Pneumonia rates, while decreasing a bit, may still be high enough to continue to warrant chest radiographs in children with high fevers, leukocytosis, and no other source of infection.

**Background:** Diagnosis of bacterial illness in young children is difficult. Most children with fever and illness have a viral etiology, but a small number may have pneumonia. The efficacy of a chest x-ray has been debated in the workup of fever in children. Before the pneumococcal conjugate vaccine (PCV) was introduced, the incidence of non-occult pneumonia was thought to be 40%; occult pneumonia had an incidence of 19% in children with concerning laboratory values. This has declined significantly since the vaccine was introduced.

**Objective:** To determine the impact of the pneumococcal vaccine in the incidence of occult and non-occult pneumonia as diagnosed by radiograph.

**Design/Participants:** Retrospective cohort study of emergency department records in a pediatric hospital. Patients were eligible if they were aged <5 years and had presented between 1996 and 2005 with a temperature >39°C, had a white blood cell count ≥20,000/μL, and had a chest x-ray performed. Those with an identifiable source of infection other than pneumonia were excluded.

**Methods:** Patients were stratified into 2 groups (before and after universal use of PCV). Pneumonia was defined as a focal infiltrate (or consolidation) on chest x-ray as read by a radiologist. Occult pneumonia was defined as diagnosis of pneumonia by radiograph without clinical respiratory symptoms.

**Results:** Of >235,000 children aged <5 years seen in the emergency department over a 10-year period, 889 met criteria for the cohort in the pre-PCV era and 335 met criteria in the post-PCV era. This was due in part to the significant decrease in the number of complete blood cell counts performed since PCV was introduced. Pneumonia was seen on x-ray in 21% of children pre-PCV and 18% after. Occult pneumonia was diagnosed in 15% of children pre-PCV and 9% after. When looking only at children aged <2 years, radiographic pneumonia was diagnosed in 17% pre-PCV and 10% after.

**Conclusions:** Pneumonia rates, while decreasing a bit, may still be high enough to continue to warrant chest radiographs in children with high fevers, leukocytosis, and no other source of infection. The incidence of pneumonia as diagnosed by chest x-ray has declined a bit since the introduction of PCV, but the incidence is still reasonably high. The decrease is likely not significant enough to warrant changing current recommendations.

**Reviewer's Comments:** I was surprised that the incidence of pneumonia did not change more than it did. However, I was surprised that is was as high as it was at all. Still, this paper does not give enough new evidence to warrant changing the recommendation. (Reviewer-Aaron E. Carroll, MD, MS).

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Keywords: Conjugate Pneumococcal Vaccination

Print Tag: Refer to original journal article
In preschool children with mild to moderate wheezing, there are no differences in treating with oral prednisolone versus a placebo.

Objective: To determine whether oral prednisolone is effective in treating viral-induced wheezing.

Participants/Methods: This study was done in England over 2 years at 3 hospitals with pediatric emergency departments. Children aged 10 months to 60 months with symptoms of a wheezing attack after a viral infection (as defined by a clinician) were enrolled. The reason for choosing 10 months was to reduce recruitment of infants with bronchiolitis. Children with shock, bacterial sepsis, on immunosuppressive therapy, and active or recent exposure to varicella were excluded from the study. Children were enrolled if they had continued wheezing after at least 10 puffs of albuterol inhaler with a spacer or albuterol nebulization. Five minutes after enrollment, they received another dose of albuterol and had an assessment using the Preschool Respiratory Assessment Measure (PRAM), which assesses the severity of the wheeze in the child. Double-blinded randomization occurred to receive either oral prednisolone or placebo in 10 mL of a strongly flavored drink. Based on recommendation from the British Thoracic Society, 10 mg daily for 5 days was given to children aged ≤24 months and 20 mg was given daily for 5 days to children aged >24 months. Discharge times were recorded as well as follow-up PRAM scores.

Results: 687 children were enrolled, with an even split between treatment and placebo groups. Actual discharge times in the hospital were similar: 13.9 hours for placebo and 11.0 hours for prednisolone (not statistically significant). There were no differences in albuterol actuations between groups. Some children were designated as high risk for asthma, and there were no differences in this subset between treatment and placebo groups. Parents filled out symptoms scores 7 days after discharge, and there were no difference between groups. Conclusions: In preschool children with mild to moderate wheezing due to a virus, there were no differences in treating with oral prednisolone versus placebo.

Reviewer’s Comments: Using corticosteroids in children should be avoided when possible. The conclusion here showed that steroids did not significantly reduce time spent in the hospital, albuterol usage, and symptom scores. The only concern was the low dosage used in the article; most pediatricians will use 2 mg/kg for dosing prednisolone; 10- and 20-mg dosage may have been subtherapeutic if a child was heavier. Using a weight-based calculation for dosing prednisolone might have a different outcome for children who weigh more than average. It also would have been interesting to see if a specific virus (respiratory syncytial virus, influenza) would have a response to steroid treatment. (Reviewer-Charles I. Schwartz, MD).
Recommendations to perform lumbar puncture on children aged <12 months with a simple febrile seizure may no longer be relevant.

**Background:** Simple febrile seizures are not uncommon, occurring in 2% to 5% of all children, and are the most common reason for seizures in children aged <5 years. The American Academy of Pediatrics (AAP) has recommended for more than a decade that a child aged <12 months with a febrile seizure undergo a lumbar puncture (LP) as part of a fever workup because it is difficult to make a diagnosis of meningitis clinically in this population. Past work, though, has shown that very few children with bacterial meningitis present with a simple febrile seizure and no other serious symptoms. This, of course, was all before introduction of the pneumococcal conjugate vaccine (PCV), which has made meningitis even more unlikely.

**Objective:** To examine if AAP recommendations for LP are being followed, to determine the rate of meningitis in those children who do receive an LP, and to see what factors are associated with the decision to do an LP.

**Design:** Retrospective chart review.

**Participants/Methods:** Patients were eligible if they were aged 6 to 12 months and presented with a simple febrile seizure to the emergency department between January 2001 and November 2005. Patients with known neurological disorders were excluded. Data abstracted included clinical history, laboratory data, and demographic data.

**Results:** Over this time period, 242 records were identified, of which 56 met inclusion criteria; >50% of these patients received LP. There was no association between age and whether LP was performed. Ten children received antibiotics before the visit to the emergency department, and of these, 4 had LP performed. Children pretreated with antibiotics were no more likely to have LP performed than were children who had not received antibiotics. All LP examinations were negative.

**Conclusions:** Recommendations to perform LP on children aged <12 months with a simple febrile seizure may no longer be relevant. Recommendations of the AAP with respect to LP for simple febrile seizures in children aged <12 months are being followed haphazardly. With the advent of the PCV, however, these recommendations may be out of date and no longer necessary. The AAP should either update this recommendation or explain why it is still necessary.

**Reviewer’s Comments:** It is interesting that the introduction of PCV seems to have warranted changing some recommendations while failing to do so in others. This is one area where we can likely stop being so invasive. The recommendations should be revisited. (Reviewer-Aaron E. Carroll, MD, MS).

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Keywords: Febrile Seizures

Print Tag: Refer to original journal article
Elbow Extension Test May Identify Fractures

Elbow Extension Test to Rule Out Elbow Fracture: Multicentre, Prospective Validation and Observational Study of Diagnostic Accuracy in Adults and Children.

Appelboam A, Reuben AD, et al:
BMJ 2008; 337 (a2428):

In both adults and children with elbow trauma, those unable to fully extend their elbows should have radiography performed because the risk of fracture is nearly 50%.

**Objective:** To assess the value of full elbow extension as a test to rule out fracture in patients with elbow injury.

**Design/Participants:** For adult patients, the study was a multicenter prospective validation study of the rule. For children, it was an observational study.

