

POEMs

PATIENT ORIENTED EVIDENCE THAT MATTERS

Practice Recommendations from Key Studies

Which cytology results predict cervical intraepithelial neoplasia?

Cox JT, Schiffman M, Solomon D. Prospective follow-up suggests similar risk of subsequent cervical intraepithelial neoplasia grade 1 or negative colposcopy and directed biopsy. Am J Obstet Gynecol 2003; 188:1406-1412.

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■ PRACTICE RECOMMENDATIONS

For women with cervical cytology results showing atypical squamous cell of undetermined significance (ASCUS) and positive results on DNA testing of a cervical sample for human papillomavirus (HPV) high-risk types, about 1 out of 8 progress to cervical intraepithelial neoplasia (CIN) grades 2 or 3 within 2 years of initial colposcopy results showing not more than CIN 1. Since women with cytology results of low-grade squamous intraepithelial lesion (LSIL) progress to CIN 2 or 3 in the same proportion, management protocols for HPV-positive ASCUS and LSIL should be identical.

■ BACKGROUND

Each year about 3 million women in the United States have cervical cytology results showing LSIL or ASCUS. Appropriate management of these cases has been the subject of some controversy. The ASCUS-LSIL Triage Study (ALTS) was a large, federally funded trial of alternative strategies for the initial management of women with mildly abnormal cytology results.

■ POPULATION STUDIED

Women were referred to the study from community practice if they had cervical cytology

results showing ASCUS or LSIL. In most cases women referred to the study had their Pap smears obtained by traditional spatula and brush technique (n=5060; 3488 with ASCUS and 1572 with LSIL).

■ STUDY DESIGN AND VALIDITY

This was a carefully designed randomized controlled trial. Allocation to treatment group was concealed from the enrolling investigator. Blinding was not feasible. However, the study providers were blinded to some test results, according to the arm of the treatment. Pathology specimens were read twice as a quality-control measure.

At the time of enrollment and 6, 12, and 18 months later, all subjects had a Thin-Prep cytology, cervical DNA testing for HPV high-risk types, and 2 cervigrams. Randomization was to 1 of 3 study arms: 1) immediate colposcopy at the time of enrollment, 2) HPV triage and colposcopy only if enrollment cytology was high-grade intraepithelial lesion (HSIL) or LSIL-ASCUS and HPV-positive testing for high-risk subtypes, or 3) conservative management with blinding to HPV results, and colposcopy performed only when cytology results showed HSIL.

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What is a POEM?

Each month, the POEMs (Patient-Oriented Evidence that Matters) editorial team reviews 105 research journals in many specialties, and selects and evaluates studies that investigate important primary care problems, measure meaningful outcomes, and have the potential to change the way medicine is practiced. Each POEM offers a Practice Recommendation and summarizes the study's objective, patient population, study design and validity, and results. The collected POEMs are available online at www.jfponline.com.

Follow-up visits were conducted at 6, 12, and 18 months in all study arms, with specimens obtained as at enrollment. Women were referred (or referred again) to colposcopy for HSIL cytology results. Women with CIN 2 or 3 diagnosed during the study had a loop electrical excision procedure. A final assessment including colposcopy was performed 24 months after enrollment, at which time the study clinician had unblinded awareness of all prior test results. Positive pathology results at any time during the study including the final assessment was used as the diagnostic “gold standard.”

■ OUTCOMES MEASURED

A secondary analysis was performed to compare cases of cytology results of HPV-positive ASCUS and LSIL and their respective risks of progression to CIN 2 or 3. The intention was to separate prevalent cases of CIN 2 and 3 from those that progressed during the 2-year follow up period. So only those women who underwent colposcopy as an initial management strategy were included. They were the women randomized to the immediate colposcopy arm of the study and those who underwent initial colposcopy based on ASCUS or LSIL with a positive HPV test. They considered a diagnosis of CIN 2 or 3 by initial colposcopy to be prevalent cases, and did recognize that a few prevalent cases of CIN 2 or 3 could have been missed at the time of initial colposcopic assessment.

■ RESULTS

The study included 1193 women with HPV-positive ASCUS and 897 cases of LSIL who were randomized to receive initial colposcopy. Initial assessment with colposcopy and biopsy when the study clinician considered it to be indicated demonstrated CIN 2 or 3 in 17% in each of these groups (203/1197 and 152/897). After excluding women with CIN 2 or 3 diagnosed at enrollment, in the remaining women—with CIN 1, negative biopsy, or negative colposcopy with no biopsy taken—12% in each group (107/905 and 87/682)

were diagnosed with CIN 2 or 3 by the end of the 2 years of follow-up. CIN 2 or 3 was diagnosed at any time during the study in 27% of the women with HPV-positive ASCUS and 28% of women with LSIL.

