Should we discontinue Pap smear screening in women aged >65 years?

EVIDENCE-BASED ANSWER

Women with a history of regular, normal Pap smear screening should discontinue screening by age 65 years (strength of recommendation [SOR]: **B**). Women without a history of serial normal Pap smears should continue screening (SOR: **B**).

EVIDENCE SUMMARY

There is little direct evidence to support discontinuation of Pap screening in older women, but indirect evidence demonstrates that screening has reduced value in women with a history of periodic, normal Pap screening.

A systematic review of 12 studies from 1995 to 2001, which included women aged 50 years and older stratified by age and outcomes, showed that the risk of high-grade cervical lesions falls with age, and that a history of normal Pap tests further reduces that risk.[1] This observational evidence is based on large population-based cohort studies and a few prospective cohort studies.

According to this review, fewer than 1 in 1000 (and possibly as few as 2 in 10,000) women aged >60 years with a history of a normal baseline Pap smear will develop cervical intraepithelial neoplasia (CIN) 3 or cancer. By comparison, women being screened for the first time had rates of CIN 3 or cancer at 2.3 per 1000 for ages 50 to 64 years, and 1.7 per 1000 for women aged 65 years.

A prospective study of older women (average age, 66.7 years) followed for 2 years after a normal Pap smear result found an incidence of Pap smear abnormalities of 110 per 4895 (23 per 1000 person-years; 95% confidence interval [CI], 18–27 per 1000), but only 1 result of the 110 was a true positive (0.2 per 1000 person-years).[2]

A retrospective review of 798 cases of CIN or worse diagnosed in Scotland from 1989 to 1990 found that 98% of CIN occurred in women aged ≤50 years.[3] Given a low prevalence of true positive high-grade Pap smears in elderly women with a history of normal Pap smear results, elderly women are disproportionately likely to have evaluations for false-positive results.[1] With an estimated sensitivity of 60% and specificity of 98%, continued Pap screening would result in at least 34 elderly women being evaluated for high-grade Pap smears for every 1 true positive; and for every 3 cases identified, 2 would be missed.[1] As a comparison, for women of all ages with a high-grade Pap smear, 70% to 75% will have CIN 2 or 3, and 1% to 2% will have invasive carcinoma.[4]

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What are Clinical Inquiries?

Clinical Inquiries answer real questions that family physicians submit to the Family Practice Inquiries Network (FPIN), a national, not-for-profit consortium of family practice departments, residency programs, academic health sciences libraries, primary care practice-based research networks, and other specialists.

Questions chosen for Clinical Inquiries are those that family physicians vote as most important through a web-based voting system.

Answers are developed by a specific method:

- FPIN medical librarians conduct systematic and standardized literature searches in collaboration with an FPIN clinician or clinicians.
- FPIN clinician authors select the research articles to include, critically appraise the research evidence, review the authoritative sources, and write the answers.
- Each Clinical Inquiry is reviewed by 4 or more peers and editors before publication in *JFP*.
- FPIN medical librarians coauthor Type I Clinical Inquiries that have required a systematic search.
- Finally, a practicing family physician writes an accompanying commentary.

Several studies support the conclusion that women aged >65 years without a history of regular normal Pap smear results continue to benefit from cervical cancer screening. A prospective study of an urban, low-income population in New York (average age, 74) who were previously inadequately screened (≥5 years since last Pap smear in 75%) or had no previous screening (25%) found an incidence of 15.9 per 1000 of abnormal Pap smear results (95% CI, 8.5–23.3).[5]

The results of Pap screening among older women were analyzed in the retrospective review from the population-based registry of the Ontario Cervical Screening Program for almost 700,000 women screened during the first 6 months in 2000.[6] In this population, over 80% of women aged ≥50 years with high-grade lesion or carcinoma had a history of either no Pap screening or a previously abnormal test result in the past 4 years. Nonparticipants in Pap screening had a 2.7 to 4 times greater risk of cervical cancer than women screened at least once before.[4]

In the US, after Medicare began coverage for Pap smear screening in women age 65 and older, increased screening has resulted in more diagnoses of carcinoma in situ and a reduction in cervical cancer.[7]

A cost-benefit analysis, designed and published in 1992, evaluated Pap smear screening in the elderly with a Markov mathematical model. This model predicted the outcomes of periodic screening, diagnosis, and treatment for cervical cancer in hypothetical cohorts of women aged 65 to 109 years.[8] The **Table** depicts the cost per year of life saved for each Pap smear screening cohort of women analyzed in the Markov mathematical model. These data demonstrate cost-effectiveness of continued screening in elderly women who have not received adequate screening previously, while showing high cost-to-benefit ratio for continued screening in women with previous normal Pap smear results.

