at more frequent intervals if high risk factors[7] are present | Annual; If 3 consecutive normal tests, consider test every 3 yrs | Every 3-5 yrs either by Pap smear or VIA |
| Screening interval for women ≥30 yrs old | Cytology screening for women 30-65 yrs old: Every 3 yrs<br>Co-testing (cytology/ HPV): every 5 yrs | | | | | | |
| HPV DNA test for screening | For women 30-65 yrs old: Every 5 yrs along w/ cytology | NA | NA | NA | NA | NA | NA |

NA = No available data

[1]Saslow D, Solomon D, Lawson HW. Castle PE, Cox JT, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin. 2012;62:147-172.

[2]Hong Kong College of Obstetricians and Gynaecologists. HKCOG guidelines: guidelines on the management of abnormal cervical cytology. Revised Nov 2008; Number 3. http://hkcog.obg.cuhk.edu.hk/public/guidelines.asp.

[3]Women <25 yrs w/ high-risk profile may be screened.

[4]Ministry of Health Malaysia, Academy of Medicine. Clinical practice guidelines; management of cervical cancer. Apr 2003. http: // www.moh.gov.my/MohPortal/cpgPublic.jsp.

[5]Domingo EJ, Dy Echo AV. Epidemiology, prevention and treatment of cervical cancer in the Philippines. J Gynecol Oncol. 2009; 20:11-16.

[6]Ministry of Health, Singapore. Cancer screening. http://www.moh.gov.sg/mohcorp/uploadedFiles/Publications/Guidelines/Clinical_Practice_Guidelines/cpg_Cancer%20Screening%20Booklet%20FINAL%20v6.pdf. Jan 2010.

[7]High risk factors: HPV infection, multiple sexual partners, early onset of sexual activity, history of sexually transmitted disease (STD), HIV infection, immunosuppression, cigarette smoking.

[8]2007 recommendations from Taiwan Association of Obstetrics and Gynecology (TAOG).

[9]Himpunan Onkologi Ginekologi Indonesia (HOGI). Pedoman Pelayanan Medik Kanker Ginekologi. Edisi 2. Jakarta: Badan Penerbit FKUI;2011.

## CERVICAL CANCER SCREENING RECOMMENDATIONS (CONT'D)

| | U.S.[1] | Hong Kong College of Obstetricians & Gynaecologists[2] | Malaysia Ministry of Health[3] | Philippine Cervical Cancer Screening Program[4] | Cervical Screen Singapore[6] | Taiwan Association of Obstetrics & Gynecology[7] | Himpunan Onkologi Ginekologi Indonesia[8] |
|---|---|---|---|---|---|---|---|
| When to stop | No screening after adequate negative prior screening (3 consecutive negative cytology results or 2 consecutive negative co-tests w/in past 10 yrs, w/ the most recent test w/ in the past 5 yrs): >65 yrs old | If 3 prior consecutive normal tests: ≥65 yrs old<br>Women >65 yrs old who have never had a Pap test or who request a test should be screened | 65 yrs old | 65 yrs old in women w/ history of consistently normal screens[5] | 69 yrs old if smear taken at 69 yrs old is negative & 2 previous negative tests w/in last 10 yrs.<br>Women >69 yrs old, w/ history of sexual activity & who have never undergone Pap smear should be screened | NA | 70 yrs old in women w/ history of consistently normal screens |