Extended-release oxybutynin and tolterodine treat overactive bladder

Diokno AC, Appell RA, Sand PK, et al. Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. Mayo Clin Proc 2003; 78:687–695.

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■ PRACTICE RECOMMENDATIONS

Extended-release versions of oxybutynin and tolterodine are similarly effective and tolerable in the treatment of women with overactive bladder. No differences are seen in reduction of weekly episodes of urge incontinence and total incontinence after 3 months of treatment. Extended-release oxybutynin is more effective than extended-release tolterodine in promoting total dryness (no episodes of incontinence) after 12 weeks of treatment. Dry mouth is more common with oxybutynin; however, other side effects are similar.

■ BACKGROUND

Overactive bladder is characterized by symptoms of urgency and frequency with or without involuntary loss of urine (urge incontinence). Overactive bladder negatively affects quality of life.¹

■ POPULATION STUDIED

Investigators at 71 US centers enrolled 799 women into this study. Enrollees averaged 21 to 60 urge incontinence episodes per week and 10 or

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more voids per day. Their average age was 60 years and more than 80% were white. About half of the patients had been treated previously with anticholinergic drugs.

■ STUDY DESIGN AND VALIDITY

Patients were randomly assigned to receive 12 weeks of treatment with extended-release oxybutynin 10 mg/d or extended-release tolterodine 4 mg/d. The patients recorded episodes of urinary urge incontinence, total incontinence, and micturition frequency in diaries at baseline, and during treatment weeks 2, 4, 8, and 12.

Both patients and investigators were blinded to treatment assignment. Researchers did not mention whether allocation was concealed. Analyses were performed by intention-to-treat. Eighty-seven percent of oxybutynin-treated and 89% of tolterodine-treated patients completed 12 weeks of treatment. Age, race, and history of previous treatment were similar between the 2 groups at baseline, as were episodes of incontinence.

■ OUTCOMES MEASURED

The primary endpoint was a reduction in episodes of urge urinary incontinence. Secondary endpoints included total incontinence episodes, micturition frequency, and adverse effects.

■ RESULTS

Both groups of patients experienced a decrease in episodes of urge urinary incontinence from about 37 per week to 11 per week. However, investigators found no difference between the treatment groups. Total incontinence episodes also decreased similarly in the 2 groups, from 43 per week at baseline to 13 per week at study end.

Although mean weekly micturition frequency was decreased to a statistically greater degree in the oxybutynin group compared with the tolterodine group, this difference is probably not clinically significant (27.7% vs 24.9%; $P=.003$; number needed to treat [NNT]=36). However, complete control of incontinence, defined as no incontinence episodes during the last week

of treatment, was reported by 23% of oxybutynin-treated and 16.8% of tolterodine-treated patients (NNT=16).

Dry mouth, although common in both groups, occurred more in oxybutynin-treated patients (29.7% vs 22.3%, number needed to harm=14).

REFERENCE

1. Abrams P, Kehheler CJ, Kerr LA, Rogers RG. Overactive bladder significantly affects quality of life. *Am J Manag Care* 2000; 6(suppl 11): S580-S590.

Carvedilol superior to metoprolol for preventing death from CHF

Poole-Wilson PA, Swedberg K, Cleland JGF, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET): a randomized controlled trial. Lancet 2003; 362:7-13.

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■ PRACTICE RECOMMENDATIONS

Among white patients with symptomatic systolic dysfunction on stable treatment with diuretics and angiotensin-converting enzyme (ACE) inhibitors, the addition of the nonselective beta-blocker carvedilol extends survival by 17% per year compared with metoprolol. This benefit translates into a number needed to treat (NNT) of 17 for 5 years. This extrapolates to an added 1.4 years of life.

It is unclear whether this benefit holds true for nonwhite patients. Carvedilol should be considered over metoprolol for treating patients with congestive heart failure to improve survival.

■ BACKGROUND

Strong evidence supports the addition of a beta-blocker for reducing mortality and hospitalization rates in patients with heart failure, and some

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Carvedilol extended survival by 17% per year compared with metoprolol

studies suggest that the nonselective beta-blocker carvedilol has a greater effect on cardiovascular indices than beta-1 selective beta blockers.

■ POPULATION STUDIED

The investigators enrolled 3029 patients with symptomatic mild to severe chronic heart failure from 341 centers in 15 European countries. Eligible patients had documented left ventricular ejection fraction of 35% or less and at least 1 cardiovascular admission during the previous 2 years. All were on stable heart failure treatment with ACE inhibitors for at least 4 weeks unless contraindicated, and on treatment with diuretics for at least 2 weeks.