> A retrospective review found that 98% of CIN occured in women aged 50 years or more

In a hypothetical cohort of elderly women who were never screened, annual Pap smear screening would cost less than $6500 per year of life saved. The cost per year of life saved in women who have received regular screening every 3 years would be $33,572.

RECOMMENDATIONS FROM OTHERS

The 2002 guidelines from the American Cancer Society recommend that women aged 70 and older who have had 3 consecutive normal Pap smear results and no abnormal results in the past 10 years may choose to stop cervical cancer screening.[9] The 2003 guidelines from the US Preventive Services Task Force recommend discontinuing Pap smear screening after age 65 if previous Pap results were consistently normal.[10] In 1994, the Canadian Task Force on Preventive Health Care recommended stopping screening at age 70 if women have had at least 4 negative Pap smear results in the preceding 10 years and if previous results were normal.[11] The American College of Obstetrics and Gynecology recommends physicians determine when to stop screening on an individual basis, and notes that limited studies of older women made it difficult to set an upper age limit for Pap smears.[12]

Medicare covers Pap smears every 3 years, but will pay for yearly screening for women who have had an abnormal Pap result in the preceding 3 years and for women at high risk of cervical or vaginal cancer.

Diana R. Curran, MD, *Hendersonville Family Practice Residency, Hendersonville, NC;* ***Sue Stigleman, MLS,*** *Mountain Area Health Education Center, Asheville, NC*

TABLE

Cost-benefit analysis of Pap smear screening

Patient	Screening frequency	Cost per year of life saved
All women aged ≥65 years	Every 3 years	$7000
Women aged ≥65 years without a previous Pap or Pap within 5 years	Every year	<$6500
Women aged ≥65 years with a history of normal, regular Pap smear results	Every 3 years	$33,572

CLINICAL COMMENTARY

Stop Pap smears at 65 for those with normal prior screening, low risk for HPV

My older patients are delighted to stop having Pap smears and want to quit as soon as possible. The test can become quite an ordeal with advancing age as cervical stenosis, vaginal atrophy, and hip arthritis increase patient discomfort and technical difficulty. Following the lead of the US Preventive Services Task Force, I stop recommending them at age 65 for most patients who have a record of recent normal Pap smear results.

However, older adults are sexual beings, and HPV transmission can occur among those who are sexually active outside a long-term mutually monogamous relationship. When counseling women with high-risk lifestyles, I will discuss the possibility of continuing regular Pap smears beyond 65 years of age.

Jon O. Neher, MD, *Valley Medical Center Family Practice Residency, Renton, Wash*

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Is the ThinPrep better than conventional Pap smear at detecting cervical cancer?

EVIDENCE-BASED ANSWER

Conclusions regarding the ThinPrep are difficult to make due to the complexity of cervical cancer screening and the lack of adequate outcome-based data. However, current evidence supports the following: the ThinPrep is more sensitive than the conventional Papanicolaou (Pap) smear at detecting cervical cancer (strength of recommendation [SOR]: **A–**, based on 1 large validating cohort study with a good reference standard and 1 systematic review). There is insufficient evidence to recommend 1 preparation over the other (SOR: **B–**, based on several systematic reviews that include studies with poor reference standards).

The ThinPrep is a cost-effective screening tool if used at 3-year intervals (SOR: **B**, based on 1 systematic review and a decision analysis model). Additional advantages of the ThinPrep include being able to perform human papillomavirus (HPV) testing on the liquid. This is the preferred triage strategy for atypical squamous cells of undetermined significance (ASCUS) Pap smears (SOR: **A**, based on a large randomized, controlled trial).

EVIDENCE SUMMARY

The conventional Pap smear is the standard screening test for cervical neoplasia. Despite success, the Pap smear has high false-negative rates due to poor sensitivity (51%; 95% confidence interval [CI], 37%–66%).[1] The ThinPrep was developed to improve sensitivity by providing a monolayer of cells to the cytologist for review. A population-based comparative analysis of good quality shows that the new technology is better at detecting cancer precursors, but other systematic reviews that include less rigorous studies can only suggest it.

The overwhelming problem with most studies is they lack adequate reference standards. Customary criteria for evaluating diagnostic tests require that a "gold standard" reference be used, and that both the abnormal and normal results are validated against it. For cervical cancer screening, the "gold standard" is histology.