**Methods:** Patients, including children aged >3 years, presenting to 5 emergency departments in southwest England from 2004 to 2006 within 72 hours of an elbow injury were eligible for study. In adults, those with full extension did not undergo radiography and were discharged with analgesia and a sling as needed. A structured follow-up phone call was done in 7 to 10 days to assess outcome. For children, the elbow extension test was done, but x-rays were obtained at the discretion of the emergency department provider. Again, patients had follow-up by phone in 7 to 10 days. Final outcome measures, particularly presence of a fracture or no suggestion of problems at 7 to 10 days, were determined by follow-up phone calls, any follow-up information obtained from a subsequent orthopedic clinic appointment if that was needed, and from x-ray reports of a radiologist blinded to results of the elbow extension test.

**Results:** Of 2127 patients presenting with elbow injury, 1740 participated in the study, of which 780 were children aged 3 to 15 years. Of 1138 adults unable to fully extend their elbows, fractures were found in 521 (43%). Of 491 children unable to fully extend, fractures were found in 210 (43%). On the other side, of 598 adults with full extension who had follow-up, fractures were ultimately found in 17 (3%). Of 289 children with full extension, fractures were ultimately found in 12 (4%). None required operative intervention.

**Conclusions:** The elbow extension test can be useful in clinical decision making. In both adults and children, those unable to fully extend their elbows should have radiography done because the risk of fracture is nearly 50%.

**Reviewer’s Comments:** The authors “advise caution” in use of the elbow extension test as a single clinical decision rule for universal use in children with elbow trauma because of the potential in children for occult supracondylar fractures as well as the higher false-positive rate (4% compared with 3% for adults). The inference is that other aspects of the examination need to be considered in children with elbow injuries, including assessment of pulses and capillary filling and of the ability to extend all fingers of the affected hand as well as other testing of peripheral nerve function. (Reviewer-Mark F. Ditmar, MD).

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Keywords: Elbow Fracture

Print Tag: Refer to original journal article
Heart failure patients with preserved left ventricular function have a similar clinical outcome as patients with reduced left ventricular function.

**Background:** Heart failure patients have a poor prognosis. The prognosis in patients with preserved left ventricular function (LVF) has been thought to be better than the prognosis in patients with reduced LVF. **Objective:** To evaluate clinical outcomes of patients with heart failure and preserved LVF compared with patients with reduced function and factors affecting prognosis. **Design:** Prospective evaluation. **Participants/Methods:** Evaluated were 289 consecutive patients hospitalized with a definite clinical diagnosis of heart failure based on typical clinical symptoms and signs: orthopnea, paroxysmal nocturnal dyspnea, elevated jugular venous pressure, ankle edema, or cardiomegaly on chest x-ray. Patients were stratified into 2 subsets based on qualitative echocardiographic LVF visual assessment of normal, preserved, mild, moderate, or severely reduced LVF. Patients were followed clinically for 1 year. Clinical outcomes including number of rehospitalizations, death, hospitalizations for any cardiac cause, and heart failure exacerbations were recorded. **Results:** More than one third (36%) of patients had preserved systolic LVF by echocardiography. These patients were more likely to be older and female, to have less ischemic heart disease, and to have more atrial fibrillation. Patients with preserved LVF received fewer β-blockers, nitrates, aspirin, and statins, but they received more calcium-channel blockers. Survival at 1 year in this group was poor and not significantly different from that of patients with reduced LVF (75% vs 71%, respectively). Adjusted survival by Cox regression analysis was not significantly different (P=0.25). Results further showed that patients with preserved LVF had fewer rehospitalizations for heart failure (25% vs 35%; P<0.05). Predictors of mortality in the whole group by multivariate analysis were age, diabetes, chronic renal failure, atrial fibrillation, residence in a nursing home, and serum sodium of ≤135 mEq/L. **Conclusions:** The prognosis of patients with clinical heart failure with or without preserved LVF is poor. The clinical outcome of patients with preserved LVF function is not significantly different from that of patients with reduced LV function. **Reviewer's Comments:** In my opinion, this was a very good study. The prognosis in patients with heart failure and preserved LVF is gradually becoming recognized as similar to that of patients with reduced LVF. Certain characteristics of patients with preserved LVF (more hypertension, LVH, diastolic dysfunction, and older age) predispose them to elevated LV end-diastolic pressures leading to heart failure. Some limitations of the study acknowledged by the authors include qualitative assessment of echocardiographic data, including patients on basis of clinical grounds and not on an objective test for heart failure, and not excluding patients with valve disease. Optimal treatment for patients with preserved LVF has yet to be defined and better treatment modalities are needed in both subsets. (Reviewer-Sahil Mehta, MD).
Brain natriuretic peptide may help guide treatment for congestive heart failure better than symptoms in patients aged 60 to 74 years.

**Background:** Therapy for congestive heart failure (CHF) is often adjusted based on symptoms. It is not known whether brain natriuretic peptide (BNP) would be a better tool to guide heart failure therapy.

**Objective:** To compare use of symptoms versus BNP in the adjustment of heart failure therapies over 18 months.

**Design:** Single-blind, randomized controlled trial.

**Participants:** Patients aged ≥60 years with New York Heart Association (NYHA) class II or greater symptoms on therapy, a hospitalization within the previous year for CHF, and BNP >400 pg/mL if age was <75 years or >800 pg/mL if age was ≥75 years. Patients were recruited to 15 centers in Switzerland and Germany.

**Methods:** 622 patients (80% with systolic heart failure) were stratified into 2 age groups: 60 to 74 years and ≥75 years. Patients were randomized to medication adjustment guided by symptoms or BNP. Medication changes were based on a guideline-driven algorithm. Goals of therapy were NYHA class II symptoms or less or BNP <2 times the upper limit of normal. Patients were evaluated at baseline and at 1, 3, 6, 12, and 18 months. The primary end points were survival free of hospitalization and quality of life at 18 months.

**Results:** Patients in the BNP-guided group were more likely to have their medication up-titrated than were those in the symptom-guided group. Survival free of hospitalization was no different in the 2 treatment groups, but survival free of heart failure hospitalization was significantly less in the 60- to 74-year-old BNP-guided group. Quality-of-life measures improved in both groups but were not significantly different. Serious side effects were no different in the 2 treatment groups.

**Conclusions:** Treatment guided by BNP does not reduce survival free of hospitalization or quality of life, but it does reduce hospitalizations due to heart failure in patients aged 60 to 74 years with CHF.

**Reviewer’s Comments:** This study suggests that physicians may need to be more aggressive in up-titrating medications in patients with heart failure. BNP-guided therapy may be a useful strategy in some patients, especially those aged <75 years. (Reviewer-Deborah L. Greenberg, MD).

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Keywords: Therapy

Print Tag: Refer to original journal article
NSAIDs in Heart Failure--Are Any Safe?

*Increased Mortality and Cardiovascular Morbidity Associated With Use of Nonsteroidal Anti-Inflammatory Drugs in Chronic Heart Failure.*

Gislason GH, Rasmussen JN, et al:

Arch Intern Med 2009; 169 (January 26): 141-149

Both COX-2 selective and nonselective NSAIDs are associated with increased mortality in patients with heart failure.

**Background:** NSAIDs, including old-fashioned over-the-counter (OTC) medications, can cause sodium and fluid retention and exacerbate heart failure (HF) but are widely perceived to be safe and often used by cardiac patients.

**Objective:** To assess the risk of hospitalization and death associated with NSAID use in patients with HF.

**Design:** Retrospective cohort study.

**Participants:** 107,000 Danish patients with HF.

**Methods:** Using the Danish central registry of hospitalizations, investigators identified all those surviving an initial hospitalization for HF from 1995 to 2004. They then reviewed the national prescription registry for NSAID prescriptions. In Denmark, OTC NSAIDs are available only in very small quantities and are not covered by health insurance as prescriptions are, so virtually all NSAIDs are dispensed by prescription. The daily dose was defined as low (for example, rofecoxib ≤25 mg/day, ibuprofen ≤1200 mg/day, or naproxen ≤500 mg/day) or high dose.

