

Human Papillomavirus Triage of Patients with Atypical Squamous Cells of Undetermined Significance on Cervical Papanicolaou Smear

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Abstract

Introduction: The recent development of affordable human papillomavirus (HPV) testing has prompted consideration of its use as adjuvant and primary screening for cervical dysplasia. This review focuses on the use of HPV testing in triage management of atypical squamous cells of undetermined significance (ASC-US) Pap smears. **Materials and Methods:** A Medline search was performed for articles relevant to HPV testing as a triage strategy for ASC-US Paps. Key references from other papers that were not included in the search were also reviewed. Findings from the major randomised trials were then summarised. **Results:** Reflex HPV testing with hybrid capture is at least as effective and potentially cheaper than repeat cytology for evaluation of an ASC-US Pap. It also avoids 50% of colposcopies that would normally be performed if immediate colposcopy were done for all ASC-US Paps, while retaining excellent negative predictive value. **Conclusion:** Reflex HPV testing using liquid-based cytology is the preferred management strategy for triage of ASC-US Paps.

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Key words: Cervical cancer screening, Cervical dysplasia, Human papillomavirus, Hybrid capture, Vaginal smears

Introduction

Cervical cancer affects >400,000 women a year worldwide,¹ and represents a significant health issue for women. In the United States (US) however, screening programmes have reduced the incidence to 8.3 cases per 100,000 women with only 14,000 cases and 5000 deaths annually.² This is largely secondary to the use of the Papanicolaou (Pap) smear with >50 million Paps performed per year in the US. As a result, there are >2.5 million women with a low-grade abnormality (atypical squamous cells of undetermined significance [ASC-US], low grade squamous intraepithelial lesion [LSIL], or atypical glandular cells of undetermined significance [AGUS]) and as many as 300,000 high-grade (HSIL) Paps a year³(Table I). Since its introduction, there has been a 46% reduction in cervical cancer mortality.⁴

The Pap Smear

The Bethesda system was introduced in 1989 to replace the previous Papanicolaou system and to improve Pap reporting accuracy. It established general diagnostic categories, introduced new and uniform descriptive terminology and diagnoses, and established specimen adequacy standards. However, it was poorly reproducible

and had a high proportion of ASC-US, as high as 10% in some areas. There was also significant confusion regarding treatment and follow-up of ASC-US specimens. The Bethesda system was revised in 2001 in order to better classify ASC-US smears, which were poorly reproducible but still associated with a significant number of high-grade abnormalities. The categories were changed to ASC-US and atypical squamous cells-favour high-grade lesion (ASC-H). ASC-US Paps have cytologic changes suggestive of a lesion but lack strict criteria for definitive interpretation. ASC-H, however, has changes suggestive of HSIL but lacks criteria for definitive interpretation and is highly predictive for HSIL lesions. This subcategory is expected to account for only 5% to 10% of all ASC Paps under the new system.

Despite efforts to improve Pap smear classification and interpretation, significant problems persist. Conventional Paps have a poor sensitivity for disease. A recent meta-analysis demonstrated a sensitivity for LSIL lesions or worse (\geq LSIL) of only 58% with a specificity of 69%.⁵ In an effort to improve the sensitivity and specificity of the Pap, liquid-based cytology was recently introduced. This involves suspension of cervical scrapings in a fluid medium for subsequent centrifugation and analysis. Sensitivity of a

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TABLE I: DISTRIBUTION OF PAP SMEARS 1

Pap result	% of all Paps
Normal	94.4%
ASC-US	4.0%
LSIL	1.2%
HSIL	0.4%

ASC-US: atypical squamous cells of undetermined significance; HSIL: high-grade squamous intraepithelial neoplasia; LSIL: low-grade squamous intraepithelial neoplasia

single thin-layer Pap of \geq ASC-US for \geq CIN3 is 61% with a specificity of 82%, while 19% are referred for colposcopy.⁶ It is worth noting that, in analysing the predictive value of Pap screening, different outcome settings (ASC-US, LSIL, HSIL) affect the predictive measures as do repeating Paps and alteration of screening intervals. However, the main limitation in cervical dysplasia screening is the lack of implementation. A recent review found that 52% of cervical cancer cases had suboptimal screening,⁷ including 28% who never had a Pap and 33% whose last Pap was $>$ 5 years prior to diagnosis. Only 34% of patients developed cervical cancer within 3 years of their last Pap. Kinney et al³ found that in 60% of cervical cancer cases in a pre-paid healthcare plan, patients had recent access to healthcare, but failed to have cervical cancer screening. The most important and recurring theme in cervical screening is that the Pap is only a screening tool. It does not yield a diagnosis and only serves to identify women who require further testing, while avoiding unnecessary testing in low-risk women.