Only 1 analysis met the standard criteria. This prospective, population-based study of 8636 women reported that the ThinPrep was significantly more sensitive than the conventional smears at detecting high-grade squamous intraepithelial lesions (HSIL) and cancer, with sensitivity rates of 92.9% and 100% vs 77.8% and 90.9%, respectively ($P<.001$).[2] This evidence demonstrates that the ThinPrep is better at detecting cervical cancer.

Several systematic reviews summarize the many studies that compare ThinPrep with the conventional Pap. Unfortunately, conclusions are difficult to interpret. A recent quantitative review implies that the ThinPrep increases cytologic diagnoses of cervical cancer and its precursors.[3] A strength of this review is the inclusion of 10 articles with histology as the reference standard. The data from 21,752 patients compared the sensitivity and specificity rates of Thin Prep with conventional Pap for detecting abnormal histology. Sensitivity rates were reported as 76% (ThinPrep) and 68% (conventional), but the differences met statistical significance in only 2 of the included studies. Similarly, the overall specificity rates of the ThinPrep vs conventional Pap was 86% vs 79%, and again the differences did not usually reach statistical significance. The authors hypothesize that widespread use of ThinPrep could potentially detect an additional 162,000 patients with HSIL and 3000 patients with invasive cervical carcinoma.

A large meta-analysis of 25 prospective studies including over 500,000 women reported that ThinPrep increased detection of low-grade squamous intraepithelial lesions (LSIL) (odds ratio [OR]=2.15; 95% CI, 2.05–2.26) and HSIL (OR=2.26; 95% CI, 1.53–1.76), but the conclusions were severely limited by lack of a reference standard and high heterogeneity between study

Advantages of the ThinPrep include being able to perform HPV testing on the liquid

populations.[4] Another review found insufficient evidence to even judge the new test.[5]

A large evidence review done for the Agency for Healthcare Research and Quality (AHRQ) concluded that the quality of the available literature is poor. Two of the 3 trials reviewed had major methodological flaws that prevented an appropriate comparison of the data to show a modestly higher sensitivity of the ThinPrep.[1] From these reviews, we cannot recommend one technique over the other.

When evaluating a new screening test, cost is important. The AHRQ review[1] and a modeled cost and outcomes analysis[6] concluded that liquid-based cytology falls within the accepted ranges of cost-effectiveness if used at 3-year screening intervals. Another computer-based model evaluated different triage strategies for ASCUS Pap smears and found that reflex HPV testing provides the same or greater life expectancy benefits and is more cost-effective.[7] This strategy requires the use of liquid-based cytology. The large ALTS trial supports the use of liquid-based cytology because it has shown HPV testing in patients with ASCUS decreases the need for colposcopy.[8] Ultimately, when deciding which Pap test is better, many things in addition to sensitivity must be considered.

RECOMMENDATIONS FROM OTHERS

The US Preventive Services Task Force concludes that the evidence is insufficient to recommend for or against the routine use of new technologies to screen for cervical cancer. They acknowledge that ThinPrep may have improved sensitivity over conventional Pap smears but may possibly have lower specificity. The Task Force notes that ThinPrep could be cost-effective with longer screening intervals and can be helpful for the management of ASCUS.[9]

No current screening guidelines specifically recommend newer Pap test technologies in favor of conventional Pap tests. These associations include American Cancer Society, American Academy of Family Physicians, American College of Preventive Medicine, and American College of Gynecology.

Camille Andy, MD, *Moses Cone Family Medicine Residency Program, Greensboro, NC;* ***Linda F. Turner, MSLS,*** *MAHEC Health Sciences Library, Asheville, NC*

CLINICAL COMMENTARY

ThinPrep's high sensitivity and viral typing may be advantageous in some cases

Because the ThinPrep is expensive and not endorsed by major medical policy groups, it is not time for family physicians to switch to the ThinPrep en masse. However, I think 2 groups will be looking carefully at this technology.

First, in settings where annual follow-up is unreliable or impractical, the ThinPrep's high sensitivity will definitely be advantageous. Second, physicians who want to use HPV-based colposcopy guidelines will appreciate the ThinPrep's viral typing capabilities, although the unresolved issue of screening frequency will remain a problem. Advertising pressures, advocacy groups, and payer response will also shape this ongoing discussion.

Jon O. Neher, MD, *Valley Medical Center Family Practice Residency, Renton, Wash*

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Does treatment of acne with Retin A and tetracycline cause adverse effects?