NA = No available data

[1]Saslow D, Solomon D, Lawson HW. Castle PE, Cox JT, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin. 2012;62:147-172.
[2]Hong Kong College of Obstetricians and Gynaecologists. HKCOG guidelines: guidelines on the management of abnormal cervical cytology. Revised Nov 2008; Number 3. http://hkcog.obg.cuhk.edu.hk/public/guidelines.asp.
[3]Ministry of Health Malaysia, Academy of Medicine. Clinical practice guidelines; management of cervical cancer. Apr 2003. http: // www.moh.gov.my/MohPortal/cpgPublic.jsp.
[4]Domingo EJ, Dy Echo AV. Epidemiology, prevention and treatment of cervical cancer in the Philippines. J Gynecol Oncol. 2009; 20:11-16.
[5]Ngelangel CA, Wang EHM. Cancer and the Philippine Cancer Control Program. Jpn J Clin Oncol. 2002;32(suppl 1):S52-S61.
[6]Ministry of Health, Singapore. Cancer screening. http://www.moh.gov.sg/mohcorp/uploadedFiles/Publications/Guidelines/Clinical_Practice_Guidelines/cpg_Cancer%20Screening%20Booklet%20FINAL%20v6.pdf. Jan 2010.
[7]2007 recommendations from Taiwan Association of Obstetrics and Gynecology (TAOG).
[8]Himpunan Onkologi Ginekologi Indonesia (HOGI). Pedoman Pelayanan Medik Kanker Ginekologi. Edisi 2. Jakarta: Badan Penerbit FKUI;2011.

## CERVICAL CANCER PREVENTION

- Mortality due to cervical cancer can be reduced by prevention, early detection & treatment
  - Patients w/ early changes of pre-cancer are asymptomatic; screening is needed to diagnose a pre-cancerous lesion
- Cervical cancer screening should be done at least once in women 30-49 yrs old; <30 yrs old if high risk for CIN2+
- Visual inspection techniques are less specific than Pap smear but are more sensitive in detecting pre-invasive lesions
  - Can be used as cervical cancer screening tools in low-resource settings or even in well-equipped health centers & cancer centers

**Pap Smear Test**

- Consists of microscopic exam of exfoliated cervical cells
- Cytology screening w/ the Pap smear test is still the most effective strategy to detect cervical cancer & precursor lesions
  - Conventional cytology & liquid-based cytology showed similar sensitivity & specificity in detecting CIN 2 or more severe diagnoses (CIN2+)
  - Effectiveness is increased when part of an organized screening program
- Reported sensitivity & specificity vary widely
  - Factors influencing accuracy include small lesion size, inadequate sampling & obscuring blood & debris
- Liquid-based preparations are now available
  - Improve specimen adequacy & cellular sampling, distribute cells evenly on the slide, decrease cell overlapping & obscuring background, & provide residual material for HPV DNA testing
- The majority of women developing invasive cervical cancer have never been screened or have not been screened adequately
- Specific recommendations on target populations & screening frequency will differ between countries
  - The recommendations attempt to balance the risk of false-negative results against potential for overtreatment of clinically insignificant lesions that occur in transient disease

**HPV DNA Testing**

- A molecular test for high-risk HPV
- Addition of HPV testing in cervical cancer screening guidelines may increase disease detection as well as length of screening intervals
  - Less specific when used alone & may identify clinically insignificant disease which may regress spontaneously
- Greater sensitivity but lower specificity in detecting CIN 2/3

