

2001 Consensus Guidelines for the Management of Women With Cervical Cytological Abnormalities

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EACH YEAR APPROXIMATELY 50 million women undergo Papanicolaou testing in the United States.¹ Of these, approximately 3.5 million (7%) are diagnosed with a cytological abnormality requiring additional follow-up or evaluation.² Determining which women with cytological abnormalities are at risk for significant cervical disease, performing appropriate diagnostic workups, and treating cancer precursors present a major public health challenge.

There are a number of reasons why comprehensive, evidence-based guidelines are needed for the management of women with cervical cytological abnormalities. One reason is that a National Cancer Institute workshop recently revised the criteria used by cytologists to render certain cytological interpretations, as well as the terminology used for reporting cervical cytology results (ie, the Bethesda System).³ Other reasons include a better understanding of the pathogenesis and natural history of human papillomavirus (HPV) and cervical cancer precursors, and the availabil-

See also pp 2114 and 2140.

Objective To provide evidence-based consensus guidelines for the management of women with cervical cytological abnormalities and cervical cancer precursors.

Participants A panel of 121 experts in the diagnosis and management of cervical cancer precursors, including representatives from 29 professional organizations, federal agencies, and national and international health organizations, were invited to participate in a consensus conference sponsored by the American Society for Colposcopy and Cervical Pathology (ASCCP).

Evidence and Consensus Process Guidelines for the management of women with cervical cytological abnormalities were developed through a multistep process. Starting 6 months before the conference, working groups developed draft management guidelines based on formal literature reviews of English-language articles published in 1988-2001, as well as input from the professional community at large, obtained using interactive Internet-based bulletin boards. On September 6-8, 2001, the ASCCP Consensus Conference was held in Bethesda, Md. Guidelines with supporting evidence were presented and underwent discussion, revision, and voting.

Conclusions Management of women with atypical squamous cells (ASC) depends on whether the Papanicolaou test is subcategorized as of undetermined significance (ASC-US) or as cannot exclude high-grade squamous intraepithelial lesion (HSIL) (ASC-H). Women with ASC-US should be managed using a program of 2 repeat cytology tests, immediate colposcopy, or DNA testing for high-risk types of human papillomavirus (HPV). Testing for HPV DNA is the preferred approach when liquid-based cytology is used for screening. In most instances, women with ASC-H, low-grade squamous intraepithelial lesion, HSIL, and atypical glandular cells should be referred for immediate colposcopic evaluation.

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ity of data from the National Cancer Institute's randomized Atypical Squamous Cells of Undetermined Significance/Low-grade Squamous Intraepithelial Lesion (ASCUS/LSIL) Triage Study (ALTS) (D. Solomon, MD, written communication, September 6-8, 2001). Moreover, existing guidelines

were developed before sensitive molecular methods for detecting high-risk types of HPV and liquid-based cytology methods became widely available. Data are now available suggesting that these new technologies, when used together, are attractive alternatives to older approaches for managing women with cer-

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tain types of cytological abnormalities (D. Solomon, MD, written communication, September 6-8, 2001).^{4,5} As a result, there is increasing pressure on clinicians to begin using these technologies and a need for clear, unbiased guidelines delineating their best use.

From September 6 through 8, 2001, the American Society for Colposcopy and Cervical Pathology (ASCCP) hosted a consensus conference in Bethesda, Md, to develop evidence-based guidelines for the management of women with cervical cytological abnormalities and cervical cancer precursors. To ensure that the guidelines reflect the needs of the diverse array of clinicians providing cervical cancer screening, the consensus conference included representatives from 29 participating professional and health organizations and federal agencies. Input from the professional community at large was obtained using a novel approach that incorporated Internet-based discussion groups. This report provides a summary of the key recommendations from that meeting with respect to managing cytological abnormalities. Comprehensive discussion of the data supporting the recommendations, as well as guidelines for the management of biopsy-confirmed cervical cancer precursors, will be posted on the ASCCP Web site (<http://www.asccp.org>) when available.

GUIDELINE-DEVELOPMENT PROCEDURES

The consensus conference included 121 invited participants. Six months before the conference, working groups began developing draft guidelines through a multistep process. Open Internet bulletin boards were used for discussing key issues and MEDLINE searches of English-language articles published between 1988 and 2001 were performed. Abstracts of articles were reviewed to determine their relevance; relevant articles were reviewed to determine whether they fulfilled a minimum, predetermined scientific standard. In instances in which published data pertaining to a key issue were missing, scant, or conflicting, expert opinions ex-

pressed on the Internet bulletin boards or by members of the working group were used to help formulate the guidelines. Draft guidelines were posted on the Internet bulletin boards for public comment. At the consensus conference, guidelines were discussed together with the supporting data, revised if necessary, and voted upon. All guidelines were accepted by a minimum of a two-thirds majority vote.

