

# POEMs

PATIENT ORIENTED EVIDENCE THAT MATTERS

Practice Recommendations from Key Studies

## Children with fever and vomiting benefit from immediate antibiotics for acute otitis media

*Little P, Gould C, Moore M, Warner G, Dunleavy J, Williamson I. Predictors of poor outcome and benefits from antibiotics in children with acute otitis media: pragmatic randomised trial. BMJ 2002; 325:22-5.*

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### ■ PRACTICE RECOMMENDATIONS

Starting antibiotics immediately in children with acute otitis media accompanied by fever or vomiting results in better symptom relief and decreased sleep disturbance when measured after 3 days, as compared with no treatment. Parents who consider these outcomes important may prefer not to delay antibiotic treatment. Conversely, children without fever or vomiting tend to have the same duration of symptoms regardless of antibiotic treatment and are suitable for a “wait and see” approach.

### ■ BACKGROUND

Which children will benefit from immediate treatment for otitis media? Acute otitis media is one of the most common childhood infections, yet there is much debate about its management. This study sought to determine symptoms that would predict which children would be at risk of prolonged symptoms and whether they would benefit from immediate antibiotic treatment.

### ■ POPULATION STUDIED

This study included 315 children aged 6 months to 10 years taken to their general practitioner with

acute otalgia and found to have otoscopic evidence of acute inflammation (dullness, erythema or bulging, cloudiness, or perforation). Otoscopic evidence alone was used if the child was too young to reliably complain of otalgia. There was a 90% follow-up rate.

### ■ STUDY DESIGN AND VALIDITY

This investigation was a secondary analysis of a previous randomized controlled trial<sup>1</sup> designed to investigate antibiotic prescribing strategies for acute otitis media. Patients were randomized based on sealed numbered envelopes (allocation concealed) into two groups. The first group started antibiotics immediately (amoxicillin, or erythromycin if the child was allergic to penicillin). In the second group, parents were given a prescription but were asked to wait 72 hours, to see if severe otalgia or fever remained, before starting the antibiotics. Parents in the delayed group were also instructed to start the antibiotics if ear discharge was still present after 10 days. This follow-up study used logistic regression to determine which symptoms, if present on day 1, were predictive of worse outcomes. Neither patients nor physicians were blinded. This non-blinded design creates a potential for bias in the way parents perceive and record symptoms. This

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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](http://www.jfponline.com).

reporting bias could affect the results in a way that favors antibiotic treatment when no difference actually exists.

### ■ OUTCOMES MEASURED

Primary outcomes were an episode of distress or night disturbance 3 days after a physician saw the patient. Physicians recorded days of illness, physical signs, and whether an antibiotic was prescribed. Parents recorded symptoms, perceived pain, number of episodes of distress, doses of acetaminophen given, and temperature.

### ■ RESULTS

Symptoms still present after 3 days were more likely in children initially presenting with temperatures greater than 37.5°C (adjusted odds ratio [OR]=4.5, 95% confidence interval [CI] 2.3–9.0), vomiting (OR=2.6, 95% CI 1.3– 5.0), or cough (OR=2.0, 95% CI 1.1–3.8).

Disturbed sleep after three days was more likely to occur in children initially with temperatures greater than 37.5°C (OR=2.4, 95% CI 1.2–4.8), vomiting (OR=2.1, 95% CI 1.1–4.0), cough (OR=2.3, 95% CI 1.3–4.2), or ear drainage (OR=2.1, 95% CI 1.2–3.9).

When measured after 3 days, children initially presenting with high temperatures or vomiting who were given immediate antibiotics showed less distress (32% for immediate versus 53% for delayed;  $P=.045$ , number needed to treat [NNT]=5) and night disturbances (26% for immediate versus 59% for delayed;  $P=.002$ , NNT=3).

Timing of antibiotics was less important in children without fever or vomiting on initial presentation; these children exhibited nearly equal rates of distress (15% for immediate treatment versus 19% for delayed treatment;  $P=.39$ ) or night disturbance (20% for immediate versus 27% for delayed;  $P=.20$ ) 3 days following the visit.

### REFERENCE

1. Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavy J. Pragmatic randomised controlled trial of two prescribing strategies for acute otitis media. *BMJ* 2001; 322:336–42.

## Six-item screening tool is sensitive for dementia

Callahan CM, Unverzagt FW, Hui SL, et al. Six-item screener to identify cognitive impairment among potential subject for clinical research. *Med Care* 2002; 40:771–81.

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### ■ PRACTICE RECOMMENDATIONS

This study provides excellent evidence that a 6-item screening tool based on orientation to date and a 3-item short-term recall is sensitive for dementia. Clinicians should consider using this simple screen in an outpatient setting, keeping in mind that the final diagnosis of dementia is a clinical judgment after full assessment and that this screen was not intended for use in following patients over time. Caution also should be exercised in extending these results to patients in the hospital, who were not included in this trial.