Exclusion criteria were contraindications to using beta-blockers; unstable cardiac disease or hypertension; and current use of calcium channel blockers, amiodarone, or class I antiarrhythmics. The patients were predominantly male (79% of the carvedilol group and 80% of the metoprolol group) and Caucasian (99% of both groups). Most (97%) of the patients had class II or class III heart failure and appear representative of patients with heart failure seen in primary care.

■ STUDY DESIGN AND VALIDITY

Using a double-blind randomized design, the researchers randomly assigned 1511 patients with symptomatic chronic heart failure to treatment with carvedilol and 1518 to metoprolol. During an initial titration phase, the dose of each beta-blocker was increased to a target dose of carvedilol 25 mg twice daily or metoprolol 50 mg twice daily. Investigators at each site were given numbered treatment kits and were told to start with the lowest-numbered kit so that allocation was concealed. Patients were then assessed every 4 months for an average of

58 months. Data were analyzed on an intention-to-treat basis. Patients who were lost to follow-up (5) or who withdrew their consent (28) were included up to the last known date of consensual contact.

This study was well done. Measures were taken to blind patients and investigators, including the use of numbered kits of medication at allocation. It is not stated whether the tablets inside the kits were identical or whether they could be recognized by the subjects or investigators.

Study groups were similar on all baseline characteristics measured, and were treated in an identical fashion except for the drugs being studied, including methods of titration to target doses. However, while predetermined target doses were reached similarly in both groups, the mean reduction in heart rate on treatment was slightly less for the metoprolol group than the carvedilol group (11.7 vs 13.3 beats/min), suggesting that the doses were not equivalent.

Complete follow-up was excellent (99%). Only 33 (1%) subjects were lost or withdrawn by the end of the study, but all were included in the analysis. The patients were primarily Caucasian men, and the results from this study may not apply to women or people in other ethnic groups.

■ OUTCOMES MEASURED

The primary endpoints were all-cause mortality and the composite endpoint of all-cause mortality or all-cause admission.

■ RESULTS

At the end of the study, 34% of the patients on carvedilol died, compared with 40% of those on metoprolol. Adjusting for potential confounders, 15 patients would have to be treated with carvedilol instead of metoprolol for almost 5 years to prevent 1 death (number needed to treat=14.7; 95% confidence interval, 9.6–35.7). Combined mortality and hospitalization rates were not statistically significantly different between the 2 groups.

Does finasteride prevent prostate cancer?

Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003; 349:215–224.

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■ PRACTICE RECOMMENDATIONS

Treatment with finasteride will, over 7 years, decrease the prevalence of prostate cancer but increase the likelihood of developing a high-grade cancer. For every 1000 men given finasteride for prostate cancer, 62 will not develop prostate cancer. In addition, 35 men will not develop benign prostatic hypertrophy, 27 will have less urinary urgency or frequency, and 21 will report less urinary retention.

However, of those that develop prostate cancer, 13 will have higher-grade cancer (Gleason score 7 or higher), 59 will have erectile dysfunction, 58 will have a loss of libido, and 131 will have reduced volume of ejaculate. This study provides no information on the clinical significance of reducing the overall rate of cancer, while increasing higher-grade tumors. Since it is unclear whether finasteride reduces morbidity or mortality, it cannot be recommended for the routine prevention of prostate cancer.

■ BACKGROUND

Androgens play an important role in the development of prostate cancer. Finasteride blocks 5 α -reductase, an enzyme that converts testosterone to the more potent dihydrotestosterone, and may therefore help prevent prostate cancer.

■ POPULATION STUDIED

The researchers recruited 24,482 men into the study over 3 years from 221 outpatient centers. Of these, 18,882 were randomized into finasteride or placebo. The men that were included in

the study were aged 55 years or older, with no significant coexisting conditions, normal digital rectal exams, and a prostate-specific antigen (PSA) level <3.0 ng/mL. The majority of men not randomized (71%) were not enrolled due to an elevated PSA level.

■ STUDY DESIGN AND VALIDITY

This was a randomized, double-blind, placebo-controlled trial. We are not told how patients were recruited or whether allocation was appropriately concealed. Enrolled patients were placed on a placebo for 3 months, with PSA levels drawn before and after that 3-month period. If their adherence to placebo use was within 20% of expected and their PSA remained <3.0 ng/mL, the men were randomized to receive either finasteride 5 mg or a placebo daily.

The study was designed to last for 7 years. Patients received annual digital rectal exams and PSA tests. Patients with an abnormal digital rectal exam or a PSA >4.0 ng/mL had ultrasound-guided prostate biopsies. Since finasteride lowers PSA levels, those patients in the finasteride group had their PSA levels multiplied by a factor of 2 to 2.3 to ensure that the biopsy rate between the 2 groups was equivalent.

