

New feature  
**UPDATE**  
**ON CERVICAL DISEASE**

NEW ADVANCES THAT ARE CHANGING PATIENT CARE  
■ BY THOMAS C. WRIGHT, JR, MD

- ▶ Improved cytology reports
- ▶ New guidelines: ASC-US triage, HPV testing
- ▶ ALTS findings
- ▶ Breakthrough on HPV vaccine

**A** 2001 adjustment in the terminology used to report cytology results was the first of 4 recent advancements that, in sum, have fundamentally changed how we interpret and follow-up Pap smears. Another breakthrough in cervical disease reveals clear potential for a vaccine for human papillomavirus (HPV). This *Update on Cervical Disease* reviews these pivotal developments:

- The 2001 revision of the Bethesda System—also known as Bethesda 3—for reporting cervical cytologic results.
- The 2001 consensus guidelines on managing women with abnormal cytology and cervical cancer precursors.
- Interim guidance on the use of HPV DNA testing as an adjunct to cervical cytology for screening.
- Findings of the National Cancer Institute's ASCUS/LSIL Triage Study (ALTS).
- A proof-of-principle trial demonstrating the potential clinical utility of a vaccine for HPV type 16 (HPV-16) in young adults.

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### **New terms aim to reduce unnecessary repeat Paps**

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

**B**y deleting a few categories, changing several definitions, and adding new information to the report, the new Bethesda System for reporting results of screening cytology has created a simpler, more precise, and more helpful report.

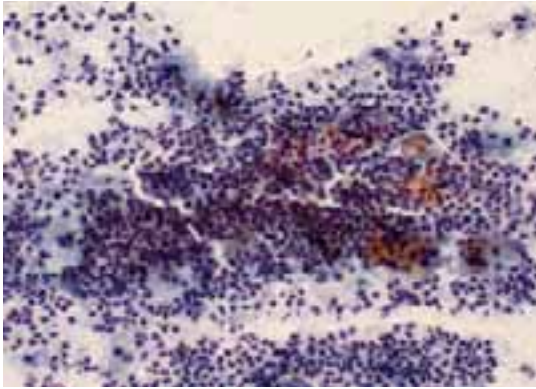
Elements of the widely utilized 1991 system were believed to cause confusion and lead to unnecessary repeat testing, as well as undue concerns and expenses; these have been refined. Key original features that served well, however, remain. For example, results are still shown in 3 distinct sections: specimen adequacy; general interpretation of normal or abnormal; and specific interpretation, or type of abnormality, if present.

**Simpler classifications with notes added** when indicated are a step forward from

**For more discussion** on the practical implications of the new terms and on the clinical utility of HPV DNA testing in different settings, see "Atypical squamous cells: The case for HPV testing," page 52, in this issue of OBG MANAGEMENT.

**FIGURE**

**When inflammation limits interpretation**



A cervical cytology specimen in which 50% to 75% of epithelial cells are obscured by inflammation was previously classified as “satisfactory for evaluation but limited by inflammation.” The new Bethesda System classifies the same specimen as “negative for intraepithelial lesion or malignancy,” and adds a statement that obscuring inflammation was present.

the standpoint of physicians and patients alike.

- **Specimen adequacy** is now either “satisfactory” or “unsatisfactory” for evaluation. The confusing category “satisfactory but limited by . . .” was eliminated because it seemed to lead to many unnecessary repeat Pap tests. Under the old system, specimens were categorized as “satisfactory but limited by . . .” for any number of reasons, including lack of a transformation-zone component, partially obscuring blood, inflammation, or poor presentation. Such specimens are now classified as “satisfactory for evaluation,” and a statement describing any flaws in the specimen is added.

- **“Benign cellular changes,”** a classification that confused patients, was also appropriately eliminated. Cases that fell into that category under the old system are now classified as “negative for intraepithelial lesion or malignancy” (ie, normal), and include a statement explaining that organisms, reparative changes, radiation effect, atrophy, or other conditions are present. **“Atypical squamous cells of undeter-**

**mined significance”** (ASCUS), which previously described all nondiagnostic or borderline squamous cytologic abnormalities, was subdivided in an attempt to reduce the number of cases inappropriately classified as having borderline changes.

ASCUS was changed to “atypical squamous cells” (ASC), with 2 subcategories: “undetermined significance” (ASC-US) and “suggestive of a high-grade squamous intraepithelial lesion” (ASC-H) (FIGURE).

**Precursor lesions** are reported as before. A 2-tiered terminology classifies cervical intraepithelial neoplasia (CIN) 1 with HPV cytopathic effects as low-grade squamous intraepithelial lesion (LSIL) and combines CIN 2 and 3 into the high-grade squamous intraepithelial lesion (HSIL) category.

**Education notes added.** Another change that will affect clinicians is the inclusion of education notes in the cytology report. In some instances, these notes may simply observe that, when managing a patient with ASC-US, the 2001 Consensus Guidelines for the Management of Women with Cervical Cytological Abnormalities should be followed. In other instances, the notes may be more problematic, such as when laboratories state that lack of a transformation-zone component does not warrant an early repeat without knowing a patient’s clinical status or history.

**Consensus guidelines on management of patients with abnormal results**

Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 consensus guidelines for the management of women with cervical cytological abnormalities. *JAMA*. 2002;287:2120-2129.

Wright TC Jr, Cox JT, Massad LS, Carlson J, Twiggs LB, Wilkinson EJ. 2001 consensus guidelines for the management of women with cervical intraepithelial neoplasia. *Am J Obstet Gynecol*. 2003;189:295-304.

**T**hese guidelines offer concrete, evidence-based protocols for managing cytologic

abnormalities and cancer precursors.