### ■ BACKGROUND

Is a six-item screening tool sensitive for dementia? Current screening tools for dementia, including the 30-item Mini-Mental Status Examination (MMSE), are cumbersome and often too time consuming to be used readily in a busy office setting. This study evaluated a new, short screening tool.

### ■ POPULATION STUDIED

Two populations were studied separately. A community group was recruited from a random sample of a predominantly African American community. The investigators enrolled 344 African Americans who were older than 65 years and had higher-than-average cognitive impairment as established by an epidemiologic screen. The average age was 74.4 years; average education was 10.4 years. Of the 344 subjects, 59.4% were female and the prevalence of dementia was 4.5%. A second group was enrolled from patients referred by family, caregivers, and clinicians to an Alzheimer disease center at a medical

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center. This sample had 651 subjects who were on average 69.6 years old and had 12.5 years of education. Of this group, 57.1% were female, 16.1% were black, and 53% were demented. The combination of community-dwelling and referral populations, with substantial numbers of African Americans and a wide range of education and cognitive impairment, suggested that the results of this study can be generalized to the typical family practice office setting.

### ■ STUDY DESIGN AND VALIDITY

This was a prospective study of a 6-item screening tool. The screening tool was derived from the MMSE and measured orientation to year, month, and day of the week and a 3-minute recall of 3 words, for a total of 6 points. All subjects underwent a battery of neuropsychiatric tests and a complete physical examination and evaluation by a geriatric psychiatrist or neurologist. Cognitive assessments included the MMSE, the Cambridge Mental Disorders in the Elderly Examination, and the Consortium for Establishment of Registry of Alzheimer Disease battery, including the Animal Fluency Test, the Boston Naming Test, Constructional Praxis, and the Word List Recall. Whenever possible, a research nurse completed a semi-structured interview to assess activities of daily living and calculate the Blessed Dementia Scale. The experimental screen was compared with the gold standard of expert clinician judgment reviewing all test results and the examination. The area under the response operating characteristic curve was compared for the screen and the MMSE to determine the relative overall accuracy of each test. The performance of the new screen also was compared with the other assessment tools.

The methodology of the study was excellent. The populations chosen were diverse; the “gold standard” was applied to all patients, and the evaluators were blind to the prior screening results for the community sample; the comparison of the screen with other instruments was explicit; and the sample size was large. Weaknesses were relatively minor: lack of information about the training of those administering the screen and whether the subjects were enrolled consecutively, lack of attention to inter- and

intra-rater reliability, and lack of assessment of education and race as confounders.

### ■ OUTCOMES MEASURED

The authors measured sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the 6-item screen. Time actually taken and physician satisfaction with the tool were not assessed.

### ■ RESULTS

In the community sample, sensitivity and specificity for 1 error or more on the 6-item test were 100% and 38.4%, respectively, for dementia, with a PPV of 6.7% and an NPV of 100%. In the referral sample, sensitivity and specificity for 1 error or more on the screener were 96.8% and 53.3%, respectively, for dementia, with a PPV of 70.0% and a NPV of 93.7%. The area under the response operating characteristic curves for the screen and the MMSE were similar, and the scores of the other instruments progressively worsened as the number of errors on the screen increased.

## Should patients with coronary disease and high homocysteine take folic acid?

*Schnyder G, Roffi M, Flammer Y, Pin R, Hess OM. Effect of homocysteine-lowering therapy with folic acid, Vitamin B12, and vitamin B6 on clinical outcome after percutaneous coronary intervention. The Swiss Heart Study: a randomized controlled trial. JAMA 2002; 288:973-9.*

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### ■ PRACTICE RECOMMENDATIONS

All patients with known coronary artery disease should take prescription strength (1 mg/d) folic acid, vitamin B<sub>12</sub> (400 µg/d), and vitamin B<sub>6</sub> (10 mg/d), which have few if any known adverse effects. In this study, therapy to reduce homocysteine levels with prescription strength folic acid (1 mg) and vitamins B<sub>12</sub> and B<sub>6</sub> for 6 months following coronary angioplasty

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reduced the risk of need for revascularization of target lesions and of overall adverse cardiac events at least 6 months following cessation of therapy.

Based on this study, it is unknown whether the benefit is related to baseline homocysteine levels or whether there is further benefit to continuing treatment beyond 6 months. Over-the-counter folic acid supplements (800 µg or less) were not studied and may not be as beneficial.

## ■ BACKGROUND

Should patients with coronary artery disease and high homocysteine levels take folic acid? Plasma homocysteine levels predict outcome after coronary angioplasty, and lowering plasma homocysteine levels significantly decreases restenosis after coronary angioplasty.

Treatment with folic acid, vitamin B<sub>12</sub>, and vitamin B<sub>6</sub> decreases homocysteine levels and lowers the short-term incidence of restenosis when given after angioplasty. This study evaluated long-term effects.