Patients who were not diagnosed with prostate cancer by the end of the study were to have end-of-study prostate biopsies. The study was terminated 15 months early by the data and safety monitoring committee, after they determined the study objective had been met.

While the researchers describe this as an intention-to-treat study, only 48% of the 18,882 men randomized were included in the final analysis. About 13.7% of the subjects did not contribute results because of early termination of the study. Almost 40% of those randomized refused to have the end-of-study prostate biopsy. It is unclear whether—or in which direction—this would bias the results of the study. The placebo run-in portion selected for more compliant patients, a situation that can overestimate the real-world effectiveness of an intervention.

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■ **OUTCOMES MEASURED**

The primary outcome of this study was the prevalence of prostate cancer. The presence of prostate cancer was based on biopsy at the end of the study, if it had not been previously diagnosed during biopsy or transurethral resection of the prostate. Other outcomes included mortality, percent of high-grade cancers (Gleason score 7–10), and biopsy rates. The researchers also gathered data on sexual and urinary side effects.

■ **RESULTS**

The number of men in the final analysis was 9060 (48% of enrollees). The incidence of prostate cancer was lower in the finasteride group (18.4% vs. 24.4%; $P=.001$; number needed to treat=16). These rates were much higher than the 6% and 4.5% the researchers expected. Significantly more high-grade cancers (Gleason grade 7–10) were seen in the finasteride group (6.4% vs 5.1%; $P=.005$; number needed to harm=77). Researchers found no significant difference in mortality between the 2 groups (7.0% vs 6.7%). Only 5 men in each group (0.05%) died of prostate cancer.

Impermeable bed covers ineffective for asthma

Woodcock A, Forster L, Matthews E, et al. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med* 2003; 349:225–236.

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■ **PRACTICE RECOMMENDATIONS**

Allergen-impermeable bed covers, as a single intervention, are ineffective for the management of asthma symptoms in adults. They are also ineffective for patients with allergic rhinitis.¹

■ **BACKGROUND**

Patients with asthma who are allergic to dust mites experience more severe symptoms when exposed to high levels of dust mite allergen. Mite-allergen-impermeable bed covers reduce the level of exposure to allergens, but it is unknown whether they reduce asthma symptoms.

■ **POPULATION STUDIED**

The investigators sent letters to 21,045 patients aged 18 to 50 years with physician diagnosed asthma who were regularly taking inhaled steroids. Patients already using allergen-impermeable bed covers or using less than 100 µg of albuterol daily were excluded. Most (1150) of 1431 patients were able to complete a daily diary card during the 4-week run-in period and were entered into the study.

■ **STUDY DESIGN AND VALIDITY**

Patients were randomized and matched for pet ownership, smoking status, and mite-specific immunoglobulin E (IgE) levels. Randomization was designed to ensure balance between the randomized groups at each practice in the study. Patients received either mattress, pillow, and quilt covers impermeable to mite allergen or ordinary control covers. The covers were fitted by a research nurse.

Examiners visited the homes of all patients at the start of the study, and a 10% random sample of patients were visited at 6 and 12 months; dust samples were collected at all visits and assayed for mite allergen.

This study was well done. The participants were typical of a primary care population. Follow-up was good; of 1150 patients randomized, 1015 (90%) completed follow-up after phase 1 and 932 (83%) completed phase 2. The investigators used concealed allocation of randomization. Although subjects were blinded, slightly more patients in the treatment group discontinued use of the bed covers, possibly because of sweating caused by the impermeable covers.

At the end of the study, both groups showed

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Both intervention and control groups may have modified their behaviors to improve asthma control

significant improvement over baseline, suggesting that subjects may have modified their behaviors to improve asthma control, or their perception of asthma control may have been altered by study participation.

OUTCOMES MEASURED

Examiners evaluated patients' morning peak expiratory flow rate during phase 1; secondary outcomes measured were evening peak expiratory flow rate, use of beta-agonists, subjective scores for daytime and nighttime symptoms, number of days of work missed, and subjective quality-of-life scores during the last 4 weeks of phase 1. During phase 2, examiners evaluated the proportion of patients who discontinued inhaled corticosteroid therapy, with a secondary outcome of proportionate reduction in the dose of inhaled corticosteroid.

RESULTS

Differences between the intervention and control groups in the primary and secondary outcome measures were not significant at the end of phase 1 or phase 2. Both the intervention and the control group patients demonstrated small but statistically significant improvement in peak expiratory flow rate (from 410.7 to 419.1 L/min in the intervention group, and from 417.8 to 427.4 L/min in the control group), and a substantial reduction in inhaled corticosteroid use during the study period (47% in the intervention group and 48% in the control group).

