3-year interval between Pap smears adequate for women with prior negative results


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■ PRACTICE RECOMMENDATIONS
This study predicts that among women aged 30 to 64 years with 3 recent, negative Papanicolaou (Pap) smears, extending the interval for cervical cancer screening from 1 to 3 years would lead to an excess risk of cervical cancer of 3 in 100,000.

For women aged 30 to 44 years, preventing 1 case of cervical cancer through yearly Pap smears would require an additional 69,665 Pap smears and 3861 colposcopies (compared with screening 3 years after the last negative Pap smear). Clinicians should feel comfortable extending the interval for Pap smears from 1 to 3 years in women with prior normal results and a high likelihood of follow-up.

■ BACKGROUND
The United States Preventive Services Task Force recommends that sexually active women receive Pap smears at least every 3 years. The American Cancer Society also recommends screening every 3 years for women aged >30 years with 3 prior normal Pap smear results.

Despite these guidelines, many physicians and patients feel uncomfortable extending the interval for screening, perhaps due to a lack of quantita-

tive information on the excess risk of cervical cancer associated with this practice. This study estimates the excess risk of cervical cancer associated with extending the screening interval for women with prior normal Pap smear results.

■ POPULATION STUDIED
The authors analyzed data from the National Breast and Cervical Cancer Early Detection Program (NBCCEDP), which has offered cervical cancer screening to low-income, uninsured women throughout the United States since 1991. Women in this program are disproportionately of lower socioeconomic status and at higher risk for cervical neoplasia.

The study included cervical cytologic and biopsy results from 938,576 women aged <65 years, obtained from 1991 to 2000. Data from this study are generalizable to primary care populations seen by family physicians.

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— STUDY DESIGN AND VALIDITY

The researchers analyzed the NBCCEDP data to determine the prevalence of biopsy-proven cervical neoplasia in women with 1–3 recent negative Pap smears. They used a Markov model of cervical dysplasia progression to predict the risk of invasive cancer in the next 3 years, assuming yearly follow-up screening or screening 3 years after the last normal result. The definition of prior recent, negative Pap smears included those performed within 3 years of each other and reported as normal or indicating presence of infection or reactive changes.

To model the effect of different screening intervals, the researchers assumed a sensitivity of 51% and specificity of 97% for Pap smears, with a positive test defined as atypical squamous cells of undetermined significance (ASCUS) or worse, and disease defined as grade 1 cervical intraepithelial neoplasia (CIN 1) or higher on biopsy. Colposcopy was assumed to be 100% sensitive and specific, and treatment of dysplasia to be 100% effective.

The strength of this study is the use of a large, prospective database to determine the initial prevalence of cervical neoplasia in women with prior normal Pap smears. The weakness is the use of a mathematical model to predict subsequent rates of cervical cancer. The predictions of this simulation depend on the initial prevalence of neoplasia and rates of progression between disease states entered into the model.

The authors sensitivity-tested the results by varying initial neoplasia prevalence estimates by a factor of 2 and assuming that CIN 2 lesions could progress either like CIN 1 or CIN 3. Varying these assumptions had relatively little impact on the results, suggesting that these are likely to be reliable estimates. The authors also assumed 100% patient compliance with follow-up in their model, and point out that the excess risk of cervical cancer associated with longer screening intervals would be greater if follow-up was incomplete. (Level of evidence: 1b)

— OUTCOMES MEASURED

Measured outcomes were the excess risk of invasive cervical cancer associated with extended screening interval and the number of Pap smears and colposcopies required to prevent 1 case of cancer with more frequent screening.

— RESULTS

Among women with 3 prior negative Pap smears, the estimated excess risk of cervical cancer associated with screening once at 3 years instead of yearly was 5 per 100,000 for women <30 years of age, 3 per 100,000 for women age 30 to 44, 1 per 100,000 for women 45 to 59, and 0 for women 60 to 64 years of age. Prevention of 1 case of cervical cancer through screening annually rather than once at 3 years would require an additional 42,621 Pap smears and 2364 colposcopies for women aged <30 years; 69,665 Pap smears and 3861 colposcopies for women aged 30 to 44; and 209,324 Pap smears with 11,502 colposcopies for women aged 45 to 59.