Colposcopy: The Gold Standard?

Until recently the options available for women with ASC-US smears were either immediate colposcopy or repeat cytology. Immediate colposcopy, although expensive, has been considered the gold standard. However, this has been questioned lately. Even with experienced colposcopists, the false negative rate is as high as 40% to 50%, as evidenced by the development of high-grade cervical intraepithelial neoplasia (CIN) after a 'negative' colposcopy. (Unpublished data from ASC-US and Low-Grade Triage Study [ALTS]).⁸ A separate meta-analysis of colposcopic impression versus histology findings demonstrated an accuracy of 89% and exact correlation rate of 61% with histology.⁹ The sensitivity of colposcopy has been noted to range from 87% to 99% with a specificity of 26% to 87%.

Aetiology — Human Papillomavirus

There is a strong association between cervical cancer and specific high-risk human papillomavirus (HPV) types. More than 100 types of HPV have been identified and as many as 30 types have been found to cause genital mucosal infection. These have been classified into high-risk types¹⁰

(16, 18, 45, 56), intermediate-risk types (31, 33, 35, 39, 51, 52, 55, 58, 59, 66, 68), and low-risk types (6, 11, 26, 42, 43, 44, 54, 70, 73). The last group is associated more with genital warts, LSIL, and recurrent respiratory papillomatosis. There is substantial evidence that the persistence of high-risk HPV is a major risk factor for high-grade CIN.^{11,12} These epidemiological studies have since been supported by laboratory studies. The integration of HPV deoxyribonucleic acid (DNA) into the cellular DNA disrupts the E2 regulatory gene of HPV leading to increased expression of E6 and E7. These genes have the ability to inhibit p53 and Retinoblastoma (Rb) gene function, respectively, and as such, they induce cellular immortalisation.¹⁰ This presents the unique opportunity to screen for the specific aetiologic factor that predisposes women to cervical dysplasia and cancer.

HPV infection is a highly prevalent sexually transmitted disease, with as many as 50% of sexually active women having been infected with 1 or more HPV types in the past.² Approximately 15% to 22% of women display evidence of current HPV infection; of these, 50% to 75% (or ~10% of the population) are infected with high-risk HPV types.^{13,14} Another study found a prevalence of all HPV types in 20 million women in the US with an annual incidence rate of 5.5 million.¹⁵ In a group of patients with no prior history of HSIL lesions, high-risk HPV types had a prevalence of 27%.¹⁶ In a study by Ho et al,¹⁷ on all HPV types, there was a 36-month incidence of 43% with a median duration of infection of 8 months. The persistence of HPV infection after 1 year was 30% with 9% persistent after 2 years. In this persistent group, there was a 50% chance of developing a high-grade cervical lesion. Once a mild cervical dysplasia has developed from HPV infection, the likelihood of progression to severe dysplasia is 1% to 2%.¹⁸ Once moderate dysplasia is present, the likelihood of progression to severe dysplasia or cancer within 2 years rises to 16%.^{18,19}

Despite the high prevalence and incidence of infection with HPV, most HPV infections are transient and disappear within several months to 2 years.^{12,20} There is a 56% chance of regression from mild dysplasia to normal and even a 44% to 53% chance of regression from moderate dysplasia to normal.^{18,19} This presents the problem of identifying women with HPV infection who are likely to progress to severe dysplasia and cancer versus those with a transient sexually transmitted infection.