Each guideline is rated using a 2-part rating system (TABLE 1).^{6,7} The letters A through E are used to indicate the "strength of recommendation" for or against the use of a particular option. Determination of the level of the evidence in the "strength of recommendation" (ie, good, moderate, or insufficient) was based on consideration of several criteria, including potential for harm if an intervention did not take place, the potential complications associated with an intervention, as well as the "quality of evidence." Therefore an exact correlation does not exist between the "quality of evidence" and the "strength of a recom-

mendation." Roman numerals I through III are used to indicate the "quality of evidence." In addition, the terms "recommended," "preferred," "acceptable," and "unacceptable" were specifically defined at the consensus conference. These terms were used because in some clinical situations there are several treatment options that have good evidence of efficacy that supports clinical use; however, based on less-defined issues such as costs or patient convenience, one method might be "preferred."

2001 CONSENSUS GUIDELINES

The 2001 Consensus Guidelines are designed to assist in the management of women with cytological abnormalities and cervical cancer precursors. It is important to recognize that in many instances the amount and quality of data available to inform the decision-making process were limited. In such cases, guidelines had to be developed from a review of studies incorporating small numbers of cases or from consensus expert opinion. It is also impor-

Table 1. Rating System for Recommendations

Rating	Criteria
Strength of Recommendation*	
A	Good evidence for efficacy and substantial clinical benefit support recommendation for use
B	Moderate evidence for efficacy or only limited clinical benefit supports recommendation for use
C	Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendations may be made on other grounds
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use
Quality of Evidence*	
I	Evidence from at least 1 randomized controlled trial
II	Evidence from at least 1 clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than 1 center), or from multiple time-series studies, or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
Terminology†	
Recommended	Good data to support use when only 1 option is available
Preferred	Option is the best (or one of the best) when there are multiple other options
Acceptable	One of multiple options when either there are data indicating that another approach is superior or when there are no data to favor any single option
Unacceptable	Good data against use

*Modified from Kish⁷ and from Gross et al.^{6,9}

†The assignment of these terms represents an opinion or vote by the consensus conference, and the assignment is not directly linked to the "strength of evidence" or the "quality of evidence."

tant to recognize that these guidelines should never be a substitute for clinical judgment. Clinicians need to practice clinical discretion when applying a guideline to an individual patient since it is impossible to develop guidelines that apply to all situations.

The guidelines use the 2001 Bethesda System for cytological classification that uses the terms LSIL and HSIL to refer to cervical cancer precursors.³ We have adopted a 2-tiered terminology for the histopathological classification of cervical intraepithelial neoplasia (CIN): CIN 1 denotes low-grade precursors and CIN 2,3 denotes high-grade precursors.⁸ Detailed algorithms describing the 2001 Consensus Guidelines, and a glossary of terms used in the guidelines, are available at the ASCCP Web site (glossary also available at <http://jama.ama-assn.org>).

ATYPICAL SQUAMOUS CELLS

The 2001 Bethesda System subdivides atypical squamous cells (ASC) into 2 categories: atypical squamous cells of undetermined significance (ASC-US) and atypical squamous cells, cannot exclude HSIL (ASC-H).³ Several considerations underlie the consensus guidelines for the management of ASC. First, even among expert cytologists, the interpretation of a cervical cytology result as ASC is poorly reproducible.⁹⁻¹¹ Second, a woman with a cervical cytology result interpreted as ASC has a 5% to 17% chance of having CIN 2,3 confirmed by biopsy, while CIN 2,3 is identified in 24% to 94% of those with ASC-H.^{5,12-20} However, the risk of invasive cervical cancer in a woman with ASC is

low (approximately 0.1% to 0.2%).^{21,22} These considerations suggest that a woman with ASC requires some form of additional workup or follow-up, but that consideration should be given to preventing unnecessary inconvenience, anxiety, cost, and discomfort. Immunosuppressed women with ASC are at increased risk for CIN 2,3, and high-risk types of HPV are frequently detected in immunosuppressed women, suggesting that these women require special consideration.^{23,24} Conversely, postmenopausal women with ASC appear to be at lower risk for CIN 2,3 than premenopausal women.^{14,25,26}

Approaches to Managing Women With ASC

Repeating cervical cytological testing at specified intervals, performing immediate colposcopy, HPV DNA testing for high-risk types, or combining a single repeat cervical cytological test with another adjunctive method are all widely used in the United States for managing women with ASC. Each of these approaches has advantages and disadvantages.