Epinephrine is efficacious for outpatient treatment of bronchiolitis


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— PRACTICE RECOMMENDATIONS

Epinephrine provides small short-term benefits in ambulatory patients with acute bronchiolitis; however, it is not definitely better than albuterol.

Data do not support using epinephrine for inpatient bronchiolitis. This question remains unanswered due to the small size of the studies included in this meta-analysis and the absence of a reliable clinical scoring system to measure response in bronchiolitis.
Inhaled epinephrine is the most frequently prescribed bronchodilator for acute viral bronchiolitis. It stimulates alpha-receptors in the bronchiolar vasculature and may potentially be more effective than other commonly used bronchodilators (ie, albuterol and ipratropium). Although some data suggest that epinephrine is more effective than placebo in ambulatory patients, its benefit has not been universally accepted due to inconsistent findings in clinical trials and a lack of demonstrated response in hospitalized patients.

In this meta-analysis, the researchers included randomized, double-blind, clinical trials evaluating the efficacy of epinephrine vs placebo or epinephrine vs other bronchodilators in the treatment of bronchiolitis for hospitalized or ambulatory patients aged 2 years or younger. Bronchiolitis was defined as wheezing (with or without cough, tachypnea, and increased respiratory effort) associated with clinical evidence of a viral infection (eg, coryza and fever).

One researcher searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and reference lists from articles to identify eligible clinical trials. Non-English-language publications were translated for evaluation. The researcher included a study if it reported at least 1 of the following outcome measures: clinical score, oxygen saturation (via oximetry), admission rates, length of hospital stay, respiratory rate, heart rate, and results of pulmonary function tests.

Two reviewers independently evaluated trials for inclusion, and only those that both agreed upon were selected. A standard form was used to note study characteristics, participants, intervention, outcomes, funding sources, and results (specifically, clinical scores of efficacy). Clinical scores were converted to standardized mean differences, since the trials used 6 different clinical scores. The Jadad scale (a validated 5-point quality assessment tool) was used to assess randomization, double-blinding, withdrawals, and dropouts from included studies. Quality ranged from very poor to very good, and all studies were included.

This research has several limitations, some of which are common to meta-analysis methodology. There is no universally accepted assessment tool for evaluating clinical response in bronchiolitis. The endpoints and reported clinical results from these studies varied. Clinical scores of efficacy were established to provide some common marker of response. They were derived by extracting data from tables, recalculations of reported results (eg, 95% confidence intervals, standard deviations, means, medians), graphs, and, in some instances, by requesting additional data from the original investigators.

Only a few studies had common clinical scores, resulting in a small number of subjects included in the multiple comparisons. A statistically significant heterogeneity was seen among the trials, and most clinical scores reflected only short-term markers of efficacy (up to 4 hours post-treatment). Additionally, the method to attain consensus for discrepancies between the 2 independent investigators that reviewed studies for inclusion was not described. (Level of evidence: 1a–)

Inpatient and outpatient study data were compared independently. Clinical scores of response at different times after treatment, changes in oxygen saturation, “improvement,” length of stay, and pallor after treatment were reported. The researchers converted the data into standardized mean differences in clinical scores (effect size).

Fourteen clinical trials (7 inpatient, 6 outpatient, and 1 unknown) were included in this meta-analysis. All the studies were small, with the largest including only 194 patients.

Compared with placebo, epinephrine showed no difference in clinical scores 30 minutes after treatment, oxygenation, or length of stay in the
inpatient studies. Clinical scores modestly improved 60 minutes after treatment. In the outpatient studies, epinephrine produced modest improvement in clinical scores compared with placebo 60 minutes after treatment, but not at 30 minutes. Oxygenation modestly improved after 30 minutes but no difference in oxygenation was seen after 60 minutes.

For the vague global outcome of “improvement,” the number needed to treat was 1.7 (95% confidence interval, 1.3–2.5). No difference was seen in admission rates.