HPV Testing

For many years, expensive and cumbersome polymerase chain reaction (PCR) techniques were the only way to identify HPV infection, however, recent advances have ushered in affordable and easy HPV testing. Unfortunately, the first generation of these HPV tests lacked sensitivity

and specificity. Recent development of the Hybrid Capture II (Digene Corporation, Gaithersburg, MD) has improved significantly on these older tests. This system uses ribonucleic acid (RNA) probes to high and intermediate HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. The specimen is denatured in the laboratory and liberated single-stranded DNA is hybridised with the RNA probes. The resulting hybrids are reacted with an antibody against the hybrid and a chemoluminescent substrate is added. The emitted light is then correlated with viral load. Overall, the built-in amplification allows detection of HPV DNA levels of as low as 1 pg/mL.²¹ In addition to development of a practical HPV test, monolayer liquid-based cytology has been introduced, providing for improved false positive rates and the ability to do HPV testing on remaining material, avoiding repeat clinical visits for evaluation of borderline cytology.

With the introduction of hybrid capture, HPV testing has been evaluated in various settings, including primary screening for dysplasia and as adjunctive testing for all women at the time of their Pap smear. In April 2003, the US Food and Drug Administration approved hybrid capture HPV testing as an adjunctive test for all women, age 30 or older. However, until further data becomes available, the most effective use of HPV testing is as a triage strategy for determining patients who require colposcopy after an ASC-US Pap smear.

HPV Testing as Triage for ASC-US Paps

Prior to HPV testing, the only options for management of women with ASC-US Paps were immediate colposcopy or repeat cytology with colposcopy at a determined threshold (such as repeat Pap of greater than or equal to ASC-US [\geq ASC-US], \geq LSIL, or \geq HSIL). Immediate colposcopy, while highly sensitive for detection of high-grade dysplasia, was considered too costly for the detection of the

TABLE II: PREVALENCE OF HIGH-RISK HPV BY PAP RESULT

Pap result	High-risk HPV by hybrid capture
ASC-US	56%
LSIL	85%
HSIL	95%

ASC-US: atypical squamous cells of undetermined significance; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial neoplasia; LSIL: low-grade squamous intraepithelial neoplasia

approximately 10% to 15% of high-grade dysplasias found in the ASC-US population. Based on previous data,²¹ high-risk HPV is only found in 40% to 60% of ASC-US patients (Table II). This has the potential for halving the number of colposcopies performed for ASC-US Paps. As many as 83% of LSIL Paps and 95% of HSIL Paps are high-risk HPV-positive which diminishes the utility of HPV testing in these groups as a triage strategy.⁸ ASC-H Paps were found to be similar to LSIL Paps with a high proportion of high-risk HPV positivity (unpublished data from ASC-US and Low-Grade Triage Study) and resulting diminished usefulness of HPV triage.

Hybrid Capture HPV Testing in ASC-US

Several studies have evaluated hybrid capture HPV testing in the setting of ASC-US Paps (Table III). The largest to date is the prospective ASC-US and Low Grade Triage Study (ALTS)⁸ which assigned a group of women with either ASC-US or Low Grade Paps into 1 of 3 arms: immediate colposcopy, repeat Pap every 6 months with an HSIL Pap as threshold for colposcopy, or reflex testing for high-risk HPV with HPV-positive women going to colposcopy. This trial posed several important issues. First, thin-layer liquid-based cytology was used for cytological screening. This allowed the performance of reflex HPV tests on residual sample material without a repeat clinical visit. Second, the trial was begun prior to the release of the

TABLE III: PERFORMANCE OF HPV HYBRID CAPTURE TESTING IN ASCUS PAPS

Study	No. of patients	Pap	Age	Referral rate	Sens HSIL (%)	Spec HSIL (%)	NPV HSIL	PPV HSIL
Solomon (ALTS) ⁸	1149	ASC-US	18+ (27)	56	96	49	98.9	19.6
Manos ²²	973	ASC-US	14-92 (40)	39	89	64	98.8	15
Morin ²³	360	ASC-US	18-50 (?)	29	89.5	74	99.2	16
Lonky ²⁴	278	ASC-US	—	46	82	59	96	21
Fait ²⁵	226	ASC-US (x2)	17-48 (28)	24	86	97	93.4	90.5
Shlay ²⁶	195	ASC-US	15-76 (34)	31	93	74	99.3	23
Ferris ^{27,28}	143	ASC-US	18+(27)	—	89	40	98.2	9.1
Bergeron ²⁹	111	ASC-US	15-75 (35)	43	83	62	97	21
Lytwyn ³⁰	87	ASC-US/LSIL	16-50 (30)	—	—	51	98	15
Lin ³¹	74	ASC-US	>50 (62)	53	100	65	100	67
Clavel ³²	23	ASC-US	15-72 (37)	48	100	57	100	9
Calculated weighted mean (%)				41	89	61	98.3	23