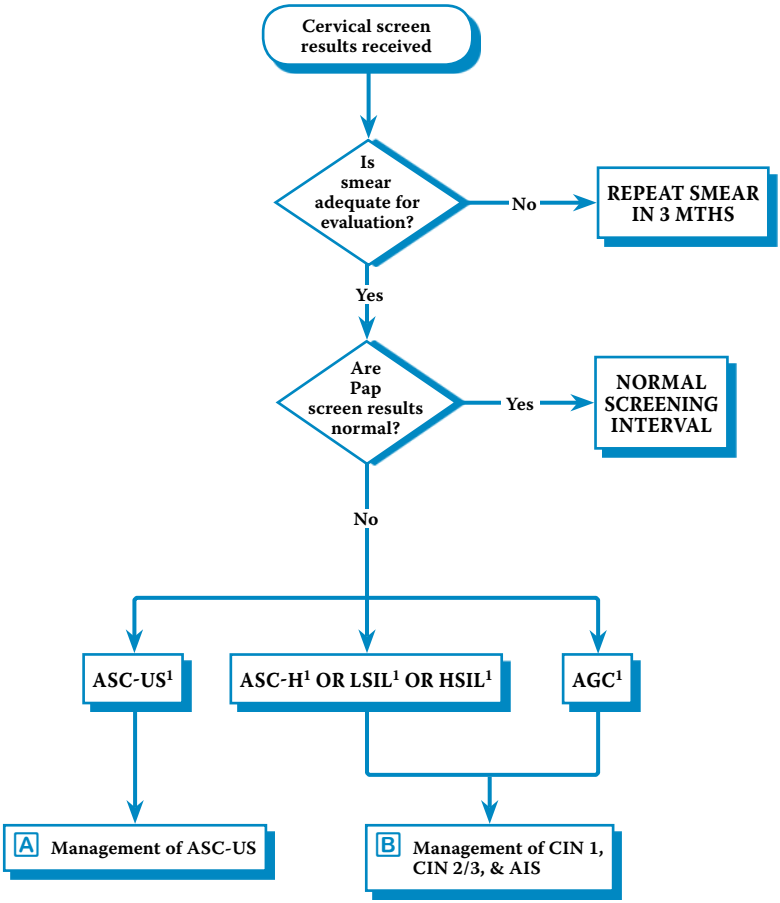
**Visual Inspection w/ Acetic Acid (VIA)**

- Naked-eye inspection of the cervix washed w/ 3-5% acetic acid
- Test is positive after detecting any acetowhite areas (low-threshold) or well-defined, opaque, acetowhite lesions close to or touching the squamocolumnar junction (high-threshold)
- Has a positive predictive value comparable to Pap smear but is more likely to achieve earlier diagnosis, follow-up, & treatment than cytology-based screening

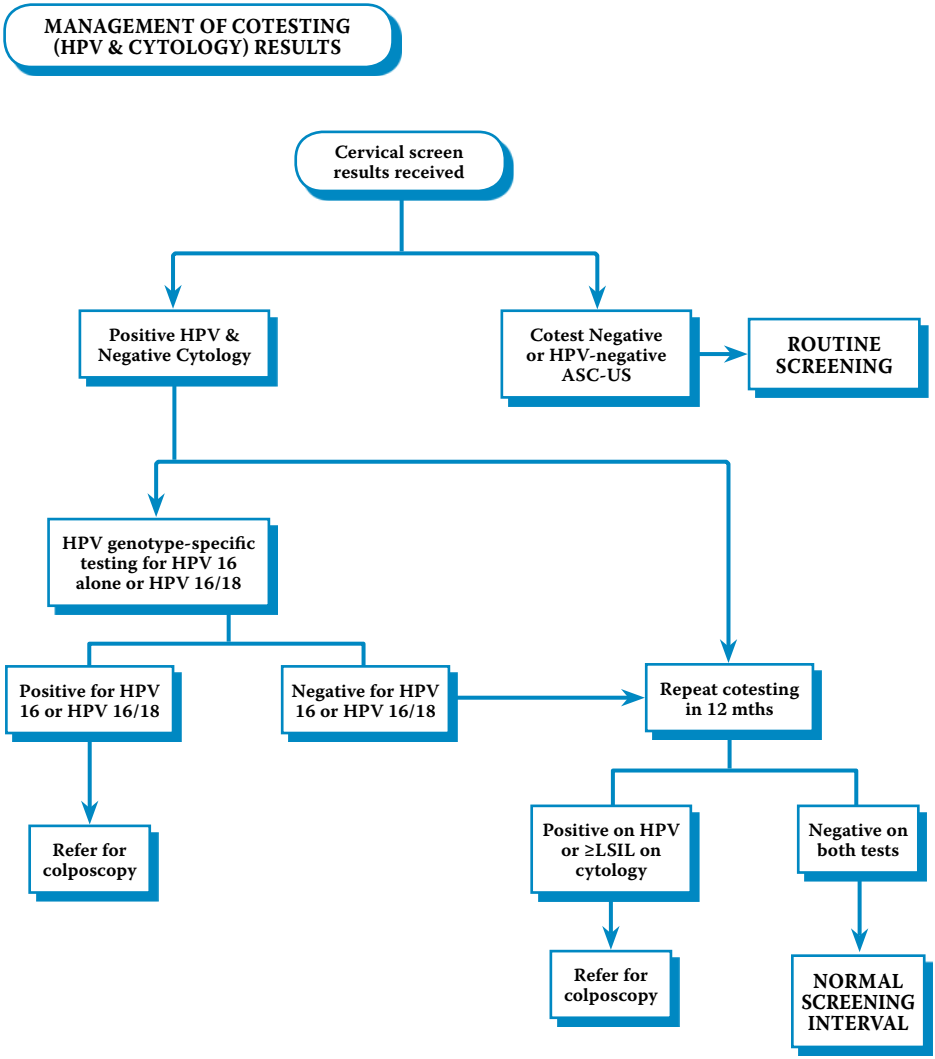
**Visual Inspection w/ Lugol's Iodine (VILI)**