When comparing epinephrine with albuterol, no differences were seen in any measured outcomes in inpatients; however, some outcomes were different among outpatients. Changes in oxygenation after 60 minutes, “improvement,” and pallor were statistically better with epinephrine compared with albuterol.

Geranium extract reduces bronchitis symptoms


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PRACTICE RECOMMENDATIONS

This study provides very good evidence that geranium root (Pelargonium sidoides) extract significantly reduces the severity and duration of acute bronchitis symptoms with minimal side effects. Clinicians should recommend this extract for acute bronchitis.

Umcka, a geranium root extract, is marketed in the US, but clinicians should keep in mind that purity and standardization of herbal products are not regulated, and that this report did not include children or pregnant women.

BACKGROUND

Acute bronchitis is common in primary care, but controversy remains about appropriate management. Symptomatic therapy is the mainstay of treatment, although antibiotics are commonly used. This randomized controlled trial assessed the effectiveness of geranium root extract in reducing bronchitis symptoms.

POPULATION STUDIED

The authors enrolled 476 adults with a clinical diagnosis of bronchitis from primary care medical centers in Germany. Subjects needed to have at least 48 hours of illness and severe symptoms, as measured by a Bronchitis Severity Score (BSS) of at least 5 points (0–4 points of severity given to each of 5 features: cough, sputum, rales/rhonchi, tussive chest pain, dyspnea). Exclusion criteria included antibiotic therapy in the previous 4 weeks; asthma; severe heart, renal, or liver disease; immunosuppression; drug or alcohol abuse; and pregnancy or lactation.

Sixty-four percent of the subjects were female and the average age was 40.5 years. At baseline, 67% of subjects were unable to work. Thus, the patients seem similar to those in a typical US practice, although customs related to absence from work due to illness may be different. Unfortunately, the study did not include information on smoking and other medical conditions, such as pulmonary disease.

STUDY DESIGN AND VALIDITY

This was a randomized, double-blind, placebo-controlled prospective study with concealed allocation. Acute bronchitis was diagnosed clinically, and the severity was assessed using the BSS. Treatment consisted of 1.5 mL of aqueous ethanolic extract (11%) of P. sidoides root 3 times daily for 7 days. Placebo was matched for color, taste, smell, and viscosity.

During follow-up visits at 3 to 5 days and 7 days, clinical exam, BSS, and other outcomes information were recorded. Analysis was by intention-to-treat; researchers did not statistically
assess possible confounding factors. Adverse events were also recorded and analyzed by frequency, severity, and likely correlation with intervention.

The methodological strength of this study was excellent. Strengths included concealed allocation, the good-quality placebo, intention-to-treat analysis, data quality assurance, and a low dropout rate. The German setting allowed the use of standardized herbal products. Weaknesses included the lack of information on the diagnostic criteria for bronchitis, lack of correction for multiple comparisons, and the lack of attention to potentially important confounding factors such as smoking, pulmonary disease, and the use of other remedies. Funding for the study was provided by the manufacturer. (Level of evidence: 1c)

■ OUTCOMES MEASURED
The primary outcome was the change in BSS on day 7. Secondary outcomes included the change in specific symptoms, change in health status and quality of life according to questionnaires, patient satisfaction, and work status. Cost and clinician satisfaction were not addressed.

■ RESULTS
Treatment and control groups were similar at the outset; follow-up was 98%. Patients taking geranium extract had lower BSS scores on day 7 than those taking placebo (3.0 points difference; P<.0001). The same pattern was found for improvement or disappearance of cough (89% vs 57%; number needed to treat [NNT]=3), hoarseness (82% vs 58%; NNT=3), headache (90% vs 62%; NNT=3), fever (97% vs 58%; NNT=3), rales/rhonchi (91% vs 57%; NNT=3).

Patients taking extract were more satisfied with treatment (75% vs 42%; NNT=3), and more returned to work at 7 days (84% vs 57%; P<.0001; NNT=4). Adverse events were rare but occurred more commonly with extract (8.6% vs 6.8%, number needed to harm=56); none were severe.