**Results:** 34% of HF patients received at least 1 prescription for a selective cyclo-oxygenase (COX)-2 inhibitor or a nonselective NSAID. Overall mortality was 56% over the study period. After correcting for severity of HF (based on other prescription data) and comorbid illness, an increased risk of death was associated with most NSAIDs, and was highest with COX-2 inhibitors and diclofenac. There was no increase with low-dose ibuprofen or naproxen. The hazard ratio (HR) for death was 1.70 for rofecoxib, 2.08 for diclofenac, 1.75 for celecoxib, 1.31 for ibuprofen (all doses), and 1.28 for naproxen (all doses). Baseline pharmacotherapy had no effect on mortality risk. The number of patients needed to treat for 1 year to cause 1 additional death ranged from 9 with rofecoxib to 53 with ibuprofen. The risk of hospitalization for HF was also increased for all NSAIDs, with the HR ranging from 1.16 for ibuprofen to 1.86 for high-dose rofecoxib. Hospitalization for acute myocardial infarction (MI) was increased by a similar amount, from an HR of 1.14 with low-dose diclofenac to 2.43 with higher doses of the same drug.

**Conclusions:** In an unselected cohort of patients with HF, use of an NSAID was associated with increased mortality as well as increased risk of hospitalization for HF or MI.

**Reviewer's Comments:** With the high overall mortality in this study, even the modest increase in risk conferred by NSAIDs contributes to substantial numbers of deaths. The proportion of patients treated with NSAIDs was striking, even though they required a physician's visit and prescription to obtain--I would guess the proportion is much higher here. I am going to try to start weeding NSAIDs out of the medication lists for my patients with HF and warning them to avoid OTC preparations. (Reviewer-Karen A. McDonough, MD).

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Keywords: NSAIDs

Print Tag: Refer to original journal article
Continuation of statin treatment provides an ongoing reduction in mortality among patients with and without a history of coronary heart disease.

Background: Beneficial effects of statins in decreasing low-density lipoprotein cholesterol (LDL-C) and in reducing cardiovascular mortality in secondary prevention have already been established in several long-term, placebo-controlled trials. Administering statin therapy for a reduction in the overall mortality in patients without coronary heart disease (CHD) has not been well assessed.

Objective: To assess effect of statin therapy on mortality in 2 cohorts: a primary prevention cohort of subjects with no indication of CHD, and a secondary prevention cohort of patients with known CHD.

Design/Participants: Retrospective, cohort study that included 229,918 adult enrollees in a health maintenance organization in Israel.

Methods: Statin treatment had been initiated from 1998 through 2006 (mean age, 57.6 years; 50.8% female). Proportion of days covered (PDC) with statins was assessed by measuring number of dispensed statin prescriptions during the interval between date of the first statin prescription and at end of follow-up.

Results: There were 4259 and 8906 deaths among the primary prevention and secondary prevention cohorts, respectively (mean of 4 and 5 years of follow-up, respectively). In both cohorts, continued treatment with statins (PDC, ≥90%) conferred a ≥45% reduction in risk of death, as compared to patients with a PDC of <10%. Also, a stronger risk reduction was found among patients with high baseline LDL-C and in patients initially treated with high-efficacy statins.

Conclusions: Higher continuity of statin treatment provided an ongoing reduction in mortality among patients with and without a known history of CHD.

Reviewer’s Comments: This is an important study illustrating an independent association between statin therapy and a reduction in mortality in patients with and without known CHD. This reduction in all-cause mortality may be secondary to the anti-inflammatory and anti-thrombotic effects of statins. This study also demonstrates that use of high-efficacy statins is associated with an improved reduction in mortality. This is important, since it highlights the need to regularly assess lipid profiles in patients, and to up-titrate statin dosages, when required, for maximal benefits. (Reviewer-Suraj Maraj, MD).

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Keywords: Statin Treatment

Print Tag: Refer to original journal article
Premature withdrawal of antiplatelet agents is associated with a 10% risk of thrombotic vascular events. In the setting of recent stent placement, particularly drug-eluting stents, these thromboses may be fatal.

Objective: To review the perioperative use of antiplatelet agents.
Methods: All available studies were identified through searching PubMed, EMBASE, and the Cochrane databases. Specific drugs of interest were aspirin, thienopyridines (clopidogrel), and glycoprotein (Gp) IIb/IIIa inhibitors (abciximab, eptifibatide). The authors independently reviewed identified abstracts and excluded those not meeting inclusion criteria.

Results: The authors review the mechanism of action, indications for, bleeding risk, and perioperative recommendations for the 3 classes of antiplatelet agents. Aspirin works by irreversibly inhibiting thromboxane A2 from platelets and prostacyclin from endothelial cells. The platelet dysfunction lasts for the life of the platelet, while the endothelial cell dysfunction lasts only during aspirin therapy. It is indicated for stable coronary artery disease, peripheral arterial disease, and as primary prevention for coronary events, for carotid endarterectomy, and for atrial fibrillation. There is little evidence of increased risk of perioperative bleeding except for intracranial surgery. Due to the risk profile, it is not recommended to stop aspirin use perioperatively except for intracranial surgery or other limited specific cases in which the small chance of bleeding outweighs the benefit of ongoing thromboprophylaxis. Thienopyridines irreversibly bind the platelet receptor and are used in patients with unstable angina and patients undergoing percutaneous coronary intervention (PCI). They must be continued for at least 4 weeks after placement of a bare metal stent, with recommendations for 1 year of treatment. There is no role in primary prevention. Bleeding risk is high. Due to the significant bleeding risk, clopidogrel should be stopped at least 5 days prior to elective surgery. However, they should not be stopped in the setting of recent drug-eluting stent implantation. Gp IIb/IIIa inhibitors competitively inhibit the Gp IIb/IIIa receptor, lasting only as long as the drug is taken. They are used in patients with acute coronary syndrome and those undergoing PCI. There is an increased risk of perioperative bleeding, although very little data. These must be discontinued for at least 12 hours preoperatively to allow normal hemostasis.

Conclusions: Premature withdrawal of antiplatelet agents is associated with a 10% risk of thrombotic vascular events. In the setting of recent stent placement, particularly drug-eluting stents, these thromboses may be fatal. There are currently no guidelines for perioperative use of these ubiquitous, potentially dangerous agents.

Reviewer's Comments: As more and more patients will continue to take these life-sustaining drugs that can significantly increase perioperative morbidity, guidelines to help us balance risk and benefit would be extremely helpful. The authors present some helpful recommendations, but the rigor of the analysis and the paucity of the data fall well short of guideline status. (Reviewer-Karen J. Brasel, MD, MPH).

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Keywords: Antiplatelet Agents

Print Tag: Refer to original journal article
Be cautious with proton pump inhibitors in patients on clopidogrel; if you need to use one, the safest is pantoprazole.

**Background:** Genetic variants in cytochrome P450 2C19 are known to inhibit clopidogrel's antiplatelet activity. Proton pump inhibitors (PPIs; except pantoprazole) are known to inhibit 2C19.

**Objective:** To evaluate the correlation between PPI use and worse outcomes in patients taking clopidogrel after myocardial infarction (MI).

**Design:** Case-control study.

**Participants:** 734 patients with recurrent MI within 90 days and 2057 control subjects in Ontario, Canada.

**Results:** The odds ratio (OR) was 1.27 for recurrent MI in all patients using PPIs along with clopidogrel. No increased risk was found in patients using pantoprazole, and the OR was 1.40 in patients using other PPIs. Although the relative risk increase appears to be modest, an approximation of the absolute risk increase is about 2%, which is close to the expected benefit of clopidogrel.

**Conclusions:** Concurrent use of PPIs decreases clopidogrel's antiplatelet effect and increases the short-term risk of recurrent MI.