EVIDENCE-BASED ANSWER

Adverse reactions to long-term tetracycline therapy are rare, and most will occur within 2 months of initiating therapy (strength of recommendation [SOR]: **B**, systematic review of ecological studies). Rare but serious drug reactions include a severe cutaneous reaction, hypersensitivity syndrome reaction, serum sickness–like reaction, and isolated single-organ dysfunction (SOR: **B**, systematic review).

Duration of antibiotic treatment is strongly associated with increased bacterial resistance (SOR: **B**, systematic review and 1 outcomes study), but antibiotics for acne do not appear to interfere with oral contraceptive efficacy (SOR: **B**, case-control study and supporting expert opinion). Laboratory monitoring is not indicated in otherwise healthy patients (SOR: **B**, consistent cohort studies).

No reports have been published regarding long-term topical tretinoin (Retin A) therapy. Short-term follow-up reports note no systemic effects (SOR: **C**, expert opinion), no teratogenicity (SOR: **B**, single case control study), and negligible systemic absorption (SOR: **B**, outcome studies). Thus, long-term topical tretinoin is presumed to be safe (SOR: **C**, expert opinion and extrapolation of pharmacologic data).

EVIDENCE SUMMARY

Tetracycline

A study of the safety of tetracycline,[1] which used reports in a drug safety database and a literature review of reported adverse events, concluded that rare but serious events do occur with tetracycline. Severe cutaneous adverse reaction was the most common reported single-organ dysfunction. Other rare events included hypersensitivity syndrome reactions and serum sickness–like reactions.

Since baseline rates of tetracycline use are unknown, it is impossible to ascertain the event rates for these rare reactions. Most of these serious adverse events occur less than 2 months after initiating therapy; they typically include general symptoms such as fever, malaise, and arthralgias, but may also include major organ involvement. The study suggested no clear treatment for these complications, but recommended discontinuing tetracycline and avoiding the entire tetracycline class of drugs.[1] No evidence supports previous concerns that tetracycline causes drug-induced lupus.

A systematic review confirms that treating acne with long-term systemic antibiotics leads to increased antimicrobial resistance.[2,3] A well-designed cohort trial showed that *Propioni-bacterium acnes* resistance was directly related to duration of antibiotic therapy.[4] This is clinically important because resistance levels correlate with therapeutic failure.[2] Rotating antibiotics on a long-term basis actually increases bacterial resistance patterns and can exacerbate the problems of increasing resistance and poor treatment outcomes.[2]

A relatively large retrospective cohort study of oral contraceptive users in a dermatological practice showed no difference in contraceptive failure rates between those prescribed common antibiotics (including tetracycline) and controls (1.6% vs 0.96%; 95% confidence interval [CI] for the difference, 0.81–2.1).[5]

CONTINUED

TABLE 1

Side effects of tetracycline and topical tretinoin

Tetracycline	Side-effect rates
Vaginal candidiasis[8]	12%
Gastrointestinal complaints[8]*	4%
Gram-negative folliculitis[9]	4%
Topical tretinoin[10]	**Maximal observed side-effect rates**
Peeling	50%
Burning	49%
Erythema	49%
Skin tightness	42%
Dryness	40%
Itching	24%

* Gastrointestinal complaints included nausea, diarrhea, black hairy tongue, esophagitis, and flatulence.

A systematic review of 8 studies reported on 777 patients taking antibiotics for acne, and examined the need for laboratory monitoring of long-term tetracycline users, including renal, liver, and blood components. The authors found only 1 adverse drug reaction (mild hyperbilirubinemia). They concluded that routine lab monitoring for all patients on long-term antibiotics for acne rarely detects clinically concerning adverse drug reactions and would be cost-prohibitive.[6]

Minor adverse side effects of tetracycline therapy are reported in about 8% of patients.[7] Some of the relatively more common and benign side effects are summarized in **Table 1**.

Topical tretinoin (Retin A)

Most published studies on topical tretinoin (Retin A) focus on the side effect of minor skin irritation. A multicenter, double-blind parallel study[10] compared the safety and efficacy of 2 formulations of tretinoin gel formulations. Adverse dermatologic side effects commonly reported are in **Table 1**. These cutaneous irritant side effects, while noted in up to 50% of treated patients, peaked in 7 days and decreased significantly over time.