- Naked-eye inspection of the cervix w/ Lugol's iodine test is positive upon detection of yellow iodine nonuptake areas in the transformation zone close to or touching the squamocolumnar junction

## MANAGEMENT OF CERVICAL CYTOLOGY RESULTS




[1]See table: The 2001 Bethesda System


MANAGEMENT OF COTESTING (HPV & CYTOLOGY) RESULTS
Cervical screen results received
Positive HPV & Negative Cytology
Cotest Negative or HPV-negative ASC-US
ROUTINE SCREENING
HPV genotype-specific testing for HPV 16 alone or HPV 16/18
Positive for HPV 16 or HPV 16/18
Negative for HPV 16 or HPV 16/18
Repeat cotesting in 12 mths
Refer for colposcopy
Positive on HPV or ≥LSIL on cytology
Negative on both tests
Refer for colposcopy
NORMAL SCREENING INTERVAL

## THE 2001 BETHESDA SYSTEM

**Interpretation of Epithelial Cell Abnormalities**

| | |
|---|---|
| **Squamous cell** | • Atypical squamous cells (ASC)<br>- Of undetermined significance (ASC-US)<br>- Cannot exclude HSIL (ASC-H)<br>• Low grade squamous intraepithelial lesion (LSIL) encompassing HPV/mild dysplasia/CIN 1<br>• High grade squamous intraepithelial lesion (HSIL) encompassing moderate & severe dysplasia, carcinoma in situ (CIS); CIN 2 & CIN 3<br>• Squamous cell carcinoma |
| **Glandular cell** | • Atypical glandular cells (AGC)<br>- Endocervical cells<br>- Endometrial cells<br>- Glandular cells<br>• Atypical<br>- Endocervical cells, favor neoplastic<br>- Glandular cells, favor neoplastic<br>- Endocervical adenocarcinoma in situ<br>• Adenocarcinoma<br>- Endocervical<br>- Endometrial<br>- Extrauterine<br>- Not otherwise specified (NOS) |

**Adapted from:** Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002;287:2114–2119.

## ABLATIVE & EXCISIONAL MODALITIES

- Choice of therapeutic option depends on patient's age, parity, child-bearing desire, prior cytology & treatment history & history of follow-up, operator experience, & nonvisualization of the transformation zone
- Both modalities have similar efficacy w/ respect to eliminating CIN & decreasing the risk of developing invasive cervical cancer
  - VIA-positive women are treated w/ cryotherapy or, if ineligible, LEEP
- May have an adverse effect on future pregnancies
- Treatment failure rate has been varied from 1-25%, usually occurs w/in 2 yrs after treatment
- Patients treated for CIN 2/3 have an increased risk of developing invasive cervical cancer w/ 56 per 100,000 for at least 20 yrs posttreatment; hence, follow-up is recommended