Although repeat cytological testing is widely used for managing women with ASC, the sensitivity of a single repeat test for detecting CIN 2,3 is relatively low (0.67-0.85) (TABLE 2).^{4,5,12,27-30} To compensate for this, previous guidelines have recommended that testing be repeated at specified intervals until a patient has several consecutive "negative for squamous intraepithelial lesion or malignancy" results before returning to routine screening.³¹⁻³³ The most appropriate

threshold for referring women for colposcopy has been evaluated in several studies and appears to be a repeat cytology result of ASC or greater.^{12,34,35} Referral thresholds of LSIL and HSIL miss many women with biopsy-confirmed CIN 2,3. There is limited information available on key parameters (eg, timing of the repeat test, number of repeats necessary) needed to design a program of repeat cytological testing. Repeating cervical cytological testing has several disadvantages compared with other management options. It can delay the diagnosis of CIN 2,3 or cervical cancer and, even in populations with good access to health care, adherence to recommendations becomes a problem for any follow-up that requires multiple visits.

The advantage of colposcopy for the evaluation of women with ASC is that it immediately informs both the woman and the clinician of the presence or absence of significant disease. A meta-analysis of the performance of colposcopy reported that the weighted mean sensitivity for distinguishing normal cervical tissue from abnormal tissue by colposcopy was 0.96 and the weighted mean specificity was 0.48.³⁶ However, since most published studies have been performed by expert colposcopists and have not uniformly obtained histological samples from normal-appearing tissue, the sensitivity of colposcopy in the published literature may be higher than would be observed in routine clinical practice. The disadvantages of colposcopy are that many women consider the procedure to be uncomfortable, referral for colposcopy may raise false con-

Table 2. HPV DNA Testing for the Management of Women With ASC*

Source, y	Patients, No.	Repeat Cytology		HPV DNA Testing	
		Sensitivity (95% CI)	% Referred (95% CI)	Sensitivity (95% CI)	% Referred (95% CI)
Ferris et al, ²⁸ 1998; Ferris et al, ³⁵ 1998†	144	0.70 (0.42-0.98)	56 (49-64)	0.89 (0.69-1.00)	43 (35-51)
Manos et al, ⁴ 1999†	995	0.76 (0.65-0.87)	38 (35-41)	0.89 (0.81-0.97)	39 (36-42)
Bergeron et al, ²⁷ 2000	111	0.67 (0.50-1.00)	32 (23-41)	0.83 (0.62-1.00)	43 (34-52)
Lin et al, ²⁹ 2000	74	NA	NA	1.00	53 (42-64)
Shlay et al, ³⁰ 2000	200	NA	NA	0.93 (0.81-1.00)	31 (25-37)
Solomon et al, ¹² †	2324	0.85 (0.81-0.89)	59 (57-61)	0.96 (0.94-0.98)	56 (54-58)

*DNA testing for high-risk types of human papillomavirus (HPV) was performed using the Hybrid Capture II HPV DNA Assay (Digene Inc, Gaithersburg, Md). ASC indicates atypical squamous cells; CI, confidence interval; and NA, not applicable.

†HPV DNA testing was performed from liquid-based cytology specimens.

cerns about cervical disease, it is expensive, and it has the potential for overdiagnosis and overtreatment.

Several large studies have evaluated the performance of DNA testing using commercially available, highly sensitive molecular methods to detect high-risk types of HPV for the management of women with ASC (Table 2). The sensitivity of HPV DNA testing for the detection of biopsy-confirmed CIN 2,3 in women with ASC is 0.83 to 1.0 and is higher than the sensitivity of a single repeat cervical cytological test (conventional or liquid-based) in all of the reported series. The negative predictive value of DNA testing for high-risk types of HPV is generally reported to be 0.98 or greater. Between 31% and 60% of all women with ASC will have high-risk types of HPV identified, but the proportion with high-risk HPV decreases with increasing age.^{5,37} It is not known how to manage women who test positive for high-risk HPV DNA, but who turn out not to have CIN.

Requiring women to return for HPV DNA testing or repeat cervical cytological testing is inconvenient and would be expected to increase cost. "Reflex" HPV DNA testing is an alternate approach, in which the original liquid-based cytology specimens or a sample co-collected for HPV DNA testing at the initial screening visit is tested for HPV DNA only if an ASC-US result is obtained.⁵ Reflex HPV DNA testing offers significant advantages since women do not need an additional clinical examination for specimen collection, and 40% to 60% of women will be spared a colposcopic examination. Moreover, women testing negative for HPV DNA can rapidly be assured that they do not have a significant lesion.

Recommended Management of Women With ASC-US

A program of repeat cervical cytological testing, colposcopy, or DNA testing for high-risk types of HPV are all acceptable methods for managing women with ASC-US (rating AI). When liquid-based cytology is used or when cocollection for HPV DNA testing can

be done, reflex HPV DNA testing is the preferred approach (AI).

DNA testing for high-risk types of HPV should be performed using a sensitive molecular test, and all women who test positive for HPV DNA should be referred for colposcopic evaluation (AII). Women with ASC-US who test negative for high-risk HPV DNA can be followed up with repeat cytological testing at 12 months (BII). Acceptable management options for women who are positive for high-risk types of HPV, but who do not have biopsy-confirmed CIN, include follow-up with repeat cytological testing at 6 and 12 months with referral back to colposcopy if a result of ASC-US or greater is obtained, or HPV DNA testing at 12 months with referral back to colposcopy of all HPV DNA-positive women (BII).

When a program of repeat cervical cytological testing is used, women with ASC-US should undergo repeat cytological testing (either conventional or liquid-based) at 4- to 6-month intervals until 2 consecutive "negative for intraepithelial lesion or malignancy" results are obtained (AII). Women diagnosed with ASC-US or greater cytological abnormality on the repeat tests should be referred for colposcopy (AII). After 2 repeat "negative for intraepithelial lesion or malignancy" cytology tests are obtained, women can be returned to routine cytological screening programs (AII).

When immediate colposcopy is used to manage women with ASC-US, women who are referred for colposcopy and found not to have CIN should be followed up with repeat cytological testing at 12 months (BII). Women with ASC-US who are referred for colposcopy and found to have biopsy-confirmed CIN should be managed according to the 2001 Consensus Guidelines for the Management of Women With Cervical Histological Abnormalities (Wright et al, unpublished data, 2001).

Because of the potential for overtreatment, diagnostic excisional procedures such as the loop electrosurgical excision procedure (LEEP) should not routinely be used to treat women

with ASC in the absence of biopsy-confirmed CIN (EII).

ASC-US in Special Circumstances

Postmenopausal Women. Providing a course of intravaginal estrogen followed by a repeat cervical cytology test obtained approximately a week after completing the regimen is an acceptable option for women with ASC-US who have clinical or cytological evidence of atrophy and no contraindications to using intravaginal estrogen (CIII). If the repeat test result is "negative for intraepithelial lesion or malignancy," the test should be repeated in 4 to 6 months. If both repeat cytological test results are "negative for intraepithelial lesion or malignancy," the patient can return to routine cytological screening, whereas if either repeat test result is reported as ASC-US or greater, the patient should be referred for colposcopy (AII).

Immunosuppressed Women. Referral for colposcopy is recommended for all immunosuppressed patients with ASC-US (BII). This includes all women infected with human immunodeficiency virus (HIV), irrespective of CD4 cell count, HIV viral load, or antiretroviral therapy.

Pregnant Women. It is recommended that pregnant women with ASC-US be managed in the same manner as nonpregnant women (BIII).

Recommended Management of Women With ASC-H

The recommended management of women with ASC-H obtained using either conventional or liquid-based cervical cytology is referral for colposcopic evaluation (AII).

When no lesion is identified after colposcopy in women with ASC-H, it is recommended that, when possible, a review of the cytology, colposcopy, and histology results be performed (CIII). If the review yields a revised interpretation, management should follow guidelines for the revised interpretation; if a cytological interpretation of ASC-H is upheld, cytological follow-up at 6 and 12 months or HPV DNA testing at 12 months is acceptable (CIII). Women

who are found to have ASC or greater on their repeat cervical cytology tests or who subsequently test positive for high-risk HPV DNA should be referred for colposcopy.

ATYPICAL GLANDULAR CELLS AND ADENOCARCINOMA IN SITU

The 2001 Bethesda System classifies glandular cell abnormalities less severe than adenocarcinoma into 3 categories³: atypical glandular cells, either endocervical, endometrial, or “glandular cells” not otherwise specified (AGC NOS); atypical glandular cells, either endocervical or “glandular cells” favor neoplasia (AGC “favor neoplasia”); and endocervical adenocarcinoma in situ (AIS).