**Reviewer's Comments:** This study suggests that concurrent use of PPIs other than pantoprazole substantially decreases or eliminates the benefit of using clopidogrel after MI. However, one substantial limitation of applying this study to a U.S. population was the low rate of intervention. Only 13% of patients had percutaneous intervention during their initial hospitalization. This probably reflects differences in health care delivery in Ontario, where <10% of acute care hospitals have the ability to do coronary interventions. Based on the results of other trials, it is quite possible that if we repeated this study in a population in which interventions (particularly stents) were used more often, the difference between patients who were and were not taking PPIs might be even larger. (Reviewer-Christopher L. Knight, MD).

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Keywords: Clopidogrel

Print Tag: Refer to original journal article
Low diastolic blood pressure and high pulse pressure are associated with a greater risk of death in older hypertensive patients.

**Background:** Hypertension is the most common cardiovascular risk factor in older adults. More than 70% of people aged ≥65 years has high blood pressure.

**Objective:** To examine the relationship between office and ambulatory systolic blood pressure, diastolic blood pressure, and pulse pressure and total mortality in older patients with hypertension.

**Design:** Observational prospective cohort study, conducted in a hypertension outpatient clinic in the University of Florence, Italy. All participants used 24-hour ambulatory blood pressure monitoring.

**Participants/Methods:** 805 patients aged ≥60 years with hypertension underwent office and ambulatory blood pressure measurements. Mortality was assessed after a mean follow-up of 3.8 years.

**Results:** Of 805 patients, 107 died after 3.8 years. Participants who died had higher systolic blood pressure and pulse pressure, and had lower diastolic blood pressure during office and ambulatory measurements. Mortality rates were greater with higher systolic blood pressure and were lower with higher diastolic blood pressure. The adjusted hazard of death increased linearly with increasing ambulatory systolic blood pressure and pulse pressure, and it decreased significantly with increasing ambulatory diastolic blood pressure.

**Conclusions:** Low diastolic blood pressure and high pulse pressure are associated with a greater risk of death in older hypertensive patients. Reaching optimal systolic blood pressure levels should not be obtained at the expense of an excessive diastolic blood pressure reduction.

**Reviewer’s Comments:** This well-designed study was conducted over a period of 5 years but included a relatively small number of patients. This study suggests that reaching a systolic blood pressure goal at the expense of an excessive diastolic blood pressure reduction (<80) may increase morbidity and mortality for high-risk patients. Future studies should search for blood pressure medicine that electively decreases systolic blood pressure rather than those that lower diastolic blood pressure. (Reviewer-Soryal A. Soryal, MD).

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Keywords: Blood Pressure Management

Print Tag: Refer to original journal article
Genotype-directed initiation of warfarin can reduce the risk of bleeding and the time it takes to achieve therapeutic international normalized ratios. This study suggests that the practice is unlikely to be cost-effective at the present time.

**Background:** Patients with the cytochrome P450 allele CYP2C9 metabolize warfarin more slowly; they are at increased risk of supratherapeutic international normalized ratios (INRs) and take longer to reach stable warfarin dosing. Patients with the vitamin K epoxide reductase VKORC1 group A haplotype require lower doses of warfarin and are at increased risk of supratherapeutic INRs. It remains unknown whether testing for these gene variants is safer or more cost-effective when initiating chronic anticoagulation therapy.

**Objective:** To model the cost-effectiveness of routinely using pharmacogenetic information to determine the initial dose of warfarin for patients with nonvalvular atrial fibrillation (AF). **Design/Methods:** Decision analysis study comparing pharmacogenetic-based dosing compared with standard induction of warfarin (nomogram based) in a hypothetical patient with AF. Studies estimate that the CYP2C9 and VKORC1 group A genotypes each confer >3-fold increased risk of major bleeding. Pharmacogenetic information reduced the time to first therapeutic INR from 7.5 to 4.8 days and reduced the risk of major hemorrhage by 0.68 (95% CI, 0.22 to 2.06). Bleeding and stroke risk were taken from well-known randomized trials of warfarin in patients with AF. The decision analysis was a Markov model of a hypothetical 69-year-old man at average risk of stroke and no contraindications to warfarin therapy.

**Results:** Using baseline assumptions, use of pharmacogenetic information resulted in a gain of 0.0026 quality-adjusted life-years (QALY). The cost of pharmacogenetic-directed dosing added $367 to the cost of induction of warfarin. The marginal cost-effectiveness of pharmacogenetic-directed warfarin dosing was $144,100 per QALY gained. Using a standard discount rate of 3% to adjust for the diminished value of deferred benefits, the adjusted cost-effectiveness was $171,800 per QALY.

**Conclusions:** Using sensitivity analysis to consider a reasonable range of values in their model, the authors concluded that there was a 10% chance of pharmacogenetic testing resulting in marginal cost-effectiveness of <$50,000 per QALY. Pharmacogenetic testing prior to induction therapy with warfarin resulted in a very small improvement in quality of life (QALY). The estimated cost of this small improvement was high, generally beyond the level that society deems cost-effective.

**Reviewer's Comments:** Decision analyses are helpful in thinking about the utility of new diagnostic tests or therapies. In this case, pharmacogenetic testing was estimated to confer a small benefit and a high marginal cost. It is also important to note that pharmacogenetic testing might delay initiation of warfarin therapy. It may be that cheaper and more rapid tests would favor pharmacogenetic testing. It may also be worthwhile when considering pharmacogenetic-based dosing in patients at higher risk for hemorrhagic complications. (Reviewer—Paul R. Sutton, PhD, MD).

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Keywords: Pharmacogenetics/Warfarin

Print Tag: Refer to original journal article
Substituting "hospital at home" care for traditional acute care in the hospital improves functional outcomes for acutely ill older adults.

**Objective:** To determine if a "hospital at home" (HaH) intervention for acutely ill older adults improves functional outcomes relative to hospitalization.

**Design:** Nonrandomized clinical trial.

**Participants:** 214 community-dwelling older adults requiring acute hospital care for pneumonia, cellulitis, or exacerbations of congestive heart failure or chronic obstructive pulmonary disease.

**Methods/Interventions:** Eligible patients were offered hospital admission or HaH care. The latter involved ambulance transport home, initial one-on-one care by an HaH nurse (mean, 17 hours), followed by at least daily nurse and physician visits. Outcome measures were changes in self-reported activities of daily living (ADL) and instrumental activities of daily living (IADL) scores from 1 month before admission to 2 weeks afterward.

**Results:** 84 subjects received HaH care, and 130 were admitted to an acute care hospital. Mean subject age was 77 years. Patients electing HaH had lower baseline functional status but otherwise did not differ significantly from patients choosing hospital care in measures of severity of acute illness, underlying health problems, or demographics. Patients treated at home had small but statistically significant improvements in IADL scores compared to hospitalized patients. More HaH patients than hospitalized patients had improvements in functional abilities (ADL scores improved in 45% vs 25%, IADL scores in 46% vs 17%), and fewer experienced functional decline (ADL decline, 21% vs 31%; IADL, 33% vs 43%), although the differences in ADL scores did not reach statistical significance (P=0.10).

**Conclusions:** HaH care was associated with modest improvements in IADL abilities and a trend toward better ADL function relative to hospital-based care.

**Reviewer's Comments:** Previous studies indicate that HaH care for older patients with acute medical illness can provide high-quality care while minimizing iatrogenic complications, reducing caregiver stress and costs and increasing patient and caregiver satisfaction. This study adds probable modest improvements in functional abilities to the potential benefits of caring for acutely ill older adults in their homes. Potentially significant study limitations include that only one third of hospitalized patients provided data regarding changes in their functional status, use of self-reporting to ascertain functional abilities, and the possibility of selection bias whereby patients who chose to be cared for at home were less ill. Study data that patients cared for at home were, in fact, more functionally impaired at baseline and had more comorbid conditions and higher measures of acute illness are reassuring that selection bias was not a major issue. The HaH care model has the potential to provide equivalent medical care to older adults while possibly better preserving functional status, and it warrants further study. (Reviewer-Jeff Wallace, MD, MPH).