ASC-US: atypical squamous cells of undetermined significance; HSIL: high-grade squamous intraepithelial neoplasia; LSIL: low-grade squamous intraepithelial neoplasia; NPV: negative predictive value; PPV: positive predictive value; Sens: sensitivity; Spec: specificity

Bethesda 2001 classification; however, subsequent analysis has confirmed the results even if the Paps were reclassified into the new system. The LSIL arm of the trial was closed early because an interim analysis had shown that 83% of women with an LSIL Pap would be referred for colposcopy due to a positive high-risk HPV test. Of ASC-US Paps, 15% of patients were found to have CIN2 or greater at the time of immediate colposcopy, suggesting a significant rate of high-grade dysplasia in what was thought to be a benign group of patients.

This trial concluded that reflex HPV testing, as a triage strategy, is effective with a sensitivity of 96% for CIN3 while referring only 56% of ASC-US patients for colposcopy. Among these 56% of patients, 28% were CIN2 or greater on histological examination, thus improving the specificity of colposcopy in this setting. If colposcopy was only performed for HSIL or greater Pap (that is, normalising ASC-US and LSIL Paps), there would only be a sensitivity of 44% for CIN3+ with a 7% referral rate. This strategy is not considered sensitive enough for the US population. The previous dominant clinical strategy, repeat cytology with colposcopy for ASC-US or greater on repeat Pap, was considered inferior to HPV testing. It provided a sensitivity of 85% for CIN3+ with a 59% referral rate; thus it was less sensitive and had a higher referral rate than HPV testing. This fact, combined with the costs included in clinical visits for repeat cytology versus the cheaper reflex HPV testing, was thought to make this strategy inferior. Long-term follow-up on these patients is still pending.

The second largest trial to date was undertaken by Manos et al.²² On a prospective cohort of 46,000 women to identify ASC-US Paps, 995 women were identified with ASC-US on a conventional Pap with an overall rate of 3.5% ASC-US, 0.9% LSIL, and 0.3% HSIL. This was a slightly older population with a mean age of 37 years versus 27 years for the ALTS trial. It excluded women with a history of CIN in the previous 6 months and all patients had colposcopy where the colposcopist was blinded to the Pap result. Similar to the ALTS Trial, Hybrid Capture II testing was used. Overall, 7% of ASC-US patients were diagnosed with high-grade dysplasia (CIN2+) at histology and 39.5% of patients were high-risk HPV-positive. The sensitivity, specificity, positive predictive value, and negative predictive value of HPV testing for high-grade dysplasia was 89%, 64%, 15% and 98.8% respectively; all with a referral rate to colposcopy of only 39%. Repeat Pap was considered inferior with a sensitivity, positive predictive value, and negative predictive value for high-grade dysplasia of 76%, 13%, and 97.4% respectively and a similar 39% referred for colposcopy. Their conclusion was that repeat cytology was inferior due to its lower sensitivity for high-grade dysplasia with equal or higher referral rates for colposcopy.

Effective — But Cost-Effective?

Several studies have examined the cost-effectiveness of various cervical screening strategies. Kim et al³³ (Table IV) evaluated various strategies for triage of ASC-US Paps including colposcopy of all ASC Paps, HPV triage with hybrid capture, repeat cytology, reclassification of all ASC as normal, and colposcopy for HSIL Paps only. They also compared thin-layer Paps with the above strategies to conventional Paps and examined screening intervals from 1 to 5 years. They found that ignoring ASC-US (colposcopy for LSIL or worse) reduces the effectiveness of screening compared to HPV testing, repeat cytology, or immediate colposcopy, especially if longer screening intervals are used. A repeat cytology strategy was dominated (less effective and more costly than a similar strategy) by reflex HPV testing, regardless of the use of thin-layer Pap versus conventional Pap. Stratification of ASC-US into ASC-H and ASC-US also did not affect the dominance of the reflex HPV testing. This was true despite the higher costs of the HPV test due to the 40% to 60% reduction in referral for colposcopy and reduction in clinic visits for repeat cytology. The immediate colposcopy strategy was prohibitively expensive at a cost of >US\$900,000 per year life saved (YLS) compared to US\$44,000/YLS for biennial liquid-based cytology with reflex HPV testing. As a comparison in the US, hemodialysis for end-stage renal disease has been accepted and mandated at a cost-effectiveness ratio of US\$60,000 to US\$128,000/YLS. The conclusion was that screening every 2 to 3 years with liquid-based cytology and reflex HPV testing to determine the need for colposcopy in ASC-US Paps was the most cost-effective strategy.

A separate cost-effectiveness study in the setting of military beneficiaries³⁴ compared HPV triage of an ASC-US Pap to repeat cytology and normalisation of ASC-US (ignoring ASC-US result, colpo only for LSIL or greater). It also compared conventional to thin-layer Pap with and without hybrid capture HPV testing (using repeat visits for

TABLE IV: COST EFFECTIVENESS OF MANAGEMENT STRATEGIES FOR ASCUS PAPS – BIENNIAL SCREENING WITH LIQUID-BASED CYTOLOGY³³

Strategy	Average lifetime costs (\$)	Absolute reduction in cancer incidence (%)	\$ per year life saved (CE ratio)
Ignore ASC-US	1423	84.03	13,700
Reflex HPV testing	1712	90.41	44,400
Repeat cytology	1820	90.15	Dominated*
Immediate colpo	1867	90.54	905,300

*Dominated: Strategy is more costly and less effective than other strategies.

ASC-US: atypical squamous cells of undetermined significance; CE: cost-effectiveness; HPV: human papillomavirus; Colpo: colposcopy

HPV tests in conventional Pap) at 1 to 3-year screening intervals. HPV triage was less expensive and more effective than repeat cytology. However, replacing conventional Pap with thin-layer Pap and HPV triage at annual screening intervals does not meet conventional cost-effectiveness thresholds (less than US\$50,000/YLS) unless the screening intervals are lengthened.

Mandelblatt et al³⁵ compared HPV testing alone to thin-layer Pap plus HPV testing (for all women, not ASC-US Triage) to Pap alone at screening intervals of 2 to 3 years. Compared to biennial Pap alone, the addition of HPV testing requires 472 women to be tested to avoid 1 case of cervical cancer and 1367 women to avoid 1 death. HPV testing alone, as a sole screening strategy, is more costly and less effective than Pap alone or Pap plus HPV. This is due to the increased costs and lower specificity of the HPV test. The authors concluded that maximal life savings are achieved by biennial Pap plus HPV testing for all women, stopping at age 65. However, this is potentially too costly due to an increased colposcopy rate and lower positive predictive value of HPV tests in younger women. HPV testing as a screening strategy, however, may be favoured in a setting with a higher HPV prevalence or if HPV testing could be provided at a lower cost of <US\$5 per test. HPV testing also potentially requires less laboratory resources and fewer technicians, which is an advantage for less developed countries.

Goldie et al¹⁴ examined the use of HPV testing in a low resource setting of South Africa. They included human immunodeficiency virus (HIV) infection status in their analysis and compared direct visual inspection with acetic acid (DVI) to conventional Pap and hybrid capture HPV testing. They found that a single visit for DVI at age 35 was the most effective strategy for countries with cost-effectiveness ratios below US\$2-3/YLS. However, if cost-effectiveness ratios were allowed to increase to >US\$50/YLS, a single lifetime HPV test at age 35 dominated other strategies. Most other options were significantly affected by the requirement for multiple clinical visits for anything other than DVI.

Conclusion

In a patient population predominantly <30 years old, HPV is more prevalent. However, the infections are more likely to be transient, resulting in more positive HPV tests with no dysplasia (false positives). Patients >30 years old are more likely to be truly positive with HPV infection that correlates with dysplasia. Use of HPV testing as a triage strategy for ASC-US Paps is effective and potentially cost-saving, especially with a conversion to thin-layer cytology Paps. However, if HPV testing is used as primary screening,

the screening intervals should be lengthened to make it cost-effective. Based on available data, the American Society for Colposcopy and Cervical Pathology has developed the following recommendations for management of the ASC-US Pap:³⁶

APPENDIX I

SUMMARY OF 2001 CONSENSUS GUIDELINES FOR THE MANAGEMENT OF WOMEN WITH CERVICAL CYTOLOGICAL ABNORMALITIES (WITH RESPECT TO ASCUS CYTOLOGY)³⁶

ASC-US

- Repeat cytology, immediate colposcopy, or HPV testing are all acceptable strategies for managing women with ASC-US.
- Hybrid capture HPV testing after ASC-US Paps has sensitivity for CIN2+ of 83% to 100% (higher than single repeat cytology) and negative predictive values of 98% or greater.
- Reflex HPV testing of ASC-US Paps spares 40% to 60% of women colposcopy and is the preferred management strategy when liquid-based cytology is used.
- ASC-US/HPV negative patients may be followed up with repeat cytology at 12 months.
- ASC-US/HPV positive patients with no CIN on colposcopy should have repeat cytology at 6 and 12 months.
- If repeat cytology strategy is used, repeat cytology should be performed at 4-6 month intervals until 2 consecutive negative Paps are obtained, with colposcopy for any repeat ASC-US or greater cytology.
- If immediate colposcopy is used, patients with no CIN on colposcopy should have repeat cytology at 12 months.
- Cervical excision procedures should not be used to treat women with ASC in the absence of biopsy-confirmed CIN.

ASC-H

- Referral to immediate colposcopy for any ASC-H regardless of whether conventional or liquid-based cytology is used.

ASC-US in Post-menopausal Women

- Treatment of atrophic changes with intravaginal oestrogen with repeat cytology one week after treatment completed is acceptable.
- If subsequent cytology is ASC-US or greater, colposcopy is indicated.

ASC-US in Immunosuppressed Women

- Referral to colposcopy for cytology of ASC-US or greater, regardless of HIV viral load or anti-retroviral therapy.

ASC-US in Pregnancy

- Manage same as non-pregnant women.

REFERENCES

- Kiviat N, Koutsky L, Paavonen J. Cervical neoplasia and other STD-related genital tract neoplasias. In: Holmes K, Mardh P, Sparling P, editors. *Sexually Transmitted Diseases*. 3rd ed. New York: McGraw-Hill, 1999:811-32.
- Prevention of Genital HPV Infection and Sequelae: Report of an External Consultants' Meeting. Atlanta: Center for Disease Control and Prevention, 1999.
- Kinney W K, Manos M M, Hurley L B, Ransley J E. Where's the high-grade cervical neoplasia? The importance of minimally abnormal Papanicolaou diagnoses. *Obstet Gynecol* 1998; 91:973-6.
- Ries L, Kosary C, Hankey B, Miller B A, Edwards B K. SEER Cancer Statistics Review, 1973-1995. Bethesda, MD: National Cancer Institute, 1998.
- Fahey M T, Irwig L, Macaskill P. Meta-analysis of Pap test accuracy. *Am J Epidemiol* 1995; 141:680-9.
- Kulasingam S L, Hughes J P, Kiviat N B, Mao C, Weiss N S, Kuypers J M, et al. Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: comparison of sensitivity, specificity, and frequency of referral. *JAMA* 2002; 288:1749-57.
- Janerich D T, Hadjimichael O, Schwartz P E, Lowell D M, Meigs J W, Merino M J, et al. The screening histories of women with invasive cervical cancer, Connecticut. *Am J Public Health* 1995; 85:791-4.
- Solomon D, Schiffman M, Tarone R. 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; 93:293-9.
- Olaniyan O B. Validity of colposcopy in the diagnosis of early cervical neoplasia—a review. *Afr J Reprod Health* 2002; 6:59-69.
- Campion M. Preinvasive disease. In: Berek J S, Hacker N F, editors. *Practical Gynecologic Oncology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:271-344.
- Koutsky L A, Holmes K K, Critchlow C W, Stevens C E, Paavonen J, Beckmann A M, et al. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *N Engl J Med* 1992; 327:1272-8.
- Hildesheim A, Schiffman M H, Gravitt P E, Glass A G, Greer C E, Zhang T, et al. Persistence of type-specific human papillomavirus infection among cytologically normal women. *J Infect Dis* 1994; 169:235-40.
- Koutsky L. Epidemiology of genital human papillomavirus infection. *Am J Med* 1997; 102:3-8.
- Goldie S J, Kuhn L, Denny L, Pollack A, Wright T C. Policy analysis of cervical cancer screening strategies in low-resource settings: clinical benefits and cost-effectiveness. *JAMA* 2001; 285:3107-15.
- Cates W, Jr. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. American Social Health Association Panel. *Sex Transm Dis* 1999; 26:S2-7.
- Peyton C L, Gravitt P E, Hunt W C, Hundley R S, Zhao M, Apple R J, et al. Determinants of genital human papillomavirus detection in a US population. *J Infect Dis* 2001; 183:1554-64.
- Ho G Y, Bierman R, Beardsley L, Chang C J, Burk R D. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 1998; 338:423-8.
- Holowaty P, Miller A B, Rohan T, To T. Natural history of dysplasia of the uterine cervix. *J Natl Cancer Inst* 1999; 91:252-8.
- Syrjanen K, Kataja V, Yliskoski M, Chang F, Syrjanen S, Saarikoski S. Natural history of cervical human papillomavirus lesions does not substantiate the biologic relevance of the Bethesda System. *Obstet Gynecol* 1992; 79:675-82.
- Saslow D, Runowicz C D, Solomon D, Moscicki A B, Smith R A, Eyre H J, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin* 2002; 52:342-62.
- Schiffman M, Herrero R, Hildesheim A, Sherman M E, Bratti M, Wacholder S, et al. HPV DNA testing in cervical cancer screening: results from women in a high-risk province of Costa Rica. *JAMA* 2000; 283:87-93.
- Manos M M, Kinney W K, Hurley L B, Sherman M E, Shieh-Ngai J, Kurman R J, et al. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. *JAMA* 1999; 281:1605-10.
- Morin C, Bairati I, Bouchard C, Fortier M, Roy M, Moore L, et al. Managing atypical squamous cells of undetermined significance in Papanicolaou smears. *J Reprod Med* 2001; 46:799-805.
- Lonky N M, Felix J C, Naidu Y M, Wolde-Tsadik G. Triage of atypical squamous cells of undetermined significance with hybrid capture II: colposcopy and histologic human papillomavirus correlation. *Obstet Gynecol* 2003; 101:481-9.
- Fait G, Kupferminc M J, Daniel Y, Geva E, Ron I G, Lessing J B, et al. Contribution of human papillomavirus testing by hybrid capture in the triage of women with repeated abnormal Pap smears before colposcopy referral. *Gynecol Oncol* 2000; 79:177-80.
- Shlay J C, Dunn T, Byers T, Baron A E, Douglas J M Jr. Prediction of cervical intraepithelial neoplasia grade 2-3 using risk assessment and human papillomavirus testing in women with atypia on Papanicolaou smears. *Obstet Gynecol* 2000; 96:410-6.
- Ferris D G, Wright T C Jr, Litaker M S, Richart R M, Lorincz A T, Sun X W, et al. Triage of women with ASCUS and LSIL on Pap smear reports: management by repeat Pap smear, HPV DNA testing, or colposcopy? *J Fam Pract* 1998; 46:125-34.
- Ferris D G, Wright T C Jr, Litaker M S, Richart R M, Lorincz A T, Sun X W, et al. Comparison of two tests for detecting carcinogenic HPV in women with Papanicolaou smear reports of ASCUS and LSIL. *J Fam Pract* 1998; 46:136-41.
- Bergeron C, Jeannel D, Poveda J, Cassonnet P, Orth G. Human papillomavirus testing in women with mild cytologic atypia. *Obstet Gynecol* 2000; 95:821-7.
- Lytwyn A, Sellors J W, Mahony J B, Daya D, Chapman W, Ellis N, et al. Comparison of human papillomavirus DNA testing and repeat Papanicolaou test in women with low-grade cervical cytologic abnormalities: a randomized trial. HPV Effectiveness in Lowgrade Paps (HELP) Study No. 1 Group. *CMAJ* 2000; 163:701-7.
- Lin C T, Tseng C J, Lai C H, Hsueh S, Huang H J, Law K S. High-risk HPV DNA detection by Hybrid Capture II. An adjunctive test for mildly abnormal cytologic smears in women > or = 50 years of age. *J Reprod Med* 2000; 45:345-50.
- Clavel C, Masure M, Bory J P, Putaud I, Mangeonjean C, Lorenzato M, et al. Hybrid Capture II-based human papillomavirus detection, a sensitive test to detect in routine high-grade cervical lesions: a preliminary study on 1518 women. *Br J Cancer* 1999; 80:1306-11.
- Kim J J, Wright T C, Goldie S J. Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. *JAMA* 2002; 287:2382-90.
- Maxwell G L, Carlson J W, Ochoa M, Krivak T, Rose G S, Myers E R. Costs and effectiveness of alternative strategies for cervical cancer screening in military beneficiaries. *Obstet Gynecol* 2002; 100:740-8.
- Mandelblatt J S, Lawrence W F, Womack S M, Jacobson D, Yi B, Hwang Y T, et al. Benefits and costs of using HPV testing to screen for cervical cancer. *JAMA* 2002; 287:2372-81.
- Wright T C Jr, Cox J T, Massad L S, Twiggs L B, Wilkinson E J. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. *JAMA* 2002; 287:2120-9.

QUESTIONS

1. With regard to Pap smears
 - a) ASC-H smears have changes suggestive of HSIL, but lack criteria for definitive interpretation.
 - b) Conventional Pap smears have poor sensitivity for disease.
 - c) Liquid-based cytology involves suspension of vaginal discharge in a fluid medium for cytology.
 - d) The main limitation in cervical dysplasia screening has been lack of implementation.
 - e) It is a useful test in symptomatic patients.
 2. Regarding HPV
 - a) High-risk types are more associated with recurrent respiratory papillomatosis.
 - b) Integration of HPV DNA into the host cellular DNA leads to stimulation of p53 and retinoblastoma gene function.
 - c) Up to 50% of sexually active women have been infected with one or more HPV types in the past.
 - d) Most HPV infections will persist for several years.
 - e) Patients with persistent HPV infection have an approximately 50% chance of developing a high-grade cervical lesion.
 3. In HPV testing
 - a) This is most effectively used to triage ASC-H smears.
 - b) This is most effectively used to triage LSIL smears.
 - c) This can significantly reduce the number of colposcopies performed for ASC-US smears.
 - d) This can be done on remaining material after monolayer liquid-based cytology.
 - e) It is less useful in women <30 years old.
 4. The ASC-US and Low Grade Triage Study (ALTS)
 - a) was a 3-arm prospective study.
 - b) concluded that reflex HPV testing for ASC-US smear as a triage is effective.
 - c) showed that repeat cytology with colposcopy for ASC-US or greater on repeat Pap was equivalent to HPV testing.
 - d) showed that reflex HPV testing as a triage for ASC-US smears has a 96% sensitivity for CIN3.
 - e) showed that LSIL smears have a small proportion of high-risk HPV types.
 5. In population screening
 - a) HPV testing on population <30 years old will lead to more false positive tests (positive HPV test with no dysplasia).
 - b) HPV testing as a triage strategy for ASC-US smear is effective, but less cost-effective than repeating cytology with colposcopy for ASC-US or greater on repeat Pap.
 - c) HPV testing, as a sole population screening tool, is cheaper and more effective than Pap alone.
 - d) HPV testing for population screening may be more useful for less developed countries.
 - e) Immediate colposcopy is an acceptable strategy for ASC-US smear.
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