The AGC category is associated with a substantially greater risk for cervical neoplasia than the ASC or LSIL categories.³⁸ Various studies have found that 9% to 54% of women with AGC have biopsy-confirmed CIN, 0% to 8% have biopsy-confirmed AIS, and less than 1% to 9% have invasive carcinoma.^{21,38-44} The 2001 Bethesda System separated AGC NOS from AGC “favor neoplasia” because it was believed that these 2 categories represent women at different risk for having significant disease, either squamous or glandular. Although the risk of having a high-grade lesion in various studies overlap, studies from individual centers have usually reported a higher risk among women with AGC “favor neoplasia” than among those with AGC NOS. Biopsy-confirmed high-grade lesions including CIN 2,3, AIS, or invasive cancer have been found in 9% to 41% of women with AGC NOS compared with 27% to 96% of women with AGC “favor neoplasia.”^{21,38-48} The cytological interpretation of AIS is associated with a very high risk of a woman having either AIS (48%-69%) or invasive cervical adenocarcinoma (38%).^{49,50}

Approaches to Managing Women With AGC and AIS

Initial Workup and Evaluation. All 3 methods (ie, repeat cytology, colposcopy, and endocervical sampling) tra-

ditionally used to evaluate women with AGC or AIS have limitations. Screening cervical cytology has a sensitivity of only 50% to 72% for identifying glandular neoplasia, and CIN is the most common form of neoplasia identified in women with a cytological result of AGC.^{38-44,51-54} Moreover, repeat cervical cytological testing has been shown to be less sensitive than colposcopy for detecting CIN 2,3 and glandular lesions in women with AGC.⁵² This supports the inclusion of colposcopy in the workup of women with AGC. However, many cases of biopsy-confirmed AIS have had no observed colposcopic abnormalities, and even combinations of cytological testing and colposcopy can miss small endocervical adenocarcinomas and AIS localized in the endocervical canal.⁵⁵ Although the sensitivity of endocervical sampling for the detection of glandular neoplasia localized in the endocervical canal is not well defined, many cases of biopsy-confirmed AIS have had no colposcopic abnormalities and in some series endocervical sampling has detected glandular neoplasia that was missed at colposcopy.^{52,55-57} Age is a key factor in determining the frequency and type of neoplasia found in women with AGC. There is a higher risk of CIN 2,3 and AIS in premenopausal women compared with postmenopausal women, and premenopausal women with AGC have a lower risk of endometrial hyperplasia or cancer.^{44,58-60} Approximately half of women with biopsy-confirmed AIS have a coexisting squamous abnormality and therefore the presence of a coexisting squamous abnormality does not change the management of women with AGC or AIS.⁶¹⁻⁶³

Subsequent Workup and Evaluation of Women in Whom Lesions Are Not Identified. Because of the poor sensitivity of colposcopy, cytology, and endocervical sampling for detecting glandular abnormalities, women with AGC who do not have cervical neoplasia detected at the initial workup continue to be at increased risk. Because the risk varies with the subclassification of AGC (ie, either NOS or “favor neoplasia”), the

most appropriate form of follow-up depends on the specific subclassification of AGC. Women with AGC NOS who have a negative initial workup have been found in some studies to be at relatively low risk for having a missed significant lesion.⁴⁷ Therefore, some authors have recommended that these patients can be followed up with repeat cytological testing.^{47,64} However, women who have persistent AGC are at high risk for significant glandular disease.^{47,48} In some studies, women with a cytological result of AGC “favor neoplasia” or AIS who have a negative initial workup have been diagnosed subsequently with significant lesions, including invasive cancers.^{39,44,52} Therefore, some authors have suggested that the risk of a significant lesion in such patients is too great to rely on repeat cervical cytological testing alone, and have suggested that a diagnostic excisional procedure be used in this situation to rule out a serious endocervical lesion.^{47,64} Other studies have reported that thermal damage can preclude the assessment of margins in electrosurgical or laser conization specimens obtained from women being evaluated for glandular cytological abnormalities and have recommended that cold-knife conizations be used in this setting.^{61,65} The management of glandular cytological abnormalities can be quite challenging and women with unexplained glandular cytological findings should be referred to a clinician experienced in the management of complex cytological situations.

Recommendations for Managing Women With AGC or AIS

Initial Evaluation. Colposcopy with endocervical sampling is recommended for women with all subcategories of AGC, with the exception that women with atypical endometrial cells should initially be evaluated with endometrial sampling (AII). Endometrial sampling should be performed in conjunction with colposcopy in women older than 35 years with AGC and in younger women with AGC who have unexplained vaginal bleeding (AII). Colposcopy with endocervical sampling is also

recommended for women with a cytological test result of AIS. Management of women with initial AGC or AIS using a program of repeat cervical cytological testing is unacceptable (EII). Currently, there are insufficient data to allow an assessment of HPV DNA testing in the management of women with AGC or AIS (CIII).