**Ablative Methods**

- Eg cryotherapy, laser ablation, electrofulguration, cold coagulation
  - Cryotherapy can be performed by trained & competent healthcare providers at all levels, eg doctors, nurses, midwives

**Excisional Methods**

- Eg cold knife conization (CKC), loop electrosurgical excision procedure (LEEP)/large loop excision of the transformation zone (LLETZ), laser conization, electrosurgical needle conization
  - Should only be performed by a trained health personnel, eg gynecologist

## A MANAGEMENT OF ASC-US

**HPV DNA Testing**

- Test for high-risk viruses only
- Can easily be done as reflex testing after liquid-based cytology
- Resumption of screening protocol after a negative result
- Refer patient for colposcopy & biopsy after a positive result

**Repeat Cytology**

- Repeat cervical cytology (Pap smear) after 12 mths
- If repeat smear is negative, repeat cytology in 3 yrs
- If positive for ≥ASC-US, refer for colposcopy

## B MANAGEMENT OF CIN 1, CIN 2/3, & AIS

**CIN 1 Preceded by ASC-US, ASC-H or LSIL Cytology**

- Repeat cervical cytology every 6-12 mths
  - After 2 negative smears, proceed w/ normal screening interval
  - If cytology is ≥ASC-US, colposcopy is recommended
- Do HPV DNA testing for high-risk types after 12 mths
  - If negative, resume normal screening interval
  - If positive, colposcopy is recommended

**Follow-up**

- If CIN 1 persists for at least 2 yrs, continued follow-up or treatment is recommended
- If treatment is selected, may proceed w/ either excision or ablation
  - Diagnostic excision is recommended for the following cases:
    - Colposcopic examination is found to be unsatisfactory
    - Endocervical sampling contains CIN
    - Previously-treated patient

**CIN 1 Preceded by HSIL or Atypical Glandular Cells-Not Otherwise Specified (AGC-NOS) Cytology**

- The following are recommended for CIN 1 preceded by HSIL or AGC-NOS cytology (w/ satisfactory colposcopic examination & negative endocervical sampling):
  - Diagnostic excisional procedure
  - Observation w/ colposcopy & cytology at 6-mth intervals for 1 yr
- Review the histological, cytological, & colposcopy findings
  - Do recommended treatment for revised interpretation

**Observation**

- For patients w/ repeated HSIL or AGC-NOS cytology results at 6- or 12-mth visit, diagnostic excision is preferred
- Routine cytological screening is recommended if after 1 yr of observation it resulted to 2 consecutive negative findings for intraepithelial lesion or malignancy

**Diagnostic Excisional Procedure**

- Recommended for patients w/ unsatisfactory colposcopic examination

**CIN 2/3**

- For patients w/ satisfactory colposcopy, excisional procedure & ablation are acceptable
- For patients w/ unsatisfactory colposcopy, excisional procedure is recommended
- For patients w/ recurrent CIN 2/3, diagnostic excisional procedure is an option

**Follow-up**

- May include cytology alone, combined cytology & colposcopy at 6 mths, HPV DNA testing at 6- to 12-mth intervals, or cotesting at 12 & 24 mths
- For patients w/ positive HPV DNA or repeat cytology result of ≥ASC-US, colposcopy w/ endocervical sampling is recommended
- For patients w/ negative HPV DNA or if 2 repeat cytology results are negative for intraepithelial lesion or malignancy, proceed w/ routine screening
- If CIN 2/3 is identified at the margins after diagnostic excisional procedure or present in endocervical sample, reassessment after 4-6 mths posttreatment is recommended using cytology w/ endocervical sampling
  - Repeat diagnostic excisional procedure is adequate while hysterectomy is preferred if excision is not possible
- For recurrent or persistent CIN 2/3, either repeat diagnostic excisional procedure or hysterectomy is recommended