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Keywords: Hospital at Home Care

Print Tag: Refer to original journal article
Sertraline and escitalopram offer the best efficacy and tolerability in a multi-drug comparison of antidepressants.

**Background:** Depression is a common problem, but satisfying to treat in many patients who respond well to therapy. A great deal of mild to moderate depression is handled by primary care physicians.

**Objective:** To compare efficacy and tolerability of multiple second-generation antidepressants.

**Design:** Systematic review and meta-analysis.

**Methods:** The methodology is relatively sophisticated. Simply put, the authors found 117 randomized controlled trials that involved drug-to-drug comparisons among antidepressants. They looked only at "second-generation antidepressants," which included selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors (such as venlafaxine and duloxetine, mirtazapine, and bupropion). They then standardized those trials for treatment response and duration of therapy to enhance comparability, defining acute treatment as 8 weeks. They also tried to capture information on tolerability of the various medications. First, they derived data for all head-to-head comparisons they could find, and then used these data to model comparisons that were never studied directly. For example, one study may have compared bupropion to sertraline, and another study may have compared citalopram to sertraline; their model allowed them to generate a theoretical comparison between bupropion and citalopram.

**Results:** Unsurprisingly, the general rule is that one antidepressant is very similar to another, and there are relatively few major differences between antidepressants in either efficacy or tolerability. However, there are a few interesting exceptions. The 2 drugs that fared the best were sertraline and escitalopram. Both were at least as effective and sometimes more effective than most comparator drugs. Compared to each other, there were no significant differences. By far the worst drug included in the analysis was reboxetine, which compared poorly in both efficacy and tolerability. Other particularly efficacious antidepressants included mirtazapine and venlafaxine, and particularly well-tolerated antidepressants included bupropion and citalopram.

**Reviewer's Comments:** In many ways, this study reinforces what I already thought, which is that most antidepressants are fairly comparable in terms of efficacy and tolerability. It also helps to validate some subtle biases I held that some drugs were perhaps slightly better or slightly more tolerable than others. For me, the most surprising result was finding sertraline among the top 2 medications in the study. In my practice, I have tended to use sertraline predominately in the elderly, and to a degree, it fell by the wayside because it was later to go generic than fluoxetine or paroxetine. I may find myself using more sertraline in the future because of this study's results. (Reviewer-Christopher L. Knight, MD).

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Keywords: Antidepressants

Print Tag: Refer to original journal article
Fiber, Antispasmodics, Peppermint Oil Inexpensive, Safe Tx for IBS

Effect of Fibre, Antispasmodics, and Peppermint Oil in the Treatment of Irritable Bowel Syndrome: Systematic Review and Meta-Analysis.

Ford AC, Talley NJ, et al:

BMJ 2008; 337 (November 13): a2313

Fiber (especially ispaghula husk), antispasmodics, and peppermint oil are all relatively inexpensive and safe agents that are effective in the treatment of irritable bowel syndrome.

**Background:** While recent emphasis on the treatment of irritable bowel syndrome (IBS) has centered on expensive pharmaceuticals that act on various gastrointestinal tract receptors, a number of other more inexpensive and safe agents have been tested in the past.

**Objective:** To assess the utility of fiber, antispasmodics, and peppermint oil in treating IBS.

**Design:** Systematic review and meta-analysis.

**Participants:** Adults with IBS.

**Methods:** The authors searched MEDLINE, EMBASE, and the Cochrane Library for randomized controlled trials in adults with IBS. The trials had to compare 1 of the 3 modalities to placebo or no treatment, to have followed patients for at least 1 week, and to have provided outcomes as either a global assessment of cure or improvement of symptoms. No language restrictions were applied. Two reviewers abstracted the data independently as dichotomous outcomes, namely improved or not improved. The risk of bias of each trial was assessed with the Jadad scale, which considers the generation of the randomization scheme, blinding, and accounting for dropouts. The data were then pooled for each treatment modality using meta-analysis.

**Results:** 12 trials assessed fiber. Overall, the relative risk (RR) of not improving was 0.87 (95% CI, 0.76 to 1.00; \( P = 0.05 \)). The effect was limited to ispaghula husk. However, when only trials with a low risk of bias were considered, the significant differences disappeared. Antispasmodics (22 trials) were also found to be beneficial, and the effect persisted in trials with a low risk of bias. Peppermint oil (4 trials) was the most effective (RR, 0.43; 95% CI, 0.32 to 0.59), and the effect was still present when only trials with a low risk of bias were considered.

**Conclusions:** Fiber (especially ispaghula husk), antispasmodics, and peppermint oil were all effective and safe for treatment of IBS.

**Reviewer’s Comments:** With so much publicity being focused on more expensive, and perhaps more toxic, agents, it is comforting to know that older, simpler, and safer agents still have a place in the management of IBS. This is particularly the case for peppermint, which was used in doses of about 200 mg 2 to 4 times daily. Peppermint has long been recognized as a smooth muscle relaxant; in fact, one of the potential side effects of its use is an increase in gastroesophageal reflux symptoms. (Reviewer-Ronald L. Koretz, MD).

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Keywords: Irritable Bowel Syndrome

Print Tag: Refer to original journal article
Colon cancer screening should be done on average-risk subjects aged 50 to 75 years, using fecal occult blood testing, sigmoidoscopy, or colonoscopy.

**Background:** In 2002, the United States Preventive Services Task Force (USPSTF) issued a recommendation for colorectal cancer (CRC) screening of average-risk subjects. At that time, the type of test to be used and age limits for screening were not established.

**Objective:** To expand the CRC screening recommendation by focusing on age limits and assessing benefits and harms of various potentially available tests, namely various tests for fecal hemoglobin (ranging from the standard guaiac-based assay for pseudoperoxidase activity of hemoglobin, more sensitive assays for this enzyme [Hemoccult SENSA], immunochemical tests [ICT] for human hemoglobin, and DNA from neoplasms), flexible sigmoidoscopy (FS), colonoscopy, and CT colonography.

**Methods:** Guidelines based on prior systematic reviews of the literature, a recent upgraded targeted systematic review (Whitlock EP et al, *Ann Intern Med* 2008; 149:638-658), and a recent decision analysis (Zauber AG, *Ann Intern Med* 2008; 149:659-669) were reviewed. Recommendations were made allegedly based on available evidence. Interventions included CRC screening by the techniques noted above as well as a combination of FS every 5 years with interval-sensitive assays for fecal hemoglobin (either Hemoccult SENSA or ICT).

**Results:** Colonoscopy was the most sensitive test for finding cancer and adenomas. However, since it was the most invasive test, non-colonoscopic tests were considered as a mechanism to reduce the absolute number that would be done. Newer fecal blood tests were more sensitive, but often less specific, than standard hemoccult. While the fecal DNA test may have been more sensitive, the data are very limited. FS every 5 years and interval fecal tests were comparable to colonoscopy or annual newer fecal blood tests. CT colonography was comparable to colonoscopy for detecting cancer and polyps >1 cm but not for smaller lesions. This technique has other problems, including potential cancer risk and lack of insight into the utility of finding extracolonic processes. Colonoscopy produced serious complications in 1 in 400 subjects; the rate for FS was almost 10-fold lower. While screening individuals aged 75 to 85 years yielded extra life-years, the additional resource utilization was large.

**Conclusions:** CRC screening should be done in average-risk subjects between the ages of 50 and 75 years using yearly sensitive tests for fecal hemoglobin, FS every 5 years, plus interval fecal hemoglobin testing, or 10-yearly colonoscopy.