There was no significant difference in degree of improvement between the 2 groups. Differences in use of beta-agonists, subjective scores for symptoms, days or work missed, and subjective quality-of-life scores were not statistically significant. The rate of discontinuation of inhaled corticosteroid therapy in phase 2 was likewise not sta-

tistically different between the groups. When mite-sensitive patients (determined by serum IgE levels prior to randomization) were analyzed separately, no significant difference in the primary or secondary outcomes was found.

REFERENCE

1. Terreehorst I, Hak E, Oosting AJ, et al. Evaluation of impermeable covers for bedding in patients with allergic rhinitis. *N Engl J Med* 2003; 349:237-246.

Local heat decreases renal colic pain

Kober A, Dobrovits M, Djavan B, et al. Local active warming: an effective treatment for pain, anxiety and nausea caused by renal colic. J Urol 2003; 170:741-744.

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PRACTICE RECOMMENDATIONS

Local heat decreases the pain, anxiety, and nausea of renal colic during emergency transport. Family physicians should offer this to patients as a supplement to routine care of renal colic pain, while watching for other studies that assess its use for different kinds of pain and in settings other than emergency transport.

BACKGROUND

Renal colic is common in primary care, but pain management is often unsatisfactory. This randomized controlled trial examined the use of local heat for the treatment of pain, anxiety, and nausea associated with renal colic.

POPULATION STUDIED

This study enrolled 100 otherwise healthy European patients, aged 19 to 40 years, with abdominal pain suspected to be secondary to

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The investigator recording the data was not allowed to touch the blanket or comment on its temperature

renal colic while being transported to the emergency department by paramedics. Subjects were those with a history of urolithiasis with new side and lower back pain measured at >60 on a visual analog scale of 0 to 100, comparable with their last episode of urolithiasis. Patients were excluded if they had cognitive impairment or problems with normal communication. The average patient was aged 28 years and had a pain score of 82/100.

While emergency transport for patients with renal colic is uncommon in the United States, the patients are probably similar to those in a typical family practice in terms of their pain and likely response to the intervention. More information about the patients' cultural background and expectations for pain management would be valuable.

■ STUDY DESIGN AND VALIDITY

The study was a prospective randomized controlled trial. Enrollment took place before transport. Patients in the experimental group were covered on the lateral abdomen and lower back by an electric blanket set at 42°C ; control patients had the same arrangement without activation of the blanket. The controls were set and locked in a box.

Patients were monitored with thermometers and a blood pressure cuff and asked to rate pain, nausea, and anxiety using visual analog scales at the beginning and at the end of the transport. The investigator recording data was not allowed to touch the blanket or the patient or comment on blanket temperature; no pain medication was given during transport. After medical records review, patients with a final diagnosis other than urolithiasis were excluded; *t* tests were used to compare within and across groups.

Strengths of the study design include randomization, concealed allocation, and the attempt to mask the investigator recording outcomes. Weaknesses were relatively minor and include lack of attention to potential confounding factors such as age, gender, or medications, and the lack of specific information about how the patients were selected before randomization, the precise positioning of the blanket, timing of the assessments, success of blinding, how adverse effects were monitored, and the uniformity of the subsequent medical evaluation.

■ OUTCOMES MEASURED

Primary outcomes were patient ratings of pain, nausea, and anxiety using a visual analog scale of 0 mm (no pain) to 100 mm (the most intense pain imaginable). Other outcomes were patient satisfaction, core temperature, blood pressure, and heart rate. Pertinent outcomes not addressed include adverse effects of treatment, cost, provider satisfaction, and need for pain medications after transport.

■ RESULTS

The researchers found no significant baseline differences between the 2 groups after randomization and follow-up was complete. Patients receiving local heat reported a significant decrease in averages of pain (83 mm to 36 mm; $P<.01$), anxiety (79 mm to 31 mm; $P<.01$), and nausea (86 mm to 41 mm; $P<.01$), whereas the patients in the control group showed no significant changes. All subjects receiving local heat had a greater than 50% reduction in their score for pain (number needed to treat=1).

Paralleling these changes, subjects receiving local heat had decreases in heart rate (91 to 69 beats/min; $P<.01$), although they had no significant changes in blood pressure or core temperature. Finally, patient satisfaction was significantly higher among patients receiving local heat (45 mm vs 20 mm; $P<.01$).

Heparin prevents recurrent VTE in cancer patients

Lee AY, Levine MN, Baker RI, et al. Low-molecular weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; 349:146-153.

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■ PRACTICE RECOMMENDATIONS

In patients with cancer and venous thromboembolism, low-molecular-weight heparin effectively reduces symptomatic recurrent venous thromboembolism (VTE) more effectively than warfarin. Although cost and logistical considerations should be considered, this study demonstrates that the use of low-molecular-weight heparin is an effective approach for the prevention of recurrent VTE in cancer patients.