Subsequent Evaluation or Follow-up. If invasive disease is not identified during the initial colposcopic workup, it is recommended that women with AGC “favor neoplasia” or endocervical AIS undergo a diagnostic excisional procedure (AII). The preferred diagnostic excisional procedure for women with AGC or AIS is cold-knife conization (BII). If biopsy-confirmed CIN (of any grade) is identified during the initial workup of a woman with AGC NOS, management should be according to the 2001 Consensus Guidelines for the Management of Women With Cervical Histological Abnormalities (Wright et al, unpublished data, 2001). If no neoplasia is identified during the initial workup of a woman with AGC NOS, it is recommended that the woman be followed up using a program of repeat cervical cytological testing at 4- to 6-month intervals until 4 consecutive “negative for intraepithelial lesion or malignancy” results are obtained, after which the woman may return to routine screening (BIII). If a result of either ASC or LSIL is obtained on any of the follow-up Papanicolaou tests, acceptable options include a repeat colposcopic examination or referral to a clinician experienced in the management of complex cytological situations (BIII).

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION

In 1996 the median rate of occurrence of LSIL in the United States was 1.6%, but laboratories serving high-risk populations report LSIL rates as high as 7.7%.^{2,66} Cytological grade is a relatively poor predictor of the grade of CIN that will be identified at colposcopy, and approximately 15% to 30% of women with LSIL on cervical cytology will have

CIN 2,3 identified on a subsequent cervical biopsy.^{21,22}

Approaches to Managing Women With LSIL

Approaches that previously have been recommended for managing women with LSIL include repeat cytological testing or colposcopy. In some clinical settings, patients with LSIL are routinely followed up using cytology alone, without an initial colposcopic evaluation. The rationale for this is that the majority of women with LSIL have either no cervical lesion or CIN 1, the majority of which spontaneously regress without treatment or are completely excised with a cervical biopsy. However, follow-up cytological studies have usually had high rates of loss to follow-up, a 53% to 76% likelihood of abnormal follow-up cytology results requiring eventual colposcopy, and a small but real risk of delaying the identification of invasive cancers.^{35,67-69} In contrast, referring all women with LSIL for colposcopy allows women with significant disease to be rapidly identified and would be expected to reduce the risk that women would be lost to follow-up. Disadvantages of colposcopy are those previously outlined for women with ASC, but they appear to be outweighed by the higher risk of abnormality in women with LSIL. Even in patients found to have biopsy-confirmed CIN 1, establishing a histopathologically confirmed diagnosis has merit since it allows a treatment plan to be developed based on knowledge of the patient's cervical lesion.

Several approaches, including HPV DNA testing and LEEP, do not appear to be useful for the initial management of women with LSIL. In the ALTS study, 83% of women referred for the evaluation of an LSIL cytology result tested positive for high-risk HPV types.⁷⁰ Receiver operator curve analysis evaluating the performance of HPV DNA testing for the detection of women with CIN 2,3 has reported a lower specificity at a given level of sensitivity among women being evaluated for LSIL, compared with those being evaluated for ASC.⁵ Loop electrosurgical exci-

sion procedures to excise the transformation zone in women referred for an abnormal cervical cytology result, but in whom biopsy-confirmed CIN has not been documented, frequently fail to identify neoplasia.^{71,72}

Management of Women With LSIL but No Cervical Lesions

Relatively few studies have addressed the issue of how to manage patients with LSIL who have satisfactory colposcopic examinations but no cervical lesions. One study found that 47% of such women had CIN diagnosed on a subsequent LEEP specimen; in the ALTS study, a considerable number of these women with LSIL who had no CIN detected at their initial colposcopic evaluation were subsequently found to have biopsy-confirmed CIN 2,3 (D. Solomon, MD, written communication, September 6-8, 2001).⁷³ Endocervical sampling reduces the risk of missed endocervical lesions among these women, as well as among women with LSIL and unsatisfactory colposcopic examinations. However, other studies of women with LSIL and an unsatisfactory colposcopic examination have found that the risk of missing a significant lesion is relatively low if neoplasia is not identified at the initial evaluation.⁷⁴ One study of 29 patients with cytology-confirmed LSIL or with biopsy-confirmed CIN 1 who had an unsatisfactory colposcopy and underwent cone biopsy identified only 2 cases of CIN 2,3 on the conization specimen and no invasive cervical carcinomas.⁷⁴

Recommendations for Managing Women With LSIL

Colposcopy is the recommended management option for women with LSIL (AII). Subsequent management options depend on whether a lesion is identified, whether the colposcopic examination is satisfactory, and whether the patient is pregnant. The routine use of diagnostic excisional procedures such as LEEP or ablative procedures is unacceptable for the initial management of patients with LSIL in the absence of biopsy-confirmed CIN (DII).

Satisfactory Colposcopy. Endocervical sampling is acceptable for nonpregnant women with satisfactory colposcopic findings and a lesion identified in the transformation zone (CII), but it is preferred for nonpregnant women in whom no lesions are identified (BII). If biopsy, with or without endocervical sampling, fails to confirm CIN and the colposcopy is satisfactory, acceptable management options include follow-up with repeat cytological testing at 6 and 12 months with a referral for colposcopy if a result of ASC-US or greater is obtained, or follow-up with HPV DNA testing at 12 months with referral for colposcopy if testing is positive for a high-risk type of HPV (BII).

Unsatisfactory Colposcopy. Endocervical sampling is preferred for nonpregnant women with unsatisfactory colposcopic findings (BII). If biopsy fails to confirm CIN and the colposcopy is unsatisfactory, acceptable management options include follow-up with repeat cytological testing at 6 and 12 months with a referral for colposcopy if a result of ASC-US or greater is obtained, or follow-up with HPV DNA testing at 12 months with referral for colposcopy if testing is positive (BII).

Women with LSIL who are found to have biopsy-confirmed CIN should be managed according to the 2001 Consensus Guidelines for the Management of Women With Cervical Histological Abnormalities (Wright et al, unpublished data, 2001).

LSIL in Special Circumstances

Postmenopausal Women. In postmenopausal patients, follow-up without initial colposcopy is an acceptable option using protocols of either follow-up with repeat cytological testing at 6 and 12 months with a threshold of ASC-US or greater for referral for colposcopy, or follow-up with HPV DNA testing at 12 months with referral for colposcopy if testing is positive (CIII).

A course of intravaginal estrogen followed by a repeat cervical cytology test approximately a week after completing the regimen is acceptable for women with LSIL who have clinical or cyto-

logical evidence of atrophy, with a referral for colposcopy if a result of ASC-US or greater is obtained and there are no contraindications to using intravaginal estrogen (CIII). If the repeat cervical cytology test result is “negative for intraepithelial lesion or malignancy,” cytological testing should be repeated in 4 to 6 months. If both repeat cytology test results are “negative for intraepithelial lesion or malignancy,” the patient can return to routine cytological screening, whereas if either repeat result is reported as ASC or greater, the patient should be referred for colposcopy (CIII).

Adolescents. In adolescents, an acceptable option is follow-up without initial colposcopy using a protocol of repeat cytological testing at 6 and 12 months with a threshold of ASC for referral for colposcopy, or of HPV DNA testing at 12 months with a referral for colposcopy if testing is positive for high-risk HPV DNA (CIII).

Pregnant Women. For the recommended management of pregnant women with a diagnosis of LSIL, see the “HSIL in Special Circumstances” section, below.

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION

A cytological diagnosis of HSIL is uncommon, accounting for only 0.45% of cytology interpretations in 1996.² Women with a cytological diagnosis of HSIL have approximately a 70% to 75% chance of having biopsy-confirmed CIN 2,3 and a 1% to 2% chance of having invasive cervical cancer.^{2,58,75}

Approaches to Managing Women With HSIL

A cytological result of HSIL identifies a woman at significant risk for having CIN 2,3 or invasive cancer; therefore, colposcopy with endocervical assessment has traditionally been considered the best approach to managing these patients.³¹ Usually, a colposcopic evaluation will identify a high-grade cervical or vaginal lesion.^{58,75,76} However, those women with HSIL in whom a high-grade cervical or vaginal lesion is not identified after col-

poscopy appear to be at considerable risk for having an undiagnosed CIN 2,3 lesion. In some studies, up to 35% of women with a biopsy diagnosis of CIN 1 and a cytological result of HSIL have been found, after additional workup, to have biopsy-confirmed CIN 2,3.^{77,78} Therefore, additional steps are usually taken when a high-grade cervical or vaginal lesion is not identified in a woman with HSIL. One of the first steps that is often taken is to perform a careful review of the colposcopic findings, biopsy results, and initial cervical cytology results. Numerous studies have shown that cytopathologists and histopathologists frequently differ in their interpretation of both cytological and histological cervical abnormalities, and that such a review can sometimes resolve the discrepancy.^{11,79-81}

Many colposcopists believe that a cytology test result of HSIL in a pregnant patient requires special consideration. Pregnancy accentuates both normal and abnormal colposcopic findings, and clinicians may not obtain appropriate cervical biopsies out of concern of increased bleeding.^{82,83} Although cervical biopsy during pregnancy is associated with an increased risk of minor bleeding, it has not been associated with increased rates of major bleeding or pregnancy loss in the large studies, and a failure to perform cervical biopsies in pregnant women has been associated with missed cancers.⁸⁴ Because of the risk of potential injury to the fetus, endocervical sampling is proscribed during pregnancy.

The approach of managing nonpregnant women with HSIL by immediate LEEP of the transformation zone (ie, “see and treat”) has been shown to be safe, efficacious, and cost-effective, particularly in the hands of expert colposcopists.⁸⁵⁻⁸⁸ However, most studies of women undergoing immediate LEEP for cytological abnormalities have reported that a significant number of the excised specimens will lack histologically confirmed CIN.^{71,72} Therefore this approach appears to be most appropriate for patients from populations at risk of loss to follow-up and for older pa-

tients in whom possible adverse effects of LEEP on fertility are not an issue.

Recommendations for Managing Women With HSIL

Colposcopy with endocervical assessment is the recommended management of women with HSIL (AII). Subsequent management options depend on whether a lesion is identified, whether the colposcopic examination is satisfactory, whether the patient is pregnant, and whether immediate excision is appropriate.

Satisfactory Colposcopy. When no lesion or only biopsy-confirmed CIN 1 is identified after satisfactory colposcopy in women with HSIL, it is recommended that, when possible, a review of the cytology, colposcopy, and histology results be performed (BIII). If the review yields a revised interpretation, management should follow guidelines for the revised interpretation; if a cytological interpretation of HSIL is upheld or if review is not possible, a diagnostic excisional procedure is preferred in nonpregnant patients (BII). A colposcopic reevaluation with endocervical assessment is acceptable in special circumstances (see below) (BIII).

Unsatisfactory Colposcopy. When no lesion is identified after unsatisfactory colposcopy in women with HSIL, a review of the cytology, colposcopy, and histology results should be performed when possible (BIII). If the review yields a revised interpretation, management should follow guidelines for the revised interpretation. If a cytological interpretation of HSIL is upheld, review is not possible, or biopsy-confirmed CIN 1 is identified, a diagnostic excisional procedure is recommended in nonpregnant patients (AII). Ablation is unacceptable (EII).

Omission of endocervical sampling is acceptable when a diagnostic excisional procedure is planned. In women with HSIL in whom colposcopy suggests a high-grade lesion, initial evaluation using a diagnostic excisional procedure is also an acceptable option (BI). Triage using either a program of repeat cytological testing or HPV DNA testing

is unacceptable (EII). Women with HSIL who are found to have biopsy-confirmed CIN should be managed according to the 2001 Consensus Guidelines for the Management of Women With Cervical Histological Abnormalities (Wright et al, unpublished data, 2001).

HSIL in Special Circumstances

Pregnant Women. It is preferred that the colposcopic evaluation of pregnant women with HSIL be conducted by clinicians who are experienced in the evaluation of colposcopic changes induced by pregnancy (BIII). Biopsy of lesions suspicious for high-grade disease or cancer is preferred; biopsy of other lesions is acceptable (BIII). Endocervical curettage is unacceptable in pregnant women (EIII). Since unsatisfactory colposcopy may become satisfactory as the pregnancy progresses, it is recommended that women with unsatisfactory colposcopic findings undergo a repeat colposcopic examination in 6 to 12 weeks (BIII). In the absence of invasive disease, additional colposcopic and cytological examinations are recommended, with biopsy recommended only if the appearance of the lesion worsens or if cytology suggests invasive cancer (BII). Unless invasive cancer is identified, treatment is unacceptable (EII). A diagnostic excisional procedure is recommended only if invasion is suspected (BII). Reevaluation with cytology and colposcopy is recommended no sooner than 6 weeks postpartum (CIII).

Young Women of Reproductive Age. When biopsy-confirmed CIN 2,3 is not identified in a young woman with cytology-confirmed HSIL, observation with colposcopy and cytology at 4- to 6-month intervals for 1 year is acceptable, provided colposcopic findings are satisfactory, endocervical sampling is negative, and the patient accepts the risk of occult disease. If a lesion appears to progress to a colposcopic high-grade lesion or if HSIL cytology persists, a diagnostic excisional procedure is recommended (BIII).

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Definitions of Terms Utilized in the Consensus Guidelines

Colposcopy is the examination of the cervix, vagina, and, in some instances the vulva, with the colposcope after the application of a 3-5% acetic acid solution coupled with obtaining colposcopically-directed biopsies of all lesions suspected of representing neoplasia.

Endocervical sampling includes obtaining a specimen for either histological evaluation using an endocervical curette or a cytobrush or for cytological evaluation using a cytobrush.

Endocervical assessment is the process of evaluating the endocervical canal for the presence of neoplasia using either a colposcope or endocervical sampling.

Diagnostic excisional procedure is the process of obtaining a specimen from the transformation zone and endocervical canal for histological evaluation and includes laser conization, cold-knife conization, loop electrosurgical excision (i.e., LEEP), and loop electrosurgical conization.

Satisfactory colposcopy indicates that the entire squamocolumnar junction and the margin of any visible lesion can be visualized with the colposcope.

Endometrial sampling includes obtaining a specimen for histological evaluation using an endometrial biopsy or a “dilatation and curettage” or hysteroscopy.

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