## ■ STUDY POPULATION

The investigators enrolled 553 participants who had successfully undergone angioplasty for at least one significant coronary stenosis (≥50%). Subjects in the treatment and control groups were predominantly male (79% and 82%), and had mean ages of 62 and 63 years. Patients were excluded if they had unstable angina, subacute myocardial infarction (within the previous 2 weeks), renal insufficiency (serum creatinine >1.8 mg/dL), or were taking vitamins.

## ■ STUDY DESIGN AND VALIDITY

The study was a randomized, double-blind, placebo-controlled trial. After successful angioplasty, defined as residual diameter stenosis less than 35% with normal flow pattern (TIMI III criteria), patients were randomly assigned to receive a supplement containing folic acid (1 mg), vitamin B<sub>12</sub> (400 µg), and vitamin B<sub>6</sub> (10 mg) or placebo daily for 6 months. Treatment was discontinued after 6 months and the participants were then followed for another 6 months. Fasting total plasma homocysteine levels were measured on admission and at 6 months.

Clinical follow-up, including noninvasive stress testing and resting electrocardiography, were performed at 6 and 12 months or sooner if symptoms recurred. All analyses were by intention to treat. Outcome data were included until the dropout time points for patients who were lost to follow-up.

The study was well designed. Consecutive patients were enrolled in a double-blinded fashion (allocation concealment unknown). Groups were similar with respect to age, smoking status, diagnosis of diabetes mellitus, hypertension, lipid profiles, previous cardiac history and drug therapy, and represented typical cardiac patients with the exceptions noted above. For a subset of patients who received follow-up invasive testing, those reading the angiograms were blinded to treatment group. It is not explicit whether those interpreting outcomes through noninvasive means were similarly blinded. If not, some investigator bias could have been introduced. Separate effects of folic acid and vitamins B<sub>12</sub> and B<sub>6</sub> as well as the effects of different doses of these vitamins could not be established.

## ■ OUTCOMES MEASURED

The main outcomes evaluated were death, cardiac death (defined as sudden, unexpected death or death related to myocardial infarction), nonfatal myocardial infarction (new Q-wave in 2 or more electrocardiogram leads), the need for repeat revascularization for proven ischemia demonstrated by either follow-up cardiac events or a positive noninvasive stress test with significant angiographic stenosis of at least 50%, or a composite of these outcomes.

## ■ RESULTS

The composite outcomes of death, cardiac death, recurrence, or need for revascularization was significantly decreased with the vitamin therapy (hazard ratio, 0.68; 95% confidence interval [CI], 0.48–0.96). For the 6 months after the angioplasty, one outcome would have been avoided for every 13 patients treated. Individually, only the need for repeat revascularization was significantly affected by therapy (hazard ratio, 0.62; 95% CI, 0.40–0.97). Adjustment for multiple risk factors including age,

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sex, and variables known to influence the need for target lesion revascularization after coronary angioplasty (use of stents, treatment of restenotic lesions, vessel size, post procedural minimal luminal diameter, target lesion location, and use of glycoprotein IIb/IIIa inhibitors) did not significantly change the relationship between homocysteine-lowering therapy and the need for repeat target lesion revascularization.

## Watchful waiting is reasonable for gallstone symptoms

*Vetthus M, Søreide O, Solhaug JH, et al. Symptomatic, non-complicated gallbladder stone disease. Operation or observation? Scand J Gastroenterol 2002; 37:834-9.*

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### ■ PRACTICE RECOMMENDATIONS

Not all patients with symptomatic cholelithiasis require surgery. Nearly half of patients with symptomatic but uncomplicated gallstone disease can be managed successfully with observation and minor dietary changes. This option is a safe one we can offer our patients.

### ■ BACKGROUND

Do all patients with symptomatic gallstone disease require surgery? Patients with symptomatic gallstones routinely undergo surgery. However, evidence for this treatment is based solely on expert opinion.

### ■ POPULATION STUDIED

The patients in this study were 137 adult, nonpregnant persons with episodic abdominal pain consistent with gallstone disease who presented to outpatient surgery clinics. The researchers confirmed the clinical diagnosis of gallstone disease with ultrasound. The study included 112 women, 20 to 77 years of age, and 25 men, 27 to 79 years. Of the 338 patients initially considered for the study, 45 were

excluded based on defined exclusion criteria (younger than 18 years or older than 80 years, pregnancy, serious comorbid illness, or suspected common bile duct stone). Researchers excluded another 156 patients because of severe symptoms (n=54), patient preference for treatment (n=79), and undefined reasons (n=23).

### ■ STUDY DESIGN AND VALIDITY

The researchers randomized 137 patients to a cholecystectomy or an observation group. Patients assigned to surgery were operated on as soon as possible. Those assigned to observation received information about their disease and were instructed to avoid foods that aggravated their symptoms. The researchers followed up with patients for a median of 67 months (range, 56-91 months) and lost 1 patient to follow-up in that time.