Topical tretinoin has been in clinical use for more than 25 years. Topical delivery results in a very low systemic exposure; plasma retinoid levels measured after topical use remain at or below endogenous levels, likely due to very limited absorption.[11] Topical tretinoin is not associated with an increased risk for major congenital disorders. A retrospective study of 215 women on tretinoin during the first trimester compared with 430 controls found that the relative risk for a major congenital anomaly was 0.7 (95% CI, 0.2–2.3). The authors concluded that topical tretinoin did not increase congenital anomaly risk.[12]

■ RECOMMENDATIONS FROM OTHERS

No clinical guidelines have been published about the long-term use of tetracycline or topical tretinoin. An ad hoc committee of the American Academy of Dermatology concluded "tetracycline

TABLE 2

Treatment recommendations to reduce antimicrobial resistance

Do not prescribe systemic antibiotics if a topical medication will suffice
Avoid concomitant topical and systemic use of different antibiotics
Antibiotic therapy should continue for no longer than necessary, with a maximum period of 6 months
Do not "switch" or "rotate" antibiotics in patients who are not responding to therapy
Try systemic retinoids if acne fails to respond within 6 months of antibiotic therapy or quickly relapses

Adapted from Cooper et al.[2]

is a rational, effective, and relatively safe drug for use in the treatment of acne vulgaris when given in a dosage of 1 gm or less per day for long term therapy."[7] Other experts, more concerned with growing antibiotic resistance, recommend steps to help prevent increasing resistance (**Table 2**).

Barbara F. Kelly, MD, Martha Burroughs, MS, AHIP, University of Colorado Health Sciences Center, Denver

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CLINICAL COMMENTARY

Use a judicious approach to topical agents and systemic antibiotics

We should use a judicious approach with appropriate use of topical agents to treat acne. In those cases where acne is not responding, systemic antibiotics can be quite effective and very well tolerated. Regarding antimicrobial resistance of *P acnes*, we should avoid changing antibiotics unnecessarily, and taper to the lowest effective dose once the acne is well controlled. I think the dictum to avoid treating with systemic antibiotics for longer than 6 months is not widely followed. Often, much longer courses of treatment are necessary. For an individual patient, the risk of developing resistant *P acnes* is often preferable to the alternatives of inadequate acne control or systemic isotretinoin. Periodic attempts should be made to discontinue antibiotics when acne is well controlled, with resumption of the same antibiotic if one continues to be needed.

Marsha Mertens, MD, *Mercy Family Medicine Residency, St. Louis, Mo*

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Is exercise treadmill testing useful for detecting heart disease in women?

EVIDENCE-BASED ANSWER

Exercise treadmill testing has a sensitivity of 70% and specificity of 61% for the detection of coronary artery disease (CAD) in women (strength of recommendation [SOR]: **A**, based on a meta-analysis). It is useful for detecting CAD in symptomatic women who have an intermediate risk as determined by age and symptoms (SOR: **C**, based on expert opinion). Exercise treadmill testing may also have an application in determining exercise capacity and potential as a tool to predict cardiovascular death in women (SOR: **A**, cohort study).

EVIDENCE-BASED SUMMARY

Few studies of exercise treadmill testing include a significant number of women, which makes it difficult to ascertain its value for detecting CAD in women. A large meta-analysis of 19 studies looked specifically at women (n=3721) and found that noninvasive exercise tests only "moderately useful" for the detection of CAD. Exercise treadmill testing in women had a specificity of 0.70 (95% confidence interval [CI], 0.64–0.75), a sensitivity of 0.61 (95% CI, 0.54–0.68), a positive likelihood ratio of 2.25 (95% CI, 1.84–2.66) and a negative likelihood ratio of 0.55 (95% CI, 0.47–0.62). In comparison, exercise treadmill testing in men had a sensitivity of 0.70 and a specificity of 0.77.[1] The **Table** demonstrates how exercise treadmill testing performs for different levels of pretest probability.

Among the theoretical reasons for the diminished accuracy of the exercise treadmill testing in women are the varying catecholamine response to exercise, a higher incidence of mitral valve prolapse, and chest wall anatomy different than that in men.[1] Also, the methods used in performing exercise treadmill testing, as well as the thresholds for an abnormal test result, were established for men. Accuracy may also be affected by the subjectivity inherent in the performance and interpretation of the exercise treadmill testing, in particular, the reading of the ST segment.[2]

A large cohort study of 2994 asymptomatic women found that those women with a below-average peak exercise capacity and heart-rate recovery rate were 3.5 times more likely to die of cardiovascular causes than women who were above average (95% CI, 1.57–7.86).[3] Another cohort study of 5721 women found that an exercise capacity of <5 metabolic equivalents (METS) tripled the risk of death as compared with those with an exercise capacity of >8 METS.[4] These studies support the role of exercise treadmill testing for risk stratification for CAD disease in women.

RECOMMENDATIONS FROM OTHERS

The Institute for Clinical Systems Improvement states that exercise treadmill testing has application for the detection of coronary artery disease in those women with an intermediate (10%–90%) pretest probability of coronary artery disease as determined by age, gender, and symptoms. The intermediate category includes women aged 30 to 49 years with typical symptoms of angina, women aged 50 to 59 years with typical or atypical symptoms of angina, and women aged 60 to 69 years with atypical or nonanginal chest pain. All other women fall into groups with pretest probability either high enough or low enough that the exercise treadmill testing is less useful.[5]

The American College of Cardiology (ACC) and the American Heart Association concluded that the diagnosis of CAD in women presents difficulties not experienced with men, due primarily to the lower sensitivity and specificity of exercise treadmill testing. The ACC recommends exercise treadmill testing for the diagnosis of CAD in patients with an intermediate pretest probability of coronary disease based on

TABLE

Post-test probabilities of coronary artery disease using exercise echocardiogram

Pretest symptoms/ probability of CAD	Post-test probability of CAD	
	Positive test (%)	Negative test (%)
Definite angina— 71% probability	85	57
Probable angina— 31% probability	50	20
Nonspecific chest pain— 6% probability	13	3

CAD, coronary artery disease.
Table adapted from Kwok et al 1999.[1]

age, gender, and symptoms. (This recommendation is described as one for which there is evidence or general agreement that a given procedure or treatment is useful and effective.)[6]

Jessie Junker, MD, MBA, Albert Meyer, MD, *New Hanover Regional Medical Center, Wilmington, NC;* *Donna Flake, MSLS, MSAS,* *Coastal AHEC Library, Wilmington, NC*

CLINICAL COMMENTARY

False-positive rate and costs may argue for stress radionuclide or echocardiogram

The relative lack of evidence regarding the diagnostic accuracy of exercise treadmill testing in women is frustrating given the prevalence of both CAD and symptoms of chest pain in women. Nevertheless, it seems clear that the false-positive rate and costs argue that unless a woman meets specific criteria (eg, International Sensitivity Index recommendations), stress radionuclide or stress echocardiogram are better initial tests. I will use exercise treadmill testing when evaluating exercise capacity in my women patients.

Lynda Montgomery, MD, MEd, *Case Western Reserve University School of Medicine, University Hospitals of Cleveland, Ohio*

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How effective are leukotriene inhibitors for asthma in children?

EVIDENCE-BASED ANSWER

Evidence on the use of leukotriene inhibitors in children is insufficient to permit conclusions regarding efficacy. Given the proven efficacy of inhaled corticosteroids in asthma management, leukotriene inhibitors should not replace inhaled corticosteroids for maintenance of asthma in children (strength of recommendation: **B**).

Current guidelines that list leukotriene inhibitors as a potential addition or alternative to corticosteroid therapy in children with asthma appear to be based on scant studies and extrapolation from adult research.

EVIDENCE SUMMARY

Asthma is characterized by inflammation of the bronchial airways. Leukotrienes are potent mediators of inflammation and are believed to contribute significantly to the inflammatory pathophysiology of asthma. Leukotriene inhibitors interfere with leukotriene production or leukotriene receptors and thus inhibit inflammation.[1]

Leukotriene inhibitors are administered orally, a significant advantage over inhalation in the pediatric population. For children, the theoretical corticosteroid-sparing effect of leukotriene inhibitors is appealing but has not been demonstrated.

In January 2002, Cochrane reviewers identified 3 studies of leukotriene inhibitor use in children that met their quality criteria for meta-analysis. Unfortunately, recent changes in asthma classification terminology make it difficult to precisely translate past studies into current practice. Based on these studies, the Cochrane reviewers concluded there is insufficient evidence to support the use of leukotriene inhibitors in children as monotherapy or as an addition to corticosteroids.[1,2]

One randomized, double-blind crossover study of 279 children with corticosteroid-dependent (persistent) asthma compared montelukast 5 mg (Singulair) once a day plus inhaled budesonide 200 μg (Pulmicort) twice a day with placebo plus budesonide (Rhinocort). Each study period lasted only 4 weeks, starting after a 4-week run-in period. Montelukast modestly improved asthma control over placebo. Compared with the placebo period, montelukast decreased the average use of beta-agonists by 1 puff per day. Asthma exacerbation days decreased by about 1 per month during montelukast treatment. The effects of montelukast and placebo on forced expiratory volume in 1 second (FEV_1), quality of life, and adverse events did not differ significantly.[3]

One randomized, open-label crossover study of 124 children with "mild" asthma found that montelukast provided equivalent control and superior patient and parent satisfaction when compared with inhaled corticosteroids. Outcomes assessed were FEV_1, school and work loss, medical resource utilization, safety, and patient and parent satisfaction. Children entering this study were self-selected to extend participation from a previous larger study that did not meet Cochrane quality criteria for inclusion in meta-analysis. The authors acknowledge the potential for selection bias.[4]

A randomized, double-blind, placebo-controlled study of 338 patients aged 12 years to adult compared zafirlukast (Accolate) with fluticasone propionate (Flovent) for control of persistent asthma. This study concluded that fluticasone was superior for all clinical outcomes measured including symptom scores, albuterol use, nighttime awakenings pulmonary function, and number of exacerbations requiring oral corticosteroids. Pooling of adult and adolescent cases in this study limits generalized application of these results to pediatric practice.[5]

RECOMMENDATIONS FROM OTHERS

The National Asthma Education and Prevention Program[6] and the Global Initiative for Asthma[7] guidelines conclude that inhaled corticosteroid, at the lowest effective dose, is the preferred therapy for children of all ages with persistent asthma whether mild, moderate, or severe.

Both guidelines list leukotriene inhibitors as a potential adjunct to corticosteroids for moderate persistent asthma, as an alternative to corticosteroids plus long-acting beta$_2$-agonist. The guidelines also list leukotriene inhibitors as an alternative treatment to inhaled corticosteroids for mild persistent asthma in patients aged >5 years. Montelukast (Singulair) is approved for use in children aged ≥12 months, zafirlukast (Accolate) is approved for children aged ≥5 years, and zileuton (Zyflo) is approved only for children aged >12 years.

Nancy E. Morden, MD, *Department of Family Medicine, University of Washington, Seattle;* ***Leilani St. Anna, MLIS, AHIP,*** *University of Washington Health Sciences Library, Seattle*

CLINICAL COMMENTARY

An inhaled corticosteroid controller should be the first step

Until evidence supports a different conclusion, I think we should continue to follow current national and global guidelines. The most important concept in both is that once a child is diagnosed with persistent asthma, starting an inhaled corticosteroid controller should be the first step.

Leukotriene inhibitors should be considered as second or third choice as a controller. The main indications for using a leukotriene inhibitor are aspirin-sensitive, exercise-induced, and nocturnal asthma. I would use a leukotriene inhibitor as a controller only if a patient could not comply with inhaled corticosteroids.

Lawrence S. Slotnick, MD, *Moses Cone Health System, Greensboro, NC*

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Which blood tests are most helpful in evaluating pelvic inflammatory disease?

EVIDENCE-BASED ANSWER

No individual or combination of blood tests can reliably diagnose pelvic inflammatory disease (PID) (strength of recommendation [SOR]: **A**, meta-analysis). The combination of white blood cell count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and vaginal white blood cells can reliably exclude PID if results for all 4 tests are normal (sensitivity=100%) (SOR: **B**, cohort study, reference standard not uniformly applied).

The combination of CRP and ESR is helpful in excluding PID (sensitivity=91%) and may be especially useful in distinguishing mild from complicated cases (SOR: **B**, small cohort study). Individual tests do not appear to significantly improve diagnostic accuracy, although the CRP and ESR are somewhat useful to rule out PID (SOR: **B**, small cohort study).

EVIDENCE SUMMARY

Because of the significant inflammatory sequelae of PID, it is the standard of care to treat women with suggestive signs and symptoms. Clinical

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TABLE

Diagnostic performance of blood tests for pelvic inflammatory disease

	Sn (%)	Sp (%)	PPV (%)*	NPV (%)*
WBC (>10,000/mm^3)[2]	57	88	88	58
ESR (>15 mm/hr)[2]	70	52	69	54
CRP (>5 mg/dL)[2]	71	66	76	60
Vaginal WBCs[2]	78	39	66	54
0 of 4 of the above positive[2]	100	18	100	65
4 of 4 of the above positive[2]	29	95	90	47
CRP >20 or ESR >15[3]	91	50	N/A	N/A
CRP >60 or ESR >40[4]	97	61	70	96
CRP (metaanalysis)[5]	74%–93%	50%–90%		
ESR (metaanalysis)[5]	64%–81%	43%–69%		

*Prevalence=60%. SN, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; WBC, white blood cells; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

diagnosis has a positive predictive value of 65% to 90% compared with laparoscopy.[1] While no single test is both sensitive and specific, a combination of biochemical tests for inflammation may improve the ability to rule out PID.