■ BACKGROUND

Patients with cancer who have had an episode of VTE have a substantial risk of both recurrent VTE and hemorrhagic complications from anticoagulation. Oral anticoagulant therapy in patients with cancer is more difficult due to the effect of drug interactions, malnutrition, liver dysfunction, chemotherapy, and poor venous access. Low-molecular-weight heparin may be an effective, practical alternative due to its predictable pharmacokinetics and drug interactions, making laboratory monitoring unnecessary.

■ POPULATION STUDIED

This multicenter study enrolled 676 of 864 eligible outpatients from 48 clinical centers in 8 countries. Eligible patients were adults with active cancer and newly diagnosed VTE (symptomatic proximal deep venous thrombosis or pulmonary embolism, or both). Patients had to be ambulatory and capable of all self-care. Patients were excluded if they had received heparin for more than 48 hours before randomization, were

already receiving oral anticoagulant therapy, were at high risk for bleeding, or had a platelet count less than 75,000/cm³.

■ STUDY DESIGN AND VALIDITY

This was a single-blinded, randomized controlled trial using concealed allocation. All 676 patients were given the low-molecular-weight heparin dalteparin in a dose of 200 IU/kg for 5 to 7 days. The 338 patients in the dalteparin group were continued at the same dose (200 IU/kg) for the remainder of the first month, followed by 150 IU/kg for 5 months. The 338 patients in the oral anticoagulant group received warfarin, with a goal international normalized ratio (INR) of 2.5 (therapeutic range 2.0-3.0), for the remainder of the 6-month study period. For subjects that developed thrombocytopenia during the study, drug dosages were adjusted according to a protocol.

Analysis was by intention-to-treat. The sample size was increased by 20% to adjust for expected losses to follow-up due to early cancer-related death. Although the investigators were unblinded, a central adjudication committee blinded to patient treatment assignment reviewed the documentation of all suspected events.

It is worth noting that the warfarin group contained a slightly greater number of inpatients, current smokers, and patients with metastatic cancer than the dalteparin group. Additionally, the INR was below the therapeutic range 30% of the time in patients treated with warfarin. During this period of subtherapeutic doses, 20 (37.7%) of the 53 thrombotic events occurred.

■ OUTCOMES MEASURED

The primary outcome measured was the first episode of recurrent VTE, either a documented symptomatic deep venous thrombosis, pulmonary embolism, or both. Secondary outcomes measured included clinically overt bleeding and death.

■ RESULTS

Both groups had similar baseline characteristics. Ninety percent of the patients had solid tumors

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and 67% had metastatic disease. In each group, approximately two thirds qualified for enrollment due to deep venous thrombosis alone, while approximately one third had a previous pulmonary embolism, with or without deep venous thrombosis.

The overall risk of VTE was significantly lower in the dalteparin group compared with the oral anticoagulant group (8.0% vs 15.8%; $P=.002$; number needed to treat=13). A similar percentage (4% to 6%) in both groups developed significant bleeding. Mortality rates during the study, which were primarily due to cancer progression, were not significantly different.

Routine induction reduces cesarean rate

Sanchez-Ramos L, Olivier F, Delke I, Kaunitz AM. Labor induction versus expectant management for postterm pregnancies: a systematic review with meta-analysis. Obstet Gynecol 2003; 101:1312-1318.

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■ PRACTICE RECOMMENDATIONS

A strategy of routine induction at or just after 41 weeks for uncomplicated pregnancies reduces cesarean sections without improving or adversely affecting neonatal outcomes. Family physicians should provide this information to their patients and continue to look for studies that provide clinical detail and directly compare the strategy of routine induction after 41 weeks with expectant management and induction after 42 weeks.

■ BACKGROUND

Pregnancies lasting beyond 41 weeks are common, but management remains controversial. This meta-analysis compared the outcomes of routine induction of labor and expectant management for uncomplicated pregnancies after 41 weeks.

■ POPULATION STUDIED

A total of 6588 subjects were enrolled in 16 trials from 10 countries over 33 years. Five of these trials took place in countries with significant higher rates of maternal and perinatal mortality than the United States. Only trials limited to uncomplicated singleton pregnancies were included; in practice, the estimated gestational age at randomization ranged from 41 to 42 weeks. No information was given about subjects' age, obstetric risk factors, and Bishop score.

Furthermore, despite the wide range of dates and countries of the trials, little information was given about routine labor management, methods of dating, induction, and intrapartum surveillance. Thus, while the results of this study apply to pregnancies between 41 and 42 weeks, generalization to US family practices is difficult.