This randomized, controlled trial was well done. The treatment groups were similar at baseline. All patients answered questionnaires about their symptoms and quality of life at randomization and at 6, 12, 24, and 60 months of follow-up. Allocation to treatment group was concealed. Neither patients nor physicians were blinded, and no mention was made as to whether the assessors of the study endpoints were blinded. The statistical analysis was performed by intention to treat. Because patients included in the study had no preferences for treatment, self-reporting of symptoms was not likely to be biased. Although the study took place in outpatient surgery clinics, the results are applicable to primary care settings in that the patients had uncomplicated gallstone disease.

### ■ OUTCOMES MEASURED

The primary outcome was the cumulative risk of having a cholecystectomy. Other outcomes measured were complications of gallstone disease and surgery.

### ■ RESULTS

Thirty-five of 69 patients (51%) randomized to the observation group eventually had cholecystectomies. Sixty of 68 patients (88%) randomized to the cholecystectomy group actually underwent surgery.

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The risk of having the surgery leveled off after 3 to 4 years. Complications were rare, with 12 of 69 observation patients (17%) and 2 of 68 surgery patients (3%) being admitted for biliary pain during follow-up. Gallstone-related complications (acute cholecystitis, common bile duct stones, or acute pancreatitis) occurred in 3 of the observation patients and 1 of the surgery patients.

## Korean red ginseng effective for treatment of erectile dysfunction

*Hong B, Ji YH, Hong JH, Nam KY, Ahn TY. A double-blind crossover study evaluating the efficacy of Korean red ginseng in patients with erectile dysfunction: a preliminary report. J Urol 2002; 168:2070-3.*

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### ■ PRACTICE RECOMMENDATIONS

Korean red ginseng (*Panax ginseng*\*) is a safe, widely available alternative remedy that improves patients' ability to achieve and maintain an erection sufficient for intercourse, even in a population with severe erectile dysfunction. It is a reasonable, nonprescription treatment, especially for men with reservations about taking sildenafil (Viagra). A 500-mg capsule of Korean red ginseng costs about 6 cents, compared with \$10 for a tablet of sildenafil.

### ■ BACKGROUND

Is Korean red ginseng effective in the treatment of erectile dysfunction? Although many treatments for erectile dysfunction are available, patients seem to prefer oral medications, such as sildenafil. Patients also may prefer herbal medicines for many reasons,

\**Panax ginseng refers to the genus and species of Korean red ginseng, and it is the most commonly used form of ginseng. Many brands in the United States are marketed under the name Panax. (Coon JT, Ernst E. Panax ginseng: a systematic review of adverse effects and drug interactions. Drug Safety 2002; 25:323-44.)*

including relatively low cost, ready availability, and safety. Ginseng is a traditional Asian remedy for sexual dysfunction that is widely used in the United States and has a reassuring safety profile.

### ■ POPULATION STUDIED

Study subjects were 45 men with erectile dysfunction without previous treatment recruited from a urology clinic in Korea. Erectile dysfunction was defined as the persistent inability to achieve and maintain erection sufficient for normal sexual satisfaction. Mean age was 54 years. About 70% of patients had moderate or severe erectile dysfunction as measured by a Korean version of the International Index of Erectile Function (IIEF), and more than 50% had at least 1 other chronic medical problem such as diabetes or hypertension. Patients excluded from the study were those with a history of radical prostatectomy, spinal cord injury, serious neurologic illnesses such as Parkinson disease and multiple sclerosis, alcohol abuse, or other herbal abuse, drug ingestion that enhances or interferes with sexual function, drug ingestion with known interaction with ginseng, hormonal therapy, and cancer chemotherapy.

### ■ STUDY DESIGN AND VALIDITY

This was a double-blind, placebo-controlled, crossover study. All patients underwent baseline evaluations including IIEF self-assessment, measurement of rigidity and tumescence experienced during audiovisual sexual stimulation, penile duplex ultrasonography, and response to an intrapenile injection of papaverine, phentolamine, and prostaglandin E<sub>1</sub>. Subjects were then randomized to receive Korean red ginseng, 900 mg three times daily, or a placebo three times daily, for 8 weeks. After a 2-week washout period, subjects received another 8 weeks of crossover treatment. Patients were assessed every 4 weeks during the two 8-week treatment periods. At the end of the study, data for all 45 subjects obtained during active treatment were compared against data obtained during placebo treatment.

This study had no serious threats to validity. No mention was made of allocation concealment, but

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this can be assumed to be present in a double-blind crossover trial with the use of an identical placebo. Follow-up was complete at 16 weeks of treatment. The study was underpowered to detect statistically significant improvement in some important clinical outcomes, such as improvement in orgasmic satisfaction or overall satisfaction for patients and their partners, and it was of relatively short duration. The manner in which the Korean red ginseng was given, three times daily, may be unreasonable for some patients. No side effects were described in the placebo or treated group. A direct comparison with sildenafil would provide better information to help patients and physicians choose between treatments.

### ■ OUTCOMES MEASURED

Improvement in erectile function was measured by self-report on the IIEF and its subscales and by objective assessments of penile blood flow, size, and rigidity.