**Reviewer's Comments:** Both 2002 and current recommendations do not consider data from randomized trials that argue against CRC screening. The only available trial of FS found that the screened group had a higher total mortality, and the 4 large trials of hemoccult have not been able to show that any life-years have been saved. (Reviewer-Ronald L. Koretz, MD).

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Keywords: Colon Cancer Screening

Print Tag: Refer to original journal article
More sensitive guaiac-based and immunochemical tests for hemoglobin are better than standard hemoccult for colorectal cancer screening, but CT colonography cannot be recommended at this time.

**Background:** The United States Preventive Services Task Force, which previously advocated colorectal cancer (CRC) screening, commissioned a systematic review to assess the various tests that could be used. **Objective:** To undertake a systematic review to assess test characteristics and potential harms from fecal occult blood tests (FOBTs)—particularly the more sensitive guaiac-based and immunochemical assays and tests—for malignancy-associated DNA, flexible sigmoidoscopy (FS), colonoscopy, and CT colonography. **Design:** Targeted systematic review. **Methods:** A systematic review was undertaken to identify data regarding the sensitivity and specificity of the indicated tests as well as any harms that are associated with them. No new information was sought regarding the efficacy of screening itself. **Results:** 2 to 3 days of FOBT was better than a single test. The newer FOBTs were more sensitive for diagnosing cancer, and perhaps also benign neoplasia, than was standard hemoccult. However, the tests were often less specific. The DNA FOBTs did appear to be more sensitive, but the data were too limited to allow any hard conclusions. CT colonography was comparable to colonoscopy for identifying both cancer and large (at least 10 mm) polyps but less sensitive for smaller polyps. Potential harms from CT colonography included cancer risk (estimated at 1 in 333 to 1 in 3000) and an unknown consequence of identifying extracolonic abnormalities. The perforation rate was very low. Colonoscopy misses 10% of adenomas, even those >10 mm. There are 2.8 serious complications for every 1000 colonoscopies undertaken; the rate is increased if polypectomy is also performed (and lower if it is not). Sensitivities of FS for cancer and adenomas are 58% to 75% and 72% to 86%, respectively. Presumably, these figures include use of colonoscopy in selected cases. There are 3.4 serious complications for every 10,000 procedures. **Conclusions:** More sensitive FOBTs are reasonable substitutes for standard hemoccult testing. CT colonography cannot be recommended at this time because of uncertainties about potential harm. **Reviewer's Comments:** The authors claimed not to have found any new reports about the impact of screening on mortality, disregarding the 2006 systematic review suggesting that hemoccult screening does not improve overall mortality because the reduction in CRC deaths is compensated for by an increase in non-CRC deaths (Moayyedi P, Achkar E. *Am J Gastroenterol* 2006; 101:380-384). The Task Force has already noted, but then disregarded, a randomized trial assessing FS indicating that total mortality was increased in the screened group (Thiis-Evensen E, et al. *Scand J Gastroenterol* 1999; 34:414-420). The assumption that CRC screening is effective and cost-effective is still open to challenge. (Reviewer-Ronald L. Koretz, MD).
CT Angiography Accurate in Diagnosing PAD


Met R, Bipat S, et al:

JAMA 2009; 301 (January 28): 415-424

The accuracy of CT angiography is slightly lower in tibial disease compared to femoropopliteal and aortoiliac disease.

**Background:** CT angiography (CTA) is increasingly used to evaluate peripheral arterial disease (PAD). Although CTA does not have therapeutic capabilities, it provides diagnostic information with a decreased contrast load compared to standard digital subtraction angiography.

**Objective:** To perform a systematic review of current studies comparing CTA with digital subtraction angiography in patients with PAD.

**Methods:** A search was performed of MEDLINE and EMBASE databases for articles using CTA to diagnose patients with claudication (PAD) from January 1966 to August 2008. A quality assessment tool was applied to all included studies; results from trials with high quality were compared to those from studies with lower quality. The primary outcome of interest was the sensitivity and specificity of CTA. Ultimately, sensitivity and specificity to detect >50% stenosis in each of several arterial segments was reported.

**Results:** 1031 articles were initially identified; 122 were duplicated, and 868 were excluded as they did not meet primary inclusion criteria. Forty-one studies were selected for full-text review. Twelve trials were excluded because primary data were not reported, 1 study included <10 patients, 3 used CTA for diagnosis of aneurysm, 3 did not provide clear reasons for use of CTA, and 2 used single-slice CTA. The 20 included studies covered 957 patients. Median study quality was 11 points (range, 6 to 15). The sensitivity for aortoiliac disease was 96% (91% to 99%) and the specificity was 98% (95% to 99%). For femoropopliteal arteries, the sensitivity was 97% (95% to 99%) and the specificity was 94% (85% to 99%). For tibial arteries, the sensitivity was 95% (85% to 99%) and the specificity was 91% (79% to 97%). The results did not differ between low- and high-quality studies.

**Conclusions:** CTA is an accurate modality to diagnose PAD.

**Reviewer’s Comments:** This report confirms the practice that has become pervasive with respect to use of CTA. It is important to remember that this still requires a contrast load, so it should be used only when absolutely necessary; many patients will require further contrast administration for catheter-based interventions. It is also important to remember that the accuracy applies only to PAD in detecting >50% stenosis; this is not generalizable to traumatic injury in which the intimal dissection may be much more difficult to detect. (Reviewer-Karen J. Brasel, MD, MPH).

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Keywords: CT Angiography

Print Tag: Refer to original journal article
Patients with erectile dysfunction, especially those who are younger, may be at increased risk for future coronary events.

**Background:** Several reports suggest a possible association between erectile dysfunction (ED) and future cardiac events, postulating that ED may be an early manifestation of vascular disease. As both entities share common risk factors (e.g., age, hypertension, and diabetes mellitus [DM]), detailed research is required to understand this relationship.

**Objective:** To investigate the association between ED and subsequent incidence of coronary artery disease (CAD), accounting for common risk factors. Design: Prospective, longitudinal cohort study.

**Participants:** Patients were randomly chosen from an ongoing larger study (Olmstead County Study of Urinary Symptoms and Health Status Among Men) where eligibility included age 40 to 79 years and no neurologic disorders or history of urologic surgery. Participants were followed up regularly with standardized tools that included assessment of erectile function. For this specific ED/CAD analysis, patients had to have a regular sexual partner and no pre-existing heart disease.

**Methods:** Participants were followed up for 10 years, biennially completing reports on erectile function. The Rochester Epidemiology Project, an ongoing surveillance program, was then used to identify patients who developed CAD (i.e., sudden cardiac death, myocardial infarction, or obstructive coronary disease on angiography). Data were collected on potential common risk factors (tobacco use, hypertension, diabetes mellitus, and body mass index). Rates of ED were compared to incident cases of CAD and stratified by age (after adjustment for confounders).

**Results:** 1402 patients (median age, 55 years) were included. Baseline prevalence of ED was 2.4% for age 40 years, 5.6% for age 50 years, 17.0% for age 60 years, and 39.0% for age 70 years. For every 2 years of the study, roughly 5% of men subsequently developed ED. New-incident CAD was identified in 11% of participants over the 10 years. After adjustment, presence of ED was significantly associated with development of CAD, with hazard ratios similar to those of hypertension and diabetes. Broken down by age, younger ED patients had a much higher incidence (nearly 50 times) of CAD than those without ED. By age 70 years, ED had little impact on likelihood of CAD.

**Conclusions:** ED appears to be a risk factor for subsequent development of CAD, especially for men aged 40 to 49 years.

**Reviewer's Comments:** This study adds to a JAMA report suggesting ED may be a predictor of future coronary events. The authors point out that this may, in fact, be different manifestations of the same disease, with smaller vessels of the penis affected earlier. Endothelial dysfunction may also play a role. Maybe it is time to think of ED as a risk factor for heart disease and consider being more aggressive in risk factor modification. (Reviewer-Mark E. Pasanen, MD).

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Keywords: Coronary Artery Disease

Print Tag: Refer to original journal article
Coordination of Care Not So Cost-Effective After All

Effects of Care Coordination on Hospitalization, Quality of Care, and Health Care Expenditures Among Medicare Beneficiaries: 15 Randomized Trials.

Peikes D, Chen A, et al:

JAMA 2009; 301 (February 11): 603-618

Coordination of care programs for older persons with chronic medical conditions may not be less expensive.

**Background:** Caring for older adults who have chronic medical conditions is part of the usual responsibilities of a clinician. The premise of geriatrics care is that we use an interdisciplinary team to guide assessment and treatment of seniors with complex medical-psychosocial conditions. Payment to physicians for education and coordination of care is not optimal, currently. As a result, many patients receive care that is not communicated among multiple providers. Recent legislation provided Medicare the mandate to study methods of care coordination, in the fee-for-service setting. Demonstration projects specifically were designed to determine if care coordination resulted in (1) reduced total Medicare expenditures, including program fees, or (2) an increased quality of health care services and patient satisfaction.

**Objective:** To describe the results of 15 randomized controlled trials, each of which used multiple types of interventions to improve coordination of care for Medicare beneficiaries (in the fee-for-service setting).

**Methods:** The programs began in 2002 and operated for 4 years. The study population included patients who had 1 or more chronic medical condition targeted by each local program. Interventions of the 15 studies varied; however, all programs assigned patients to a care coordinator. Almost all programs made major attempts to improve communication between physicians and patients as well as attempts to improve transitions in care. The Center for Medicare and Medicaid Services paid each program a fee of about $164 per member per month for the trial.

**Results:** Only 1 of 15 programs showed a significant decrease in the rate of hospitalization of their Medicare beneficiaries. This program was able to decrease their rate of hospitalization by 17%. One program had an increase in hospitalization rate compared to the control group, and the other 13 programs showed no significant difference in hospitalizations. None of the 15 care coordination programs decreased health care expenditures. With 2 programs, patients in treatment groups described that their physicians were doing a good job at keeping in touch with each other and explaining their treatments. Generally, those who were in the treatment groups at these sites had better patient satisfaction.

**Conclusions:** Care coordination, as outlined by the interventions at these 15 Medicare demonstration sites, did not decrease hospitalization rates or health care expenditures.

**Reviewer's Comments:** This study deals a major blow to the premise that coordination of care will help a Medicare population. There is major legislation that is being reviewed by Congress to support improved funding of geriatric assessments and management. The premise is that this intervention should be targeted to improve outcomes of care for vulnerable elders. This study causes clinicians to pause. (Reviewer-Michael L. Malone, MD).

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Keywords: Care Coordination

Print Tag: Refer to original journal article
Prolonged Intravenous Therapy Versus Early Transition to Oral Antimicrobial Therapy for Acute Osteomyelitis in Children.
Zaoutis T, Localio AR, et al:

Pediatrics 2009; 123 (February): 636-462

With equivalent treatment success and decreased rates of central line-related complications, early transition to oral antibiotics may soon become the new standard of care for treatment of osteomyelitis.

**Background:** It has long been the standard of care that cases of osteomyelitis were treated with 4 to 6 weeks of IV antibiotics. However, as the burden of catheter-related adverse events becomes better understood, some clinicians have tested early transition to oral antibiotics with success. No study to date, however, has compared this treatment's failure rate against standard IV antibiotic administration.

**Objective:** To compare the effectiveness of early transition from IV to oral antibiotics versus prolonged IV antibiotic therapy to treat pediatric osteomyelitis.

**Design:** Retrospective cohort study.

**Participants:** 1969 children aged 2 months to 17 years with a diagnosis of acute osteomyelitis. Exclusion criteria included comorbidities known to complicate osteomyelitis such as any immunodeficiency, pyogenic arthritis, cellulitis, and/or osteomyelitis of the face, orbits, or head.

**Methods:** Investigators used the Pediatric Health Information System (PHIS), a database with information from 40 children's hospitals that includes information on demographics, diagnoses, procedures, medications, and re-hospitalizations. Children with an ICD-9 code of osteomyelitis were stratified into 1 of 2 groups: transition or prolonged IV therapy. The primary outcome was treatment failure, which was defined as re-hospitalization within 6 months with an ICD-9 code of acute or chronic osteomyelitis, a complication associated with acute osteomyelitis, or a surgical procedure related to osteomyelitis. Secondary outcomes looked at re-hospitalization within 6 months for any reason or catheter-related complications. Finally, validation of data collection through PHIS was performed by chart reviews at 13 hospitals.

**Results:** The treatment failure rates between the 2 groups were equivalent at approximately 5%. Children in the prolonged IV group experienced more catheter-related complications and were more likely to be re-admitted for any reason. Validation of data collected showed no statistically significant discrepancies.

**Conclusions:** There was no increased rate of treatment failure in the group with early transition to oral antibiotics. However, those in the prolonged IV antibiotic group demonstrated higher rates of catheter-related complications and re-hospitalization for any reason.

**Reviewer's Comments:** These authors did an excellent job designing a study to assess how best to treat acute osteomyelitis. They looked at the potential harm and an increase in failure rate, as well as possible benefits and decreased complications to help readers make a well-educated decision. Since treatment failures were equivalent, but the complication rate was decreased, it seems that early transition to oral antibiotics would be a preferred treatment plan. However, the one flaw of the study is that it does not define "early transition." Practitioners are left to determine that for themselves. (Reviewer-Lisa Humphrey, MD).

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Keywords: Osteomyelitis

Print Tag: Refer to original journal article
Although many parents own thermometers, they still rely on palpation to measure fever in their infants.

**Background:** Since newborns and small infants have unreliable symptoms when infected, providers regularly tell parents to bring in any infant aged <3 months who has a fever for evaluation. Unfortunately, parents often do not use a thermometer to measure temperature; this means that pediatricians are often presented with an afebrile child in clinic with a report of a tactile temperature at home. The reliability of such a report is unknown.

**Objective:** To examine how often parents rely on palpation to determine fever in infants, and how accurate these assessments are.

**Design/Participants:** Prospective study of infants presenting to an emergency department over a 1-year period in 2004 to 2005.

**Methods:** Parents of children aged <3 months were given a survey consisting of scripted questions about fever measurement. Parents were asked if the child had a fever. They were then watched to see if and where they palpated the infant after that question. Those who did not were then asked to palpate the infant. Parents were also asked if they owned and used a thermometer. Vital signs were measured on all infants in the emergency department.

**Results:** A total of 96 infants took part in this study. Of parents, 57% reported that palpation was the usual method to check for a fever; 87% reported using palpation at least occasionally. Although almost 80% of parents reported owning a thermometer, almost half still reported using palpation as a regular means of checking for fever. Overall, parents palpating their infants had test characteristics for accurately identifying fever (sensitivity, 81%; specificity, 82%; positive-predictive value, 59%; and negative-predictive value, 91%). However, some of these parents had used a thermometer at home. When these parents were eliminated from the analysis, the remaining parents were less accurate in identifying fever (sensitivity, 67%; specificity, 84%; positive-predictive value, 33%; and negative-predictive value, 95%).

**Conclusions:** Many parents continue to use palpation to measure for fever in their infants, even if they own a thermometer. Palpation seems to overestimate presence of a fever, but it is more accurate when a child is afebrile. We should continue to encourage parents in the proper use of thermometers in order to obtain accurate measurements of temperature.

**Reviewer’s Comments:** What is amazing is that most of these people own thermometers, yet still trust their hands more. We really need to do a better job of teaching parents to use the thermometers they have! (Reviewer-Aaron E. Carroll, MD, MS).

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Keywords: Fever

Print Tag: Refer to original journal article
Does Vitamin K Reduce Bleeding Events in Over-Anticoagulated Patients?

Oral Vitamin K Versus Placebo to Correct Excessive Anticoagulation in Patients Receiving Warfarin: A Randomized Trial.

Crowther MA, Ageno W, et al:

Ann Intern Med 2009; 150 (March 3): 293-300

Vitamin K does not reduce bleeding events in over-anticoagulated patients.

**Background:** It is common practice to administer oral vitamin K to counteract a supratherapeutic international normalized ratio (INR) in order to prevent major bleeding events. Little is known whether vitamin K reduces bleeding without actually increasing the risk for thromboembolism.

**Objective:** To compare low-dose oral vitamin K versus placebo in patients with supratherapeutic INRs.

**Design:** Multicenter, placebo-controlled randomized trial with concealed allocation.

**Participants:** Patients were enrolled from 14 anticoagulant therapy clinics in Canada, the U.S., and Italy. INR values were between 4.5 and 10.0, and there was no evidence of bleeding at enrollment.

**Methods:** Main outcomes were bleeding events (in particular, major bleeding events), thromboembolic events, or death. Major bleeding events were defined as all fatal events, events requiring transfusions of ≥2 units of packed red blood cells, or need for any therapeutic intervention necessary to stop bleeding. The vitamin K dose was 1 single dose of 1.25 mg versus placebo.

**Results:** 8 patients in the vitamin K group versus 4 in the placebo group were lost to follow-up, leaving 347 versus 365 patients for the intention-to-treat analysis. The INR had decreased by 2.8 in the vitamin K group versus 1.4 in the placebo group ($P < 0.001$) within 24 hours of administration. After 7 days, there were 9.2 bleeding events in the placebo group versus 7.9 in the vitamin K group ($P = 0.52$). After 90 days, there were 16.3% of patients in the placebo group with bleeding versus 15.8% in the vitamin K group ($P = 0.86$). Major bleeding events occurred in 1.1% in the placebo group and 2.5% in the vitamin K group ($P = 0.22$). Four patients in the vitamin K group had a thromboembolic process versus 0.8% in the placebo group ($P = 0.62$).

**Conclusions:** Low-dose oral vitamin K, compared to placebo, did not decrease bleeding events in patients with supratherapeutic INRs between 4.5 and 10.0. There were also no differences in the frequency of thromboembolic processes (including cerebrovascular accidents).

**Reviewer's Comments:** The strength of this study is that it is set up as a randomized placebo-controlled study with concealed allocation. Furthermore, there was an intention-to-treat analysis and complete follow-up for almost all patients. The weakness was that the study was not powered enough to detect small differences in low-frequency major bleeding events. I have my reservations as to the "lower-than-usual" dose of vitamin K (1.25 mg). Common practice is mostly 2.5 to 5.0 mg, depending on the INR level. Also, the authors did not provide us with information as to differences of comorbidities (such as liver disease) between groups nor presence of potential interactions with warfarin, such as medications. Nevertheless, this important study addresses an extremely common clinical scenario in older patients. (Reviewer-Norman G. Egger, MD).

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Keywords: Warfarin

Print Tag: Refer to original journal article
Osteonecrosis of the jaw presents with exposed, devitalized bone that may be asymptomatic initially.

Background: Osteonecrosis of the jaw (ONJ), characterized by exposed and devitalized bone of the maxilla or mandible, has been increasingly recognized as a complication of bisphosphonate therapy, primarily in cancer patients receiving the drugs intravenously. The inciting event for ONJ is usually dental extraction, although periodontal disease and denture trauma have also been implicated. The incidence with oral alendronate, widely used for osteoporosis, has been thought to be low. The American Dental Association has not recommended any specific counselling or change in dental therapy for alendronate-treated patients.

Objective: To describe a single institution’s experience with ONJ in patients taking oral alendronate.

Design: Retrospective cohort study.

Participants: Unselected patients of the University of Southern California Dental Clinic.

Methods: An electronic record review was performed to identify patients treated with alendronate, patients with ONJ, and all patients having dental extractions. ONJ was staged as stage 1 (asymptomatic exposed, necrotic bone), stage 2 (exposed necrotic bone associated with pain and infection), or stage 3 (exposed, necrotic bone with pain and infection plus extraoral fistula, pathologic fracture, or extensive osteolysis).

Results: 13,730 patients were seen in the clinic. Of these, 208 reported they took alendronate, and 9 of these (all longstanding patients of the dental school, and none referred because of ONJ) developed stage 2 or 3 ONJ. ONJ patients were all women aged 63 to 80 years, and all had taken alendronate for at least 1 year for osteoporosis (dose, 70 mg/week). The inciting event was tooth extraction in 4 patients and denture trauma in 5. Overall, one third of 13,000 patients seen in the clinic and one third of 208 alendronate patients had dental extractions. However, 4 of 66 alendronate patients developed ONJ after extraction but none of the untreated patients did.

Conclusions: Oral alendronate is associated with ONJ after dental extractions or dental trauma.

Reviewer’s Comments: In patients treated with oral bisphosphonates, tooth extractions should be avoided unless necessary (this seems to me to be good general advice). If extraction is needed, the authors suggest that top-notch dental hygiene and oral chlorhexidine rinses pre- and post-procedure may help prevent ONJ. In practice, I will ask a patient about recent dental follow-up and look for major dental problems before electively starting a bisphosphonate and ask her to make sure her dentist knows about her treatment before procedures are performed. (Reviewer-Karen A. McDonough, MD).

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More Evidence That Hormone Tx Increases Risk for Breast Cancer

Breast Cancer After Use of Estrogen Plus Progestin in Postmenopausal Women.
Chlebowski RT, Kuller LH, et al:

The increased risk of breast cancer seen in women on hormone therapy quickly declines to baseline values with cessation of treatment.

Background: Initial reports from the 2002 Women's Health Initiative (WHI) showed an increased risk of breast cancer in women treated with combined estrogen/progestin therapy, which led to dramatic decreases in hormone use in the United States. Shortly thereafter, breast cancer rates also began to decline. To completely understand risks of hormone therapy (HT), multiple analyses of the WHI have been performed.

Objective: To further analyze data from the WHI for temporal trends in the diagnosis of breast cancer, both during the study and in post-intervention analysis.

Methods: These analyses were performed on randomized trial data and the simultaneous observational cohort, taking into account risk factors for breast cancer and frequency of mammography as related to hormone use. The randomized clinical trial looked at >16,000 women (aged 50 to 79 years) randomized to either combined HT or placebo. The observational study followed >40,000 women with similar entry criteria and collected data on use of HT, risk factors for breast cancer, mammography use, and new diagnoses of breast cancer.

Results: In the randomized clinical trial, rates of breast cancer in the HT arm were slightly lower over the first 2 years. However, rates of breast cancer increased steadily over the 5-year time interval, resulting in an increased risk seen at the study's termination (HR, 1.26). More than 15,000 women had data collected after the study was terminated (at which time women had been instructed to stop their appointed treatment). Over the following 2.5 years, there was a steady decline in breast cancer rates, with no differences in other risk factors or mammography. After 2.5 years, adjusted breast cancer rates were similar to those at study onset. As for the observational dataset, women taking HT had, on average, a longer duration of hormone exposure than those in the randomized trial. Therefore, breast cancer rates were steady across the early parts of that study, with women on HT having roughly twice as many breast cancers. Slightly more mammograms were performed in those on HT, but not nearly enough to explain these differences. As HT use declined, breast cancer rates declined.

Conclusions: The increased risk of breast cancer seen in women taking HT in clinical, and observational analyses quickly returned to baseline values with the cessation of HT. This decline cannot be explained by changes in mammography use.

Reviewer's Comments: At this point, there seems to be little doubt that combined HT increases the risk of breast cancer. In the first 2 years of treatment, however, no significant differences were seen in women who were relatively hormone naïve. After a few years, the risk clearly increases then declines quickly with cessation of treatment. (Reviewer-Mark E. Pasanen, MD).

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Keywords: Cancer

Print Tag: Refer to original journal article