■ STUDY DESIGN AND VALIDITY

The investigators searched for randomized trials comparing routine labor induction vs expectant management for pregnancies of at least 41 weeks gestation with clearly documented outcome data. The search included electronic databases, review articles, textbook chapters, PubMed, MEDLINE, and Cochrane databases from 1966-2002 without language restriction. Data were extracted by 2 investigators independently, with differences resolved by consensus; similarly, study quality was scored by 2 investigators blinded to investigators and institutions.

Meta-analyses were done using Stata software, using both fixed and random effects models for dichotomous outcomes and unstandardized mean differences for continuous outcomes. To test for homogeneity, the Breslow-Day method and L'Abbe plots were used. Publication bias was assessed by the Egger test and funnel plots. Preplanned sensitivity analysis assessed the impact of individual studies.

Strengths of this analysis included the thoroughness of the search, the careful extraction of

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the data, and the attention to heterogeneity. The major weakness was the lack of an appropriate comparison group to elective induction at 41 weeks—in 4 trials, physicians intervened at 43 weeks, in 4 others at 44 weeks, and 2 trials did not specify. Other weaknesses include lack of attention to important confounding variables such as obstetric management and methods of dating, induction, and fetal surveillance, as well as lack of power for perinatal deaths and lack of attention to the impact of study quality on study outcome.

■ OUTCOMES MEASURED

The primary outcomes were cesarean delivery rate and perinatal mortality. Secondary outcomes included meconium-stained fluid, meconium aspiration syndrome, meconium below the cords, fetal heart rate abnormalities during labor, cesarean delivery for fetal heart rate abnormalities, abnormal Apgar scores, and neonatal intensive care unit admissions. Outcomes important in the US context such as cost, patient satisfaction, and provider satisfaction were not addressed.

■ RESULTS

For most analyses, investigators found no evidence of heterogeneity. Women who underwent labor induction had lower cesarean delivery rates (20% vs 22%; odds ratio [OR]=0.88; 95% confidence interval [CI], 0.78–0.99; number needed to treat=50), as well as a lower rate of meconium-stained fluid (OR=0.75; 95% CI, 0.66–0.84) and caesarean section for fetal heart rate abnormalities (OR=0.77; 95% CI, 0.61–0.96).

There were no significant differences in meconium below the cords, meconium aspiration, Apgar scores <7, neonatal intensive care unit admissions, or perinatal mortality. Investigators found no evidence of publication bias, and sensitivity analysis revealed that no studies had a disproportionate impact on the outcomes.

Nebulized epinephrine does not help bronchiolitis

Wainwright C, Altamirano L, Cheney M, et al. A multicenter, randomized, double-blind controlled trial of nebulized epinephrine in infants with acute bronchiolitis. N Engl J Med 2003; 349:27–35.

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■ PRACTICE RECOMMENDATIONS

Nebulized epinephrine does not improve clinical status or reduce the length of the hospital stay in infants aged <1 year with acute bronchiolitis. It also does not reduce clinical scores during or shortly after medication administration.

In this study, infants requiring oxygen and intravenous fluids—presumably the sickest infants in the study—required longer hospital stays if they received epinephrine. A wheezing infant may be presenting with a first episode of asthma, so a trial of bronchodilators would seem reasonable; however, it appears that the primary intervention for bronchiolitis is supportive treatment, with supplemental oxygen, intravenous fluids, and ventilatory support when needed.

■ BACKGROUND

Bronchiolitis is a common viral infection of the lower respiratory tract, accounting for hospitalization of approximately 1% of healthy infants. Because of bronchiolar swelling, the use of bronchodilators and anti-inflammatory agents makes sense in managing bronchiolitis. However, steroids have not shown clear evidence of benefit, and studies of epinephrine have had mixed results.

■ POPULATION STUDIED

Infants (aged <1 year) were enrolled if they were admitted to any of 4 Queensland, Australia, hospitals with bronchiolitis. The diagnosis of bronchiolitis was made based on history and

CONTINUED

clinical findings consistent with bronchiolitis, including wheezing with or without crackles and respiratory distress with retractions.

Criteria for exclusion included receiving corticosteroids in any form within 24 hours before presentation, or receipt of bronchodilators within 4 hours before presentation. Infants were not enrolled if they required ventilatory support before their parents could give consent for participation in the study. Infants with prior episodes of wheezing, cardiac disease, or cystic fibrosis were not included.

■ STUDY DESIGN AND VALIDITY

This was a multicenter, randomized, double blind, placebo-controlled study. Allocation appears to have been adequately concealed. Patients were randomly assigned to receive three doses of nebulized epinephrine 1% solution or placebo at 4-hour intervals within 24 hours after their admission to the hospital.

The study was well-designed and well-executed. A clinical pathway was used to help provide more consistent care between hospitals and treatment groups. The study was powered to detect an approximately 28-hour difference in length of hospital stay.

■ OUTCOMES MEASURED

The 2 primary outcomes were the length of the hospital stay and the time until the infant was ready for discharge. The second time was defined by a criterion standard, and may more accurately reflect the clinical response, as other factors—such as transportation—might affect the actual time of discharge.

Secondary outcomes included changes in clinical scores before and after nebulization therapy and the time that supplemental oxygen was required. Clinical scores were based on measurements of oxygen saturation, respiratory rate, and respiratory effort. Nursing staff also recorded respiratory and heart rates, respiratory effort, oxygen saturation, supplemental oxygen requirements, and blood pressure

before and 30 and 60 minutes after delivery of the drug.

■ RESULTS

The groups were essentially equal at study entry. Treatment with epinephrine, compared with placebo, had no significant effect on the length of the hospital stay (58.4 vs 69.5 hours) or the time until the infant was ready for discharge (46.5 vs 47.7 hours). There was no significant difference between the groups in the time receiving supplemental oxygen or in the rates of intensive care or ventilatory support. In those patients who required both oxygen and intravenous fluids, the use of epinephrine appeared to prolong the time until ready for discharge (135.9 vs 80.2 hours; $P=.02$).

Epinephrine also increased the heart rate. An hour after treatment, the mean heart rate was 151 beats/min in the epinephrine groups vs 138 beats/min in the placebo group. Infants with a family history of asthma or atopy, who are likely to have higher rates of asthma, did no better with epinephrine.

Red clover extracts not effective for hot flashes

Tice JA, Ettinger B, Ensrud K, et al. Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) study: a randomized trial. JAMA 2003; 290:207-214.

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■ PRACTICE RECOMMENDATIONS

Both red clover extracts and placebo equally reduce the frequency of hot flashes. Providers should encourage patients to avoid spending money on supplements and instead add soy to their diet. In general, however, if patients are already convinced that something works, don't discourage them.

CONTINUED

Promensil, Rimostil, and placebo reduced hot flushes by 34%–41%, with no differences between groups

■ BACKGROUND

Women in countries where the diet contains large amounts of soy report a much lower incidence of menopausal symptoms than women in Western countries.¹ Since isoflavones cause selective estrogen receptor stimulation, they are hypothesized to be the active ingredients in soy. Isoflavones from other plants, such as red clover, are similarly marketed for the treatment of menopausal symptoms, often without any basis from well-designed research.

■ POPULATION STUDIED

Postmenopausal women were recruited from the community in 3 states. Women consuming more than 2 alcoholic drinks a day or soy products more than once a week were excluded. After exclusions, 252 women with at least 35 hot flushes per day and with a follicle-stimulating hormone level of >30 mIU/mL were enrolled. More than 80% of subjects were white.

■ STUDY DESIGN AND VALIDITY

Subjects meeting inclusion criteria who were at least 80% compliant after a 2-week run-in period were randomized to receive 1 of 2 supplements or placebo. The supplements, Promensil (82 mg of total isoflavones per day) and Rimostil (57 mg of total isoflavones per day), differed slightly in their proportions of individual isoflavones. Women were contacted by telephone at 1, 4, and 8 weeks to assess effects and concerns and were asked to keep hot-flush frequency diaries. Final evaluation was done at a clinic visit at 12 weeks.

Subjects, investigators, and staff at both sites were blind to treatment group assignment (concealed allocation assignment) until all data collection was completed. The study

population may not be representative of all women seeking relief of hot flushes, as many women complain of significant hot flushes in the perimenopausal period. In addition, the race distribution was uneven and may not represent some practitioners' patient populations.

Any findings about the benefit or lack thereof for red clover isoflavone extracts may not be generalizable to all isoflavone-containing foods and herbs. Although isoflavones are purported to be responsible for reducing the number of hot flushes, the whole plant product may be effective when the extract alone is not. Finally, isoflavones may be more effective when taken twice daily.

■ OUTCOMES MEASURED

Outcomes measured were the number of hot flushes, scores on the Greene Climacteric quality-of-life scale, and urinary excretion of isoflavones.

■ RESULTS

Promensil, Rimostil, and placebo all reduced hot flushes by 34% to 41%, without any significant differences between the treatment groups. Scores on the Greene Climacteric quality-of-life scale improved significantly in all 3 groups, but again without significant differences between the groups. Researchers found no significant correlation of change in the number of hot flushes with changes in total isoflavone excretion. Per-protocol (analyzing only those who took their pills) results were similar to the intention-to-treat analysis. Significant adverse effects were not seen in any of the groups.

REFERENCE

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