### ■ RESULTS

After 8 weeks of treatment, patients showed significant improvement in mean IIEF scores compared with placebo (baseline,  $28.0 \pm 16.7$ ; Korean red ginseng,  $38.1 \pm 16.6$ ; placebo,  $30.9 \pm 15.7$ ). When taken individually, scores for erectile function, sexual desire, and intercourse satisfaction were significantly improved in the treated group. Scores for orgasmic function and overall satisfaction were not statistically improved. Sixty percent of treated patients experienced an improvement in erection as opposed to 20% of the placebo group (number needed to treat, 2.5). In particular, scores on questions relating to penetration and maintenance were significantly higher for the Korean red ginseng group. No data were reported for partner satisfaction.

## Metronidazole gel ineffective for minimally abnormal Pap

*Ferrante JM, Mayhew DY, Goldberg S, Woodard L, Selleck C, Roetzheim RG. Empiric treatment of minimally abnormal Papanicolaou smear with 0.75% metronidazole gel. J Am Board Fam Pract 2002; 15:347-54.*

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### ■ PRACTICE RECOMMENDATIONS

Empiric treatment of women with minimally abnormal Papanicolaou smears (limited by inflammation, benign, or reactive cellular changes) with 0.75% metronidazole vaginal gel is ineffective in yielding a higher rate of reversion to normal cytology when compared with no treatment.

### ■ BACKGROUND

Is metronidazole vaginal gel effective in the management of the minimally abnormal Papanicolaou smear? *Gardnerella vaginalis* infection, or bacterial vaginosis, has been suggested in a number of studies as a cofactor for the development of cervical intraepithelial neoplasia and as being associated with an increased relative risk of developing cervical intraepithelial neoplasia. Bacterial vaginosis also has been linked with acute and chronic inflammatory changes of the cervix. Metronidazole is often used in the treatment of bacterial vaginosis and thus may be helpful in the management of the minimally abnormal Papanicolaou (Pap) smear.

### ■ POPULATION STUDIED

The population consisted of women 18 years or older undergoing routine Pap smear screening in an outpatient primary care setting who were found to have minimally abnormal cytology (defined as limited by inflammation, benign or reactive cellular changes).

### ■ STUDY DESIGN AND VALIDITY

After completing a thorough medical and behavioral questionnaire, 145 patients meeting inclusion criteria were randomized in a single blind fashion to the treatment or control group. Treatment consisted of 0.75% metronidazole vaginal gel in 1 filled applicator, used once daily for 5 days. The control group received no treatment. Pap smears were repeated 3 to 4 months after the initial screening, and patients completed a follow-up questionnaire. Patients' medical providers and pathologists evaluating cytology

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studies were blinded to the group assignments.

The study was well designed. Treatment and control groups were demographically similar, and the distribution of cytologic findings on initial Pap smear was similar in each group. The study was limited by lack of testing for *G vaginalis* at initial screening, making it difficult to ascertain the proportion of patients in the control and treatment arms harboring asymptomatic bacterial vaginosis. It is uncertain whether or not allocation assignment was concealed; patients were assigned to the treatment or control arm via a table of random numbers without the use of a matched placebo gel. Another potential limitation was the relatively low-risk demographic profile of the treatment and control arms, thereby restricting extrapolation of these data to populations at higher risk.

#### ■ OUTCOMES MEASURED

The main outcome measure was defined as a normal Pap smear at follow-up examination after 3 to 4 months.

#### ■ RESULTS

Of the 145 women initially enrolled, 31 (21%) were lost to follow-up. Follow-up Pap smear cytology reverted to normal in 61 of the remaining 114 patients, including 54% (n=37) of the control group and 44% (n=24) of the treatment group (difference not statistically significant). The final sample size of 114 patients provided an 80% power to detect a 25% difference in resolution rates. Subgroup analysis of specific initial cytologic findings on the screening Pap smears and of patient characteristics failed to yield any subgroup for which metronidazole treatment was beneficial, including cytology limited by inflammation.

## Early radical prostatectomy improves disease-specific but not overall survival

*Holmberg L, Bill-Axelsson A, Helgesen F, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. N Engl J Med 2002; 347:781-9.*

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#### ■ PRACTICE RECOMMENDATIONS

For now, a reasonable strategy is to consider watchful waiting as an acceptable alternative to radical prostatectomy for patients with early prostate cancer and a lifespan of less than 10 years. For other patients, discuss the benefits and risks of the treatment options, balancing expected side effects of the operation and the impact of other illnesses on survival with the possible benefit of the operation or other kinds of treatment.

We still lack sufficient evidence whether early detection by PSA screening can reduce morbidity or mortality.

In this study, radical prostatectomy for early prostate cancer decreased disease-specific mortality, but did not improve overall mortality. A companion study<sup>1</sup> showed that non-nerve-sparing radical prostatectomy yielded no difference in subjective quality of life, although clinically important increases in erectile dysfunction (number needed to harm [NNH]=3) and urinary leakage (NNH=4) did occur, compared with watchful waiting.