A prospective cohort study of 120 women presenting to an ambulatory center with symptoms of PID evaluated the tests commonly used to support the clinical diagnosis of PID.[2] The objective criteria used for diagnosis included histologic evidence of acute endometritis via endometrial biopsy, purulent exudates in the pelvis on laparoscopy, or microbiologic evidence of *Neisseris gonorrhea* or *Chlamydia trachomatis* from the upper genital tract. The **Table** shows the sensitivities, specificities, and predictive values for an elevated white blood cells (>10,000/mm), ESR (>15 mm/hr), CRP (>5 mg/dL), and increased vaginal white blood cells (>3 white blood cells/high-power field) for detection of PID. If all 4 test results are negative, PID is reliably ruled out with a sensitivity of 100%. These results may be an overestimate, as the gold standard was not uniformly applied.

The role of CRP and ESR in the diagnosis of acute PID was studied in 41 women with clinically suspected acute PID who presented to a university department of obstetrics and gynecology.[3] Women underwent laparoscopy, endometrial sampling, and cultures of the upper genital tract to confirm the diagnosis. When considered together, a positive value in either the ESR (cutoff level of 15 mm/hr) or CRP (cutoff >20 mg/dL) had a sensitivity of 91% and a specificity of 50%.

Another report looked at the ability of ESR and CRP to differentiate between mild, moderate, and severe PID in 72 women undergoing laparoscopy at a university department of gynecology.[4] The cutoff levels were ESR >40 mm/hr and CRP >60

mg/dL. If either test was abnormal, the sensitivity and the negative predictive value for severe disease were 97% and 96%, respectively (**Table**). All patients with tuboovarian abscess or perihepatitis and 6 of 7 patients who had anaerobic bacteria isolated from the fallopian tubes tested positive with these cutoff levels.

A meta-analysis from 1991 found 12 studies, not including any of the above studies, and assessed the laboratory criteria for the diagnosis of PID. No single or combination diagnostic indicator was found to reliably predict PID. However, the CRP and the ESR were useful in ruling out PID, with good sensitivities for CRP in 4 of 4 studies analyzed (74%–93%) and for the ESR in 4 of 6 studies (64%–81%). Ten of 12 studies used laparoscopy as the gold standard.[5]

RECOMMENDATIONS FROM OTHERS

The Centers for Disease Control and Prevention makes no specific recommendation for the use of specific blood tests in the diagnosis of PID.[1] The Association for Genitourinary Medicine states that an elevated ESR or CRP supports the diagnosis of PID.[6]

Mary N. Hall, MD, Laura Leach, MLIS, *Carolinas Healthcare System, Charlotte, NC*

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CLINICAL COMMENTARY

When diagnosing PID, a clinician must have a high index of suspicion

PID is a difficult diagnosis to make, without clear-cut diagnostic guideposts. The sequelae of PID can be so serious that clinicians must not miss this diagnosis. If results of all 4 tests described above are negative, this can reliably rule out the diagnosis.

Unfortunately, no set of tests can reliably confirm the diagnosis in all cases. The traditional triad of lower abdominal pain, cervical motion tenderness, and adnexal pain are still taught as the classic findings for diagnosing PID. The clinician must also have a high index of suspicion, particularly with teen-agers with abdominal pain, and when the pain is indolent and lingering.

Nonetheless, a recent study concludes there is insufficient evidence to support existing clinical diagnostic criteria and recommends that the clinical criteria for PID be redefined. In a group of patients with laparoscopically confirmed PID, no variable (abnormal vaginal discharge, fever >38°C, vomiting, menstrual irregularity, ongoing bleeding, symptoms of urethritis, rectal temperature >38°C, marked tenderness of pelvic organs on bimanual examination, adnexal mass, and ESR >15 mm) reliably predicted the disease, and found, rather, that most had low specificity and sensitivity. The chance of having PID based on the presence of lower abdominal pain was 79%. Three variables predicted 65% of the cases of PID: elevated ESR, fever, and adnexal tenderness. When evaluating patients for admission, some authors add "the desire to bear children" to the standard admission criteria, which include severity of sickness, pregnancy, possible need for surgical intervention, lack of response to oral medications, or immunosuppression.

Ellen Beck, MD, *University of California–San Diego*