4. Benninger MS, Anon J, Mabry RL. The medical management of rhinosinusitis. *Otolaryngol Head Neck Surg* 1997; 117(3 Pt 2): S41–S49.
5. Clement PA, Bluestone CD, Gordts F, et al. Management of rhinosinusitis in children: consensus meeting, Brussels, Belgium, September 13, 1996. *Arch Otolaryngol Head Neck Surg* 1998; 124:31–34.

What is the best approach for patients with ASCUS detected on Pap smear?

EVIDENCE-BASED ANSWER

DNA testing for human papillomavirus (HPV), especially if the sample can be obtained at the same time as the Papanicolaou (Pap) smear, can guide the management of women whose test result shows atypical squamous cells of undetermined significance (ASCUS). Those who test positive for high-risk types of HPV should be referred for colposcopy (strength of recommendation [SOR]: **B**), and those with a negative test result may resume regular Pap testing in 12 months (SOR: **B**). If HPV testing is unavailable, an alternative strategy is to repeat the Pap smear at 4- to 6-month intervals. After 2 negative Pap smears are obtained, usual screening may resume. But if either of the repeat Pap smears results in ASCUS or worse, the woman should be referred for colposcopy (SOR: **B**).

EVIDENCE SUMMARY

Although only 5% to 10% of women with the result of ASCUS on a Pap smear have a high-grade squamous intraepithelial lesion (HSIL), estimates suggest that more than one third of these lesions are identified during follow-up to ASCUS Pap smears.[1]

The recent ASCUS-LSIL Triage Study (ALTS), a multicenter randomized trial, directly addressed the appropriate evaluation of ASCUS.[2] The trial compared 3 management strategies for ASCUS Pap smears: reflex HPV-DNA testing (the initial Pap sample is tested for HPV only if the results are ASCUS), immediate referral for colposcopy, and repeat Pap smears. Reflex HPV testing had a sensitivity of 96% for detecting HSIL and a negative predictive value of 98%. The 44% of women with ASCUS who tested negative for high-risk HPV were able to avoid colposcopy. A single repeat Pap smear within 4 to 6 months, with referral for colposcopy if abnormal, had a sensitivity of 85% (sensitivity might be expected to improve with a second repeat test) and a similar colposcopy referral rate.[2]

A cost-effectiveness analysis that modeled data from the trial found that reflex HPV testing was most cost-effective.[3] For women aged 29 years or older, HPV testing resulted in a much lower colposcopy referral rate, 31% vs 65% for younger women, without sacrificing sensitivity.[4]

RECOMMENDATIONS FROM OTHERS

Evidenced-based guidelines were developed at a consensus conference sponsored by the American Society for Colposcopy and Cervical Pathology in September 2001.[5] Recommendations were also made for women with ASCUS in special circumstances. Pregnant women should be managed the same way as nonpregnant women; immunosuppressed women should be referred for colposcopy; and postmenopausal women, who are at a lower risk for HSIL, may try a 3- to 6-week course of intravaginal estrogen followed by repeat Pap smears 1 week after estrogen treatment and again 4 to 6 months later.

If either repeat test is reported as ASCUS or greater, the woman should be referred for colposcopy. Any woman with a Pap smear reported as ASCH (atypical squamous cells, cannot exclude HSIL) should be referred for colposcopy.[5]

The US Preventive Services Task Force recently concluded that evidence is insufficient to recommend for or against the routine use of HPV testing as a primary screening test for cervical cancer, but they did not address the management of abnormal Pap smears.[6]

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CLINICAL COMMENTARY

Thin-prep Pap smears can make workup of ASCUS easier for physician and patient

The management of ASCUS Pap smears has often confused primary care doctors. This is confounded by the fact that it is often a challenge to ensure that patients follow our recommendations. How could we blame them—after all, who wants to undergo 4 Pap smears instead of 1? The advent of thin-prep Pap smears, with reflex HPV testing on the same specimen, has simplified our lives. By obtaining routine thin-prep Pap smears and then reflex HPV testing for only high-risk HPV types, fewer Pap smears and colposcopic exams are needed, without reducing the detection of HSIL. Best of all, fewer women are overtreated or lost to follow-up.

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REFERENCES

1. Manos MM, Kinney WK, Hurley LB, et al. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. *JAMA* 1999; 281:1605–1610.
2. Solomon D, Schiffman M, Tarone R; ALTS Study Group. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. *J Natl Cancer Inst* 2001; 93:293–299.
3. Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. *JAMA* 2002; 287:2382–2390.
4. Schiffman M, Solomon D. Findings to date from the ASCUS-LSIL Triage Study (ALTS). *Arch Pathol Lab Med* 2003; 127:946–949.
5. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ; ASCCP-Sponsored Consensus Conference. 2001 Consensus guidelines for the management of women with cervical cytological abnormalities. *JAMA* 2002; 287:2120–2129.
6. US Preventive Services Task Force. Screening for cervical cancer: recommendations and rationale. AHRQ Publication No. 03-515A. January 2003. Rockville, Md: Agency for Healthcare Research and Quality. Available at: www.ahcpr.gov/clinic/uspstf/uspscerv.htm. Accessed on January 27, 2004.

LEVEL II CLINICAL INQUIRIES

Are ARBs or ACE inhibitors preferred for nephropathy in diabetes?

EVIDENCE-BASED ANSWER

Angiotensin receptor blockers (ARBs) have been shown to reduce the progression of nephropathy in several consistent studies. While ACE inhibitors have not been as well studied for the endpoint of nephropathy, patients with nephropathy exhibit reduced mortality when treated with an ACE inhibitor (strength of recommendation: **A**, based on randomized controlled trials).

EVIDENCE SUMMARY

The RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study[1]—a multicenter, randomized, double-blind, placebo-controlled trial—followed 1513 patients with type 2 diabetes and nephropathy over a mean of 3.4 years. Patients were randomized to receive losartan (Cozaar) or placebo, both taken in addition to conventional anti-hypertensive therapy (but not including renin-angiotensin-aldosterone system antagonist medications). The primary outcome was a composite of a doubling of serum creatinine, end-stage renal disease, or death. The number needed to treat (NNT) for the composite outcome was 34. The NNT for a doubling of the serum creatinine was 25, and for end-stage renal disease was 17.

The 2-year IRMA (Irbesartan Microalbuminuria) study,[2] a multicenter, randomized, double-blind, placebo-controlled trial, randomized 590 patients with type 2 diabetes, hypertension, and persistent microalbuminuria to receive 150 or 300 mg of irbesartan (Avapro) or placebo. Additional antihypertensive agents were allowed in each arm with the exception of ACE inhibitors, ARBs, and dihydropyridine calcium-channel blockers. The primary outcome was the development of overt

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