Clinicians should understand that these results might not apply to patients with highly undifferentiated cancer; patients identified by screening to have elevated prostate-specific antigen (PSA) concentrations and no clinically symptomatic disease; or patients with significant comorbidities.

#### ■ BACKGROUND

Does radical prostatectomy for early prostate cancer improve survival? Radical prostatectomy is frequently used in treating early prostate cancer, but there is little evidence that the operation is efficacious. This randomized controlled trial compared radical prostatectomy with watchful waiting, in patients with early prostate cancer.

#### ■ POPULATION STUDIED

Study subjects included 695 Swedish men with newly diagnosed prostate cancer. Inclusion criteria

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were age younger than 75 years, well or moderately well-differentiated disease as defined by World Health Organization criteria, no known metastatic disease, ability to consent to and undergo radical prostatectomy, and life expectancy of at least 10 years. The average age of the study subjects was 65 years; only 5% of patients had their cancers diagnosed through screening. Most patients (75%) had stage T2 disease, with cancer clinically apparent but confined to the prostate. No information was provided about comorbid illnesses or racial composition that could influence prognosis. These patients appeared similar to patients who might present to a US family practice with early, but not the earliest, disease. Thus, these results may not generalize to many patients discovered in screening programs. Caution should also be extended in applying these results to African American men or men with significant medical comorbidities.

#### ■ STUDY DESIGN AND VALIDITY

This randomized, controlled, multicenter study used concealed treatment allocation assignment. Subjects were assigned to radical prostatectomy or watchful waiting. Traditional radical prostatectomy was performed without an emphasis on sparing potency. During regularly scheduled follow-up exams, PSA levels, bone scans, and chest x-rays were obtained. Orchiectomy or hormone therapy was recommended for prostatectomy patients with local progression, and transurethral resection for local progression in the watchful waiting group. A blinded independent committee analyzed data extracted from patient records and determined end points. Crossover between the groups after randomization was approximately 7%. Analysis was by intention to treat; relative hazards were estimated using Cox proportional-hazards models, controlling for age, tumor stage, Gleason score, and PSA level.

The methodology was excellent: strengths include a randomized design, concealed allocation, complete follow-up, statistical design, and blinded assessment of outcomes. Weaknesses include a lack of attention to confounding by comorbid conditions and a lack of power regarding the assessment of overall mortality.

#### ■ OUTCOMES MEASURED

Primary outcomes were death from prostate cancer and all-cause mortality. Secondary outcomes were rates of metastatic disease and local progression. A companion study assessed quality of life, but cost of treatment and patient satisfaction were not addressed.

#### ■ RESULTS

Complete follow-up was achieved with a median duration of 6.2 years. Men in the radical prostatectomy group had lower prostate cancer mortality than patients in the watchful waiting group at 8 years (absolute risk difference [ARD]=6.6; 95% confidence interval [CI], 2.1–11.1; number needed to treat [NNT]=15). No significant difference was found in all-cause mortality between the groups. Rates of distant metastasis and local progression were significantly less for the prostatectomy group than for the watchful waiting group (ARD=13.9; 95% CI, 8.0–19.8; NNT=7; ARD=41.8; 95% CI, 35.2–48.4; NNT=2, respectively).

#### REFERENCE

1. Steineck G, Helgesen F, Adolfsson J, et al. Quality of life after radical prostatectomy or watchful waiting. *N Engl J Med* 2002; 347:790–6.

## Suturing unnecessary for hand lacerations under 2 cm

Quinn J, Cummings S, Callahan M, Sellers K. Suturing versus conservative management of lacerations of the hand: randomised controlled trial. *BMJ* 2002; 325:299–300.

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#### ■ PRACTICE RECOMMENDATIONS

Hand lacerations less than 2 cm long without tendon, joint, fracture, or nerve complications and not involving the nail bed can be cleaned and dressed without suturing, with similar cosmetic results and time to resume normal activities.

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Moreover, managing these uncomplicated hand lacerations conservatively could result in better use of medical resources and improved patient satisfaction due to less pain and less time spent in the emergency department.

## ■ BACKGROUND

Do hand lacerations less than 2 cm require suturing? The value of wound closure and whether it is ever needed have never been studied objectively. Determining which wounds do not need closure could decrease pain and inconvenience for patients and decrease unnecessary use of medical resources.

## ■ POPULATION STUDIED

Patients in this study arrived at the Emergency Department of the University of California, San Francisco, Medical Center with full-thickness lacerations of the hand less than 2 cm in length and without tendon, joint, fracture, or nerve complications. The 91 participants were male and female patients (mean age, 39 years), with 95 lacerations that would normally be closed. Patients were excluded if they had diabetes, if they were receiving anticoagulants or chronic steroids, or if their lacerations were due to a bite or puncture wound or involved the nail bed.