Experts in many disciplines (including epidemiology, gynecology, gynecologic oncology, cytopathology, pathology, family planning, and others), and 29 professional societies and federal and international agencies developed these guidelines in 2001, specifically to reflect the terminology changes that arose from Bethesda 3.

Full recommendations are available free from the *JAMA* website, and algorithms for managing each type of cytological abnormality are available free from the American Society for Colposcopy and Cervical Pathology (ASCCP) Web site (<http://asccp.org>).

**HPV testing is recommended.** These newest guidelines (published in *JAMA* in 2002 and the *American Journal of Obstetrics and Gynecology* in 2003) recognize the clinical utility of HPV DNA testing in a number of settings:

- patients with ASC-US,
- follow-up after colposcopy for an abnormal Pap when the patient does not have a CIN,
- conservative follow-up after biopsy-confirmed CIN 1, and
- posttreatment follow-up of CIN 2,3.

To minimize costs, enhance patient and provider convenience, and reduce the anxiety that accompanies an abnormal cytologic result, the guidelines recommend reflex HPV DNA testing for women with ASC-US on liquid-based cytology, and when co-collection of a specimen for future HPV DNA testing is an option at the time of primary cytologic screening.

**Conservative follow-up for biopsy-confirmed CIN 1** is a considerable change from previous management recommendations. Previously, routine treatment for all women with this finding was typical practice. The new guidelines recommend conservative follow-up without treatment, provided the woman has a satisfactory colposcopic examination.

## Use of HPV testing and cytology in combination for screening

Wright TC, Schiffman M, Solomon D, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. *Obstet Gynecol.* 2004;103:304-309.

Use of high-risk HPV DNA testing as an adjunct to cervical cytology for screening women aged 30 years and older was approved by the US Food and Drug Administration in March 2003, but many clinicians are uncertain of the best way to utilize HPV DNA testing and how to manage various combinations of results on cervical cytology and high-risk HPV DNA testing. To address the need for information, interim guidelines were jointly developed last spring by the National Cancer Institute, ASCCP, and American Cancer Society.

### Key recommendations:

■ **Frequent HPV testing discouraged.** If HPV DNA testing is used for primary screening in women 30 years of age and older, it should be used no more often than every 3 years, provided both tests are negative.

■ **In some cases, retesting may be better than immediate colposcopy.** Women with negative cytology who test positive for high-risk HPV DNA can forego immediate colposcopy. Instead, they can be safely followed by repeating both tests in 6 to 12 months. Approximately half of these women have transient HPV infections and will become HPV DNA-negative by the next visit. These transiently infected women are at low risk for CIN 2,3 or cancer and can simply be rescreened with both tests in 3 years, provided the repeat cytology is also negative.

■ **Colposcopy is warranted for persistent infection.** Women with persistent HPV DNA-positive tests have roughly a 1 in 10 chance of having CIN 2,3—similar to the risk of a woman with ASC-US. Until we gain additional data from long-term studies, the most conservative approach is colposcopic evaluation.

## ALTS data clarify management of cytologic abnormalities

The ASCUS-LSIL Triage Study Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. *Am J Obstet Gynecol.* 2003;188:1383-1392.

The ASCUS-LSIL Triage Study Group. A randomized trial on the management of low-grade squamous intraepithelial lesion cytology interpretations. *Am J Obstet Gynecol.* 2003;188:1393-1400.

Last summer saw publication of data from the prospective component of ALTS, a 3-arm clinical trial in which women with ASCUS or LSIL were randomized to either immediate colposcopy; high-risk HPV DNA testing and referral to colposcopy if positive; or follow-up with serial cytology, with colposcopy only if the HSIL developed.

After 2 years, all women found not to have CIN 2,3 at any point in the study were referred for colposcopy. ALTS provided much of the evidence used to develop the 2001 consensus guidelines—vital resources for management of women with cytologic abnormalities.

### Key findings

▪ **HPV testing unhelpful in women with LSIL.** HPV DNA testing does not appear to be useful in the routine management of women with LSIL because more than 80% test positive for high-risk HPV DNA.

▪ **No follow-up necessary for HPV-negative ASCUS.** Approximately 50% of women with ASCUS test negative for high-risk HPV DNA, with a very low prevalence of significant cervical disease. These patients do not require additional follow-up, but should be rescreened in 12 months.

▪ **Sensitivity of colposcopy called into question.** One of the most surprising findings was the poor performance of colposcopy, which is much less sensitive than previously thought, even when conducted with strict quality control in academic programs. In ALTS, colposcopy in women randomized to immediate exami-

nation failed to identify one third of CIN 2,3 lesions eventually found during the 2-year prospective study.

## HPV vaccine proves effective

Koutsky LA, Ault KA, Wheeler CM, et al. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med.* 2002;347:1645-1651.

A precommercial HPV-16 recombinant vaccine has clearly demonstrated the potential of a vaccine to block specific high-risk HPV infections. As a result, several large HPV vaccine trials have been initiated, and some form of vaccine should be commercially available in the next 4 to 6 years.

The vaccine tested is composed of viral-like particles, which are produced by DNA cloning the L1 capsid gene of HPV and then expressing the L1 capsid protein in specialized culture systems capable of producing conformationally correct proteins.

**No persistent infection in the treatment group.** In a large, double-blind, placebo-controlled study, young women received 3 doses of the recombinant vaccine or placebo and were followed for a median of 17.4 months. The incidence of persistent infection with HPV-16 was 3.8 per 100 woman-years in the placebo group versus 0 per 100 woman-years in the HPV-16 vaccine group. All cases of biopsy-confirmed CIN 2,3 associated with HPV-16 occurred in the placebo group. ■

*Dr. Wright is on the Speaker's Bureaus of Cytyc Corporation and TriPath Imaging, Inc.*

Next month

UPDATE  
ON CHRONIC PELVIC PAIN