Donepezil minimally effective for patients with vascular dementia

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■ PRACTICE RECOMMENDATIONS
Donepezil (Aricept—a potent acetylcholinesterase inhibitor) had small effects on mentation for patients with mild to moderate vascular dementia as measured by validated instruments of cognition.

Donepezil’s side effects are similar to placebo at 5 mg but double at 10 mg, with no improvement in the patient’s cognition. Even though this medication was minimally effective, there are no other highly effective medical treatments for vascular dementia. Therefore, if a patient chooses a trial of donepezil, the lower, 5-mg dose should be offered.

The medication’s effect is likely a class effect and not an individual drug effect; therefore, rivastigmine (Exelon) and galantamine (Reminyl) are 2 other acetylcholinesterase inhibitors that should also be considered. Cost is similar for all 3 drugs at about $130.00 per month.

■ BACKGROUND
Donepezil provides some benefits in cognition, global function, and activities of daily living for patients with mild to moderate dementia from Alzheimer disease. There has been no conclusive evidence of similar beneficial effects of cholinergic agents in vascular dementia.

■ POPULATION STUDIED
The researchers studied an international group

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Although donepezil is minimally effective, there are no more effective treatments for vascular dementia of men and women (n=603), average age 74 years, with Mini-Mental State Examination (MMSE) scores between 10 and 26 (out of a possible 30) and radiographic abnormalities consistent with cerebrovascular disease. Patients were classified as having probable vascular dementia (70%) or possible (30%) vascular dementia according to criteria of the National Institute of Neurologic Disorders and Stroke.

Patients were excluded if they had neurodegenerative disorders, Alzheimer dementia, new strokes, psychiatric disorders including major depression, or other serious medical conditions.

■ STUDY DESIGN AND VALIDITY
This was a 24-week, double-blind, randomized (masked allocation) study. Patients received single daily doses of donepezil (5 or 10 mg) or matching placebo. Researchers performed psychometric evaluations, physical and neurological examinations, laboratory determinations, and measurements of vital signs at screening, baseline, and (together with checks for medication compliance and adverse events) at weeks 6, 12, 18, and 24.

The groups were similar in baseline characteristics. Researchers analyzed the subjects in the groups to which they were assigned (intention-to-treat analysis). A total of 79% of patients completed the entire study; dropout rates and reasons for doing so were equal in the placebo and 5-mg groups, but increased in the 10-mg group due to larger numbers of adverse events. Most of the patients were from the US and Canada, with a smaller proportion from other countries. The results are likely generalizable to primary care practice. (Level of evidence: 2b)

■ OUTCOMES MEASURED
The primary efficacy outcome measured was cognition as assessed by the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Clinician’s Interview-Based Impression of Change-Plus version (CIBIC-plus). Secondary efficacy endpoints were based on the MMSE, the Sum of the Boxes of the Clinical Dementia Rating (CDR-SB), and the Alzheimer’s Disease Functional Assessment and Change Scale (ADFACS).

■ RESULTS
While the donepezil-treated groups showed statistically significant improvement as measured by the ADAS-cog (2 points improvement vs no change in placebo group), as many patients got worse as got better as measured by the CIBIC-plus. MMSEs improved by $1.04 \pm 0.21$ ($P<.05$) and $1.49 \pm 0.20$ ($P<.001$) points in the 5- and 10-mg groups, respectively, compared with $0.39 \pm 0.23$ in the placebo group. Activities of daily living did not deteriorate as much in the treatment groups—$0.64 \pm 0.36$ ($P<.05$) for the 5-mg group and $0.53 \pm 0.38$ ($P<.05$) for the 10-mg group, compared with $1.44 \pm 0.42$ for placebo.

Adverse events were similar to placebo in the 5-mg group (22%) but double in the 10-mg group (44%). The most common side effects included nausea, diarrhea cramps, anorexia, vomiting, headache, and abnormal dreams.
First-trimester tests for trisomies 21 and 18 as sensitive as triple screen


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PRACTICE RECOMMENDATIONS
First-trimester screening for trisomies 21 and 18 with maternal serum markers and ultrasonographic measurement of fetal nuchal translucency is more sensitive than second-trimester “triple screen.” Application of this finding to general practice is limited by lack of access to radiologists trained in this more specialized prenatal ultrasound measurement.

BACKGROUND
Women who are deemed to have abnormal calculated risks for trisomy 21 (Down syndrome—the most common trisomy) or trisomy 18 (Edwards syndrome, a much less common but more severe type of aneuploid pregnancy) and elect to undergo second-trimester triple screening are counseled on ultrasound and confirmatory fetal karyotype testing, typically amniocentesis.

A woman electing to terminate a pregnancy confirmed to be with a trisomy 21 or trisomy 18 fetus in the second trimester experiences decreased privacy and increased risk relative to a similar elective termination in the first trimester; consequently, efforts have been made to identify and evaluate first-trimester screening tests for trisomies 21 and 18 (at which time chorionic villus sampling is the most likely confirmatory test).

A further goal is to increase the specificity of the screening test(s) for trisomies 21 and 18 so that fewer women are subjected to the anxiety and uncertainty of a false-positive screening test or, more importantly, exposed to the risk of undesired miscarriage of a normal fetus during confirmatory testing.

Several small prospective studies have independently assessed first-trimester maternal serum markers or fetal ultrasound; the present study seeks to combine these methods of screening among a larger population of women at multiple centers.

POPULATION STUDIED
Women at 12 academic prenatal diagnostic centers in the US and Canada who were between 10 4/7 and 13 6/7 weeks gestation were offered first-trimester screening if they met inclusion criteria: a singleton gestation that was not the product of a donor oocyte, no significant recent vaginal bleeding, no other indications for prenatal diagnosis, and no diabetes. A total of 8816 eligible patients consented.

Fifty percent of these subjects were aged >35 years, an age range representing the most readily identified subset of patients with increased risk for trisomies 21 and 18. Most (83%) of the women were white; thus, minority groups were underrepresented.

STUDY DESIGN AND VALIDITY
First-trimester screening consisted of maternal serum measurements of free beta human chorionic gonadotropin and pregnancy-associated plasma protein A, along with ultrasonographic measurement of fetal nuchal translucency. These biochemical markers and ultrasound measurement were analyzed independently and together to compute patient-specific risks.

The cutoff to define an abnormal test was chosen to identify a risk of 1 in 270 for trisomy 21 and 1 in 150 for trisomy 18. These values are consistent with the cutoffs used for standard second-trimester screening. The patient-specific first-trimester risks were, in turn, analyzed for sensitivity and specificity. Most (93%) of the
With first-trimester screening, 85% of women aged ≥35 years could avoid an invasive diagnostic procedure.

Strengths of study design and application include the number of women, the use of multiple testing centers, the use of a common laboratory to process maternal serum tests, specific training, certification and quality review of ultrasonographers, and large percentage of subjects included in the final analysis. Limitations include the underrepresentation of ethnic minorities. (Level of evidence: 1b)

OUTCOMES MEASURED
The primary study outcomes were sensitivity and specificity of the first-trimester screening tools as determined by knowledge of fetal karyotype or newborn phenotype.

RESULTS
The investigators found that a combination of maternal age, the 2 serum markers, and nuchal translucency in the first trimester was 89% sensitive and 89% specific for identification of trisomy 18 (11 cases) or 21 (61 cases). The stated sensitivity and specificity of second-trimester triple screen for trisomy 21 are 65% and 95%, respectively.

First-trimester screening was more sensitive in women aged ≥35 years (91.2% vs 80.0%) but less specific. The false-positive rate was 16.8% in women ≥35 years and only 4.7% in women <35 years. In women ≥35 years, this protocol identified all 11 cases of trisomy 18 and 90% of those involving trisomy 21.

The investigators conclude that if first-trimester screening replaced advanced maternal age as the primary criteria whereby to recommend prenatal karyotyping, 85% of women aged ≥35 years could avoid an invasive diagnostic procedure. Paired (serum markers and ultrasound) first-trimester screening was superior to serum markers alone (P=.006), but not significantly different than ultrasound alone.

High-dose azithromycin or amoxicillin-clavulanate for recurrent otitis media?


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PRACTICE RECOMMENDATIONS
Use high-dose azithromycin for 3 days if antibiotics are needed, instead of a 10-day course of high-dose amoxicillin-clavulanate for the treatment of recurrent or persistent acute otitis media. For every 10 children using azithromycin instead of amoxicillin-clavulanate, there is 1 additional clinical cure at 1 month and 1 less episode of diarrhea. However, no difference in clinical success is seen at 2 weeks.

BACKGROUND
High-dose amoxicillin-clavulanate is recommended for children with acute otitis media (AOM) who have not improved on previous treatment or have had recent antimicrobial exposure. Azithromycin is an alternative only for patients with documented allergy to beta-lactam antibiotics.

POPULATION STUDIED
The authors studied 304 patients aged between 6 months and 6 years with recurrent or persistent AOM. AOM was diagnosed by the presence of at least 2 of the following: decreased or absent mobility of the tympanic membrane, yellow or white discoloration, opacification, or acute perforation with purulence. In addition, 1 of the following had to be present to make the diagnosis: ear pain within 24 hours, hyperemia...
After 1 month, the clinical response rate of azithromycin was slightly greater than amoxicillin-clavulanate of the tympanic membrane, or bulging of the tympanic membrane.

Recurrent AOM was defined as at least 1 episode within 30 days of enrollment, 3 or more episodes within 6 months of enrollment, or at least 4 episodes within 12 months of enrollment. Persistent AOM was defined as the presence of signs and symptoms after at least 48 hours of antibiotic treatment. Sixty-eight percent of children had recurrent AOM and 19% had persistent AOM; the remainder had both. Forty-three percent of patients had their first episode of AOM before 6 months of age.

**STUDY DESIGN AND VALIDITY**

Patients were enrolled into the trial in 13 US and 5 Latin American centers. Patients were randomly assigned to receive high-dose amoxicillin-clavulanate at 90/6.4 mg/kg/d for 10 days plus azithromycin placebo or high-dose azithromycin, 20 mg/kg/d, for 3 days plus amoxicillin-clavulanate placebo. Clinical, otoscopic, and safety assessments were made at baseline, after 2 weeks, and at the end of the study (days 28–32). Additionally, tympanocentesis was performed before the study drug was administered and pathogens from middle-ear fluid samples were isolated and identified.

Both patients/caregivers and investigators were blinded to treatment assignment. Allocation concealment was not mentioned. Analyses were performed by intention-to-treat. Of 304 patients, 4 were excluded from the safety analysis (no reason given). Of the remaining 300 patients, 4 were excluded from analysis due to incorrect diagnosis or because they did not meet inclusion criteria. The percentage of children attending day care was similar in both treatment groups. Numbers of patients with persistent AOM, recurrent AOM, or both were not different between groups. (*Level of evidence: 1b*)

**OUTCOMES MEASURED**

The primary endpoint of the study was clinical response (cure, improvement, or worsening) at day 28 to 32. The secondary endpoint was clinical response at days 12 to 16. Adverse effects were also recorded.

**RESULTS**

After 1 month, the clinical response rate (cure or improvement) of azithromycin was slightly greater than amoxicillin-clavulanate—72% vs 61%, respectively (*P* = .047, number needed to treat=9). At days 12 to 16, clinical success rates were similar between the 2 groups (about 85%). With children in whom a bacterial pathogen was identified (55%), clinical success rates did not significantly differ. The incidence of diarrhea was higher in the amoxicillin-clavulanate patients (29.9% vs 19.6%; number needed to harm=10; *P* = .045).

**REFERENCE**


**DRUG BRAND NAMES**

- Amoxicillin/clavulanate • Atacand
- Azithromycin • Zithromax
- Donepezil • Aricept
- Galantamine • Reminyl
- Ipratropium • Atrovent; Apo-Ipravent
- Rivastigmine • Exelon