## ■ STUDY DESIGN AND VALIDITY

This research was a randomized, controlled study. Neither patients nor physicians were blinded; however, 2 independent physicians blinded to treatment assignment assessed endpoints. Initial allocation to the treatment group was concealed from enrolling physicians. Patients were randomized to be treated with only tap water irrigation or sutures after the wound was anesthetized and cleaned. Both groups received identical antibiotic ointment and gauze dressing for 24 to 48 hours. Patients returned in 8 to 10 days, at which time the wound was assessed and assigned a wound score according to a previously validated clinical wound scale. At 3-month follow-up, a research assistant took digital photographs of the patients' healed wounds, which were then rated for cosmetic appearance according to a previously

validated visual analog scale.

This was a well-done study. Although patients and their physicians were not masked to therapy, assessors of the primary endpoint were blinded. The design allowed assessment of several outcomes important to both patients and physicians. Follow-up attendance at 3 months was 87% in the suture treatment group and 83% in the conservative treatment group.

## ■ OUTCOMES MEASURED

The primary outcome was cosmetic appearance after 3 months as assessed by the physicians and the patients. The authors also measured duration of treatment, pain during treatment, and time for patients to resume normal activities.

## ■ RESULTS

The primary outcome of cosmetic appearance as assessed by physicians blinded to treatment did not differ between patients treated with sutures and those under conservative management (visual analog score, 83/100 vs 80/100 mm; mean difference, 3; 95% confidence interval [CI], -1 to 8). Patients' ratings of their wound appearance at 3 months were similar (83 vs 82 mm; mean difference, 1; 95% CI, -7 to 9). The mean time to receive treatment was significantly longer in the suture group than in the conservative treatment group (19 vs 5 min). Pain was less in the conservative treatment group than in the suture group (visual analog score, 13 vs 31 mm), whereas time to resume normal activities was the same in both groups (3.4 days).

## Early invasive strategy for acute cardiac ischemia is cost effective

*Mahoney EM, Jurkovitz CT, Chu H, et al. Cost and cost-effectiveness of an early invasive vs conservative strategy for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. JAMA 2002; 288:1851-8.*

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CONTINUED

## ■ PRACTICE RECOMMENDATIONS

In patients with unstable angina and non-ST segment myocardial infarction treated with aspirin, heparin, and tirofiban, an early invasive strategy with routine angiography and appropriate revascularization has better clinical outcomes, at a relatively minimal increase in cost.

## ■ BACKGROUND

Is an early invasive strategy (routine catheterization or revascularization) cost effective in the treatment of unstable angina and non-ST segment elevation MI? Earlier studies showed that a conservative strategy was safer after less severe myocardial infarcts. However, therapeutic advances with glycoprotein IIb/IIIa inhibitors and coronary artery stenting have changed this finding. The TACTIC trial demonstrated that an early invasive strategy for unstable angina and non-ST segment elevation myocardial infarction is superior to a more conservative approach in reducing major cardiac events at 6 months. This study examined initial hospitalization and total 6-month costs and estimated the long-term cost effectiveness of these 2 strategies.

## ■ POPULATION STUDIED

This study enrolled 2220 men and women with unstable angina or non-ST segment elevation myocardial infarction. Subjects were enrolled if they presented within 24 hours of symptom onset and were candidates for coronary angiography and revascularization. The researchers excluded patients with persistent ST segment elevation, secondary angina, percutaneous coronary revascularization, or coronary bypass surgery within 6 months, increased risk of bleeding, left bundle branch block, severe congestive heart failure, serious systemic disease, or an elevated serum creatinine. Primary cost analysis included only patients recruited at US non-Veterans Affairs hospitals (n=1722).

## ■ STUDY DESIGN AND VALIDITY

The study was a single-blinded, randomized, controlled trial that used concealed allocation to randomize patients to an early invasive or conservative

treatment strategy. All patients were treated with 325 mg of aspirin daily, intravenous heparin, and tirofiban (a glycoprotein IIb/IIIa inhibitor). Subjects randomized to the early invasive strategy underwent a coronary angiogram within 4 to 48 hours and subsequent revascularization as indicated. In the conservative treatment group, subjects received catheterization only if their routine stress test was positive or if they developed recurrent ischemia.

This cost-effectiveness study was based on a well-done randomized controlled trial. The researchers employed appropriate methods for the cost analysis, using regression models to impute missing initial hospitalization and follow-up costs, thereby minimizing possible bias. The primary limitation was that follow-up was conducted over just 6 months. Investigators used data from the PURSUIT and Framingham studies to estimate life expectancy of patients. It is unclear whether these data appropriately reflected changes in cardiac therapy over the past decade.

## ■ OUTCOMES MEASURED

The primary economic endpoint was total 6-month costs for all patients recruited at US non-Veterans Affairs hospitals. Other outcomes measured were initial hospitalization costs, costs per death prevented, and costs per year of life gained. Direct costs associated with hospitalizations, emergency department visits, outpatient visits and procedures, nursing home and rehabilitation stays, cardiac medications, and costs from lost productivity were considered within a 6-month follow-up. Inpatient, emergency department, and outpatient charges were obtained from Medicare billing data. Drug costs were obtained from Red Book average wholesale prices. Complete cost data were available for 86% of patients, with missing data equally distributed between groups.

## ■ RESULTS

Although the initial hospitalization costs were significantly higher for the invasive strategy group, these costs were nearly offset at the 6-month follow-up. The average total costs at 6 months were almost equivalent for the invasive and conservative strate-

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gies (\$21,813 vs \$21,277, respectively). The absolute difference in costs was \$586 (95% confidence interval, -1087 to 2486). No significant difference was found for any subgroup except for patients with diabetes, for whom costs were significantly higher in the invasive group. The estimated cost per death or myocardial infarction prevented for the invasive strategy was \$17,758, whereas the cost per year of life gained ranged from \$8371 to \$25,769, depending on model assumptions.

## Warfarin plus aspirin more effective than aspirin alone for secondary prevention of MI

Hurlen M, Abdelnoor M, Smith P, et al. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002; 347:969-74.

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### ■ PRACTICE RECOMMENDATIONS

Compared with aspirin alone, aspirin plus warfarin (goal for international normalized ratio, 2-2.5) or warfarin alone (goal for international normalized ratio, 2.8-4.3) results in fewer reinfarctions and thromboembolic events.

Treating 1000 patients for 1 year would result in approximately 10 fewer reinfarctions and 3 fewer strokes at a cost of 4 more major bleeding episodes. In addition, many patients will not be able to tolerate warfarin therapy. For highly motivated patients at low risk of bleeding, warfarin or warfarin plus aspirin is more effective than aspirin for secondary prevention of myocardial infarction.

### ■ BACKGROUND

Is warfarin plus aspirin or high-dose warfarin more effective than aspirin alone to prevent a second heart attack? Researchers have found conflicting results as to whether warfarin is better than aspirin in preventing a second myocardial infarction in

patients with established coronary artery disease. A meta-analysis suggested that high-intensity warfarin or moderate-intensity warfarin plus aspirin is more effective than aspirin alone.<sup>1</sup> This study is the latest and largest one to address this question.

### ■ POPULATION STUDIED

The investigators studied 3630 men and women younger than 75 years admitted for acute myocardial infarction. Acute myocardial infarction was defined as typical chest pain, appropriate electrocardiogram changes, and a creatinine kinase level higher than 250 U/L or an aspartate aminotransferase level higher than 50 U/L. The investigators excluded patients with contraindications to study drugs, malignant disease, or anticipated poor compliance. Control and intervention groups were similar with respect to comorbid diseases, medication usage, and demographics.

### ■ STUDY DESIGN AND VALIDITY

This study was a randomized, open label, multicenter investigation based in Norway. The intervention groups were a warfarin group (goal: international normalized ratio [INR], 2.8-4.3) and a warfarin plus aspirin group (goal: INR, 2-2.5, plus 75 mg of aspirin daily). The control group received 160 mg of aspirin daily. Patients were followed for a mean of 4 years with clinical examinations conducted in the general practice setting. Every 6 months subjects received questionnaires assessing compliance, adverse events, and new thromboembolic events.

Randomization was done centrally, with good allocation concealment. Overall, the study design was excellent, with good patient follow-up. Although the doses of warfarin probably were more closely monitored because of participation in a study, the monitoring was performed in a general practice environment. Thus, it is likely that results would be similar in a primary care setting. In addition, the benefits and harms seen in this study may not apply to the target INR of 2.0 to 3.0 commonly recommended and used for patients with atrial fibrillation.

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## ■ OUTCOMES MEASURED

The primary outcome was a combined outcome of death, re-infarction, or thromboembolic stroke. The researchers also measured major and minor bleeding events. Major bleeding was defined as a cerebral hemorrhage or any blood loss requiring surgery or transfusion.

## ■ RESULTS

The risk of death, reinfarction, or thromboembolic stroke was significantly decreased when warfarin was used: 15% for the warfarin plus aspirin group and 16.7% for the warfarin group vs 20% for the aspirin group. This correlated with a relative risk of 0.71 for the warfarin-plus-aspirin group (95% confidence interval [CI], 0.60–0.83; number needed to treat [NNT]=67 per year) and 0.81 for the warfarin group (95% CI, 0.69–0.95; NNT=100 per year) compared with aspirin alone. Relative risk reduction in the composite outcome was due primarily to a decrease in re-infarction (relative risks of 0.56 and 0.74 for the warfarin and warfarin plus aspirin groups, respectively) and thromboembolic stroke (relative risks of 0.52 and 0.52 for the warfarin and warfarin plus aspirin groups, respectively). There was no difference in mortality among groups. Major bleeding episodes were more common in the warfarin-plus-aspirin group (0.57% per year; number needed to harm [NNH] = 250 per year) and the warfarin group (0.68% per year; NNH=200 per year) than in the aspirin group (0.17% per year). There were no statistical differences in benefit or harm between the intervention groups. Nearly 33% of patients in the intervention groups needed to discontinue warfarin at some point.

## REFERENCE

1. Anand S, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. *JAMA* 1999; 282:2058–67.

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