**Adenocarcinoma-in-situ (AIS)**

- Prior to any subsequent treatments, excisional biopsy is required in all patients w/ AIS
- Studies have shown that in majority of AIS patients, diagnostic excisional procedure is curative
  - Failure rate ranges from 0-9%
- One of the most useful predictors of residual disease is the margin status
  - Another predictor is endocervical sampling at the time of biopsy
- If family is complete, total hysterectomy can be an option
- If future fertility is desired, conservative management is recommended
  - If the margins of the specimen or endocervical sampling contains CIN or AIS, re-excision is preferred to increase the probability of complete excision
    - Reevaluation is recommended at 6 mths using a combination of cytology, HPV DNA testing, & colposcopy w/ endocervical sampling
  - Long-term follow-up is strongly suggested w/ negative margins

**Microinvasion/Cancer**

- Refer to Cervical Cancer - Treatment Disease Management Chart

# Dosage Guidelines

| VACCINES, ANTISERA & IMMUNOLOGICALS | | |
|---|---|---|
| **Drug** | **Dosage** | **Remarks** |
| 9-valent human papillomavirus (types 6, 11, 16, 18, 31, 33, 45, 52, 58) recombinant vaccine | **Females >9 yr:**<br>0.5 mL IM x 3 doses at 0, 2 & 6 mth | **Adverse Reactions**<br>• Inj site reactions: Pain, swelling, erythema, pruritus<br>• Systemic reactions: Headache, dizziness, fever, nausea<br>**Special Instructions**<br>• Inj IM into the deltoid region of the upper arm or in the higher anterolateral area of the thigh<br>• Use w/ caution in patients w/ thrombocytopenia or any coagulation disorder |
| Bivalent human papillomavirus (types 16 & 18) recombinant, ASO4 adjuvanted vaccine | **Females 9-14 yr:**<br>0.5 mL IM x 2 doses at 0 & 6 mth<br>***or***<br>0.5 mL IM x 3 doses at 0, 1 & 6 mth<br>**Females ≥15 yr:**<br>0.5 mL IM x 3 doses at 0, 1 & 6 mth | **Adverse Reactions**<br>• Inj site reactions: Pain, swelling, erythema<br>• Systemic reactions: Fever, headache, N/V, diarrhea, abdominal pain, pruritus, urticaria, arthralgia<br>**Special Instructions**<br>• Inj IM into the deltoid region of the upper arm or in the higher anterolateral area of the thigh<br>• For the 2-dose schedule, if the 2nd dose is administered before the 5th mth after the 1st dose, a 3rd dose should always be administered<br>• Use w/ caution in patients w/ impaired immune response, thrombocytopenia or any coagulation disorder |
| Quadrivalent human papilloma-virus (types 6, 11, 16, 18) recombinant vaccine | **Females 9-13 yr:**<br>0.5 mL IM x 2 doses at 0 & 6 mth<br>***or***<br>0.5 mL IM x 3 doses at 0, 2 & 6 mth<br>**Females ≥14 yr:**<br>0.5 mL IM x 3 doses at 0, 2 & 6 mth | **Adverse Reactions**<br>• Inj site reactions: Mild-moderate pain, swelling, erythema, pruritus, hematoma<br>• Systemic reactions: Fever, dizziness, headache, nausea<br>**Special Instructions**<br>• Inj IM into the deltoid region of the upper arm or in the higher anterolateral area of the thigh<br>• For the 2-dose schedule, if the 2nd vaccine dose is administered earlier than 6 mths after the 1st dose, a 3rd dose should always be administered<br>• Use w/ caution in patients w/ impaired immune response, thrombocytopenia or any coagulation disorder |

***All dosage recommendations are for non-elderly adults w/ normal renal & hepatic function unless otherwise stated.***
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*Products listed above may not be mentioned in the disease management chart but have been placed here based on indications listed in regional manufacturers' product information.*

*Specific prescribing information may be found in the latest MIMS.*

*Please see the end of this section for the reference list.*