

Reference List

1. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360(9326):23-33.
Notes: CORPORATE NAME: Heart Protection Study Collaborative Group.
Abstract: BACKGROUND: It has been suggested that increased intake of various antioxidant vitamins reduces the incidence rates of vascular disease, cancer, and other adverse outcomes. METHODS: 20,536 UK adults (aged 40-80) with coronary disease, other occlusive arterial disease, or diabetes were randomly allocated to receive antioxidant vitamin supplementation (600 mg vitamin E, 250 mg vitamin C, and 20 mg beta-carotene daily) or matching placebo. Intention-to-treat comparisons of outcome were conducted between all vitamin-allocated and all placebo-allocated participants. An average of 83% of participants in each treatment group remained compliant during the scheduled 5-year treatment period. Allocation to this vitamin regimen approximately doubled the plasma concentration of alpha-tocopherol, increased that of vitamin C by one-third, and quadrupled that of beta-carotene. Primary outcomes were major coronary events (for overall analyses) and fatal or non-fatal vascular events (for subcategory analyses), with subsidiary assessments of cancer and of other major morbidity. FINDINGS: There were no significant differences in all-cause mortality (1446 [14.1%] vitamin-allocated vs 1389 [13.5%] placebo-allocated), or in deaths due to vascular (878 [8.6%] vs 840 [8.2%]) or non-vascular (568 [5.5%] vs 549 [5.3%]) causes. Nor were there any significant differences in the numbers of participants having non-fatal myocardial infarction or coronary death (1063 [10.4%] vs 1047 [10.2%]), non-fatal or fatal stroke (511 [5.0%] vs 518 [5.0%]), or coronary or non-coronary revascularisation (1058 [10.3%] vs 1086 [10.6%]). For the first occurrence of any of these "major vascular events", there were no material differences either overall (2306 [22.5%] vs 2312 [22.5%]; event rate ratio 1.00 [95% CI 0.94-1.06]) or in any of the various subcategories considered. There were no significant effects on cancer incidence or on hospitalisation for any other non-vascular cause. INTERPRETATION: Among the high-risk individuals that were studied, these antioxidant vitamins appeared to be safe. But, although this regimen increased blood vitamin concentrations substantially, it did not produce any significant reductions in the 5-year mortality from, or incidence of, any type of vascular disease, cancer, or other major outcome.
2. Andraws R, Berger JS, Brown DL. Effects of antibiotic therapy on outcomes of patients with coronary artery disease: a meta-analysis of randomized controlled trials. *JAMA* 2005; 293(21):2641-7.
Abstract: CONTEXT: Although *Chlamydia pneumoniae* infection has been associated with the initiation and progression of atherosclerosis, results of clinical trials investigating antichlamydial antibiotics as adjuncts to standard therapy in patients with coronary artery disease (CAD) have been inconsistent. OBJECTIVE: To conduct a meta-analysis of clinical trials of antichlamydial antibiotic therapy in patients with CAD. DATA SOURCES: The MEDLINE and Cochrane Central Register of Controlled Trials databases were searched from 1966 to April 2005 for English-language trials of antibiotic therapy in patients with CAD. Bibliographies of retrieved articles were searched for further studies. Presentations at major scientific meetings (2003-2004) were also reviewed. Search terms included antibacterial agents, myocardial infarction, unstable angina, and coronary arteriosclerosis. STUDY SELECTION: Eligible studies were prospective, randomized, placebo-controlled trials of antichlamydial antibiotic therapy in patients with CAD that reported all-cause mortality, myocardial infarction, or unstable angina. Of the 110 potentially relevant articles identified, 11 reports enrolling 19,217 patients were included. DATA EXTRACTION: Included studies were reviewed to determine the number of patients randomized, mean duration of follow-up, and end points. End points of interest included all-cause mortality, myocardial infarction (MI), and a combined end point of MI and unstable angina. DATA SYNTHESIS: Event rates were combined using a random-effects model. Antibiotic therapy had no impact on all-cause mortality among treated vs untreated patients (4.7% vs 4.6%; odds ratio [OR], 1.02; 95% confidence interval [CI], 0.89-1.16; P = .83), on the rates of MI (5.0% vs 5.4%; OR, 0.92; 95% CI, 0.81-1.04; P = .19), or on the combined end point of MI and unstable angina (9.2% vs 9.6%; OR, 0.91; 95% CI, 0.76-1.07; P = .25). CONCLUSION: Evidence available to date does not demonstrate an overall benefit of antibiotic therapy in reducing mortality or cardiovascular events in patients with CAD.

3. Bettuzzi S, Brausi M, Rizzi F, Castagnetti G, Peracchia G, Corti A. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. *Cancer Res* 2006; 66(2):1234-40.

Abstract: Green tea catechins (GTCs) proved to be effective in inhibiting cancer growth in several experimental models. Recent studies showed that 30% of men with high-grade prostate intraepithelial neoplasia (HG-PIN) would develop prostate cancer (CaP) within 1 year after repeated biopsy. This prompted us to do a proof-of-principle clinical trial to assess the safety and efficacy of GTCs for the chemoprevention of CaP in HG-PIN volunteers. The purity and content of GTCs preparations were assessed by high-performance liquid chromatography [(-)-epigallocatechin, 5.5%; (-)-epicatechin, 12.24%; (-)-epigallocatechin-3-gallate, 51.88%; (-)-epicatechin-3-gallate, 6.12%; total GTCs, 75.7%; caffeine, <1%]. Sixty volunteers with HG-PIN, who were made aware of the study details, agreed to sign an informed consent form and were enrolled in this double-blind, placebo-controlled study. Daily treatment consisted of three GTCs capsules, 200 mg each (total 600 mg/d). After 1 year, only one tumor was diagnosed among the 30 GTCs-treated men (incidence, approximately 3%), whereas nine cancers were found among the 30 placebo-treated men (incidence, 30%). Total prostate-specific antigen did not change significantly between the two arms, but GTCs-treated men showed values constantly lower with respect to placebo-treated ones. International Prostate Symptom Score and quality of life scores of GTCs-treated men with coexistent benign prostate hyperplasia improved, reaching statistical significance in the case of International Prostate Symptom Scores. No significant side effects or adverse effects were documented. To our knowledge, this is the first study showing that GTCs are safe and very effective for treating premalignant lesions before CaP develops. As a secondary observation, administration of GTCs also reduced lower urinary tract symptoms, suggesting that these compounds might also be of help for treating the symptoms of benign prostate hyperplasia.

4. Christakis NA, Allison PD. Mortality after the hospitalization of a spouse. *N Engl J Med* 2006; 354(7):719-30.

Notes: Kazuki Yoshida; 14 March 06

Abstract: BACKGROUND: The illness of a spouse can affect the health of a caregiving partner. We examined the association between the hospitalization of a spouse and a partner's risk of death among elderly people. METHODS: We studied 518,240 couples who were enrolled in Medicare in 1993. We used Cox regression analysis and fixed-effects (case-time-control) methods to assess hospitalizations and deaths during nine years of follow-up. RESULTS: Overall, 383,480 husbands (74 percent) and 347,269 wives (67 percent) were hospitalized at least once, and 252,557 husbands (49 percent) and 156,004 wives (30 percent) died. Mortality after the hospitalization of a spouse varied according to the spouse's diagnosis. Among men, 6.4 percent died within a year after a spouse's hospitalization for colon cancer, 6.9 percent after a spouse's hospitalization for stroke, 7.5 percent after a spouse's hospitalization for psychiatric disease, and 8.6 percent after a spouse's hospitalization for dementia. Among women, 3.0 percent died within a year after a spouse's hospitalization for colon cancer, 3.7 percent after a spouse's hospitalization for stroke, 5.7 percent after a spouse's hospitalization for psychiatric disease, and 5.0 percent after a spouse's hospitalization for dementia. After adjustment for measured covariates, the risk of death for men was not significantly higher after a spouse's hospitalization for colon cancer (hazard ratio, 1.02; 95 percent confidence interval, 0.95 to 1.09) but was higher after hospitalization for stroke (hazard ratio, 1.06; 95 percent confidence interval, 1.03 to 1.09), congestive heart failure (hazard ratio, 1.12; 95 percent confidence interval, 1.07 to 1.16), hip fracture (hazard ratio, 1.15; 95 percent confidence interval, 1.11 to 1.18), psychiatric disease (hazard ratio, 1.19; 95 percent confidence interval, 1.12 to 1.26), or dementia (hazard ratio, 1.22; 95 percent confidence interval, 1.12 to 1.32). For women, the various risks of death after a spouse's hospitalization were similar. Overall, for men, the risk of death associated with a spouse's hospitalization was 22 percent of that associated with a spouse's death (95 percent confidence interval, 17 to 27 percent); for women, the risk was 16 percent of that associated with death (95 percent confidence interval, 8 to 24 percent). CONCLUSIONS: Among elderly people hospitalization of a spouse is associated with an increased

risk of death, and the effect of the illness of a spouse varies among diagnoses. Such interpersonal health effects have clinical and policy implications for the care of patients and their families.

5. Cunningham R, Dale B, Undy B, Gaunt N. Proton pump inhibitors as a risk factor for *Clostridium difficile* diarrhoea. *J Hosp Infect* 2003; 54(3):243-5.
Abstract: *Clostridium difficile* is the main infectious cause of colitis in hospital inpatients. The incidence is increasing, and it is associated with significant mortality, morbidity, and increased length of stay. The main risk factor is use of broad-spectrum antibiotics, and antibiotic restriction is the most effective control measure. We carried out a retrospective case-control study to investigate whether use of proton pump inhibitors (PPI) was an additional risk factor. PPI use within the preceding eight weeks was associated with an increased risk of *C. difficile* diarrhoea (odds ratio 2.5, 95% CI 1.5-4.2). Reduction of unnecessary PPI use may be an additional strategy to reduce the incidence of this infection.
6. Dulloo AG, Duret C, Rohrer D *et al.* Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *Am J Clin Nutr* 1999; 70(6):1040-5.
Abstract: **BACKGROUND:** Current interest in the role of functional foods in weight control has focused on plant ingredients capable of interfering with the sympathoadrenal system. **OBJECTIVE:** We investigated whether a green tea extract, by virtue of its high content of caffeine and catechin polyphenols, could increase 24-h energy expenditure (EE) and fat oxidation in humans. **DESIGN:** Twenty-four-hour EE, the respiratory quotient (RQ), and the urinary excretion of nitrogen and catecholamines were measured in a respiratory chamber in 10 healthy men. On 3 separate occasions, subjects were randomly assigned among 3 treatments: green tea extract (50 mg caffeine and 90 mg epigallocatechin gallate), caffeine (50 mg), and placebo, which they ingested at breakfast, lunch, and dinner. **RESULTS:** Relative to placebo, treatment with the green tea extract resulted in a significant increase in 24-h EE (4%; $P < 0.01$) and a significant decrease in 24-h RQ (from 0.88 to 0.85; $P < 0.001$) without any change in urinary nitrogen. Twenty-four-hour urinary norepinephrine excretion was higher during treatment with the green tea extract than with the placebo (40%, $P < 0.05$). Treatment with caffeine in amounts equivalent to those found in the green tea extract had no effect on EE and RQ nor on urinary nitrogen or catecholamines. **CONCLUSIONS:** Green tea has thermogenic properties and promotes fat oxidation beyond that explained by its caffeine content per se. The green tea extract may play a role in the control of body composition via sympathetic activation of thermogenesis, fat oxidation, or both.
7. Falguera M, Martin M, Ruiz-Gonzalez A, Pifarre R, Garcia M. Community-acquired pneumonia as the initial manifestation of serious underlying diseases. *Am J Med* 2005; 118(4):378-83.
Abstract: **PURPOSE:** Community-acquired pneumonia is common among patients with coexisting illnesses and it can be the initial manifestation of these comorbid diseases. The objectives of our study were to evaluate the frequency of this association and to analyze whether certain characteristics could predict the presence of unknown comorbid conditions. **SUBJECTS AND METHODS:** Over a 5-year period, we prospectively studied 660 consecutive patients with community-acquired pneumonia seen at our institution. In a subgroup of these patients, diagnosis of previously unknown comorbid conditions was established during follow-up. Characteristics of these patients were compared with data from the remaining sample of patients. **RESULTS:** Prior underlying diseases were present in 298 (45%) patients. One or more new comorbid conditions were found in 41 (6%), of which diabetes (14 cases), malignancies (12 cases), chronic obstructive pulmonary disease (8 cases), and human immunodeficiency virus (HIV) infection (5 cases) were the most common. In the comparative study, a bacterial etiology, positive blood cultures, and hospitalization were more frequently found ($P < 0.05$) in patients with new comorbid conditions than atypical microorganisms or viruses, negative blood cultures, or outpatient care. **CONCLUSION:** In the initial diagnostic workup of patients with community-acquired pneumonia, the possibility of unknown comorbid conditions should be carefully evaluated.

8. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350(22):2247-56.
 Abstract: BACKGROUND: It remains uncertain whether the choice of resuscitation fluid for patients in intensive care units (ICUs) affects survival. We conducted a multicenter, randomized, double-blind trial to compare the effect of fluid resuscitation with albumin or saline on mortality in a heterogeneous population of patients in the ICU. METHODS: We randomly assigned patients who had been admitted to the ICU to receive either 4 percent albumin or normal saline for intravascular-fluid resuscitation during the next 28 days. The primary outcome measure was death from any cause during the 28-day period after randomization. RESULTS: Of the 6997 patients who underwent randomization, 3497 were assigned to receive albumin and 3500 to receive saline; the two groups had similar baseline characteristics. There were 726 deaths in the albumin group, as compared with 729 deaths in the saline group (relative risk of death, 0.99; 95 percent confidence interval, 0.91 to 1.09; P=0.87). The proportion of patients with new single-organ and multiple-organ failure was similar in the two groups (P=0.85). There were no significant differences between the groups in the mean (+/-SD) numbers of days spent in the ICU (6.5+/-6.6 in the albumin group and 6.2+/-6.2 in the saline group, P=0.44), days spent in the hospital (15.3+/-9.6 and 15.6+/-9.6, respectively; P=0.30), days of mechanical ventilation (4.5+/-6.1 and 4.3+/-5.7, respectively; P=0.74), or days of renal-replacement therapy (0.5+/-2.3 and 0.4+/-2.0, respectively; P=0.41). CONCLUSIONS: In patients in the ICU, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.
9. Forman MR, Levin B. Calcium plus vitamin D3 supplementation and colorectal cancer in women. *N Engl J Med* 2006; 354(7):752-4.
10. Gage BF, Birman-Deych E, Radford MJ, Nilasena DS, Binder EF. Risk of osteoporotic fracture in elderly patients taking warfarin: results from the National Registry of Atrial Fibrillation 2. *Arch Intern Med* 2006; 166(2):241-6.
 Notes: REVIEWED BY - RYOSUKE MIYAMOTO
 Abstract: BACKGROUND: Vitamin K allows for gamma-carboxylation of glutamyl residues, a conversion that activates clotting factors and bone proteins. Vitamin K antagonists such as warfarin inhibit this process. Our goal was to quantify the association between warfarin and osteoporotic fractures in patients with atrial fibrillation. METHODS: This was a retrospective cohort study of Medicare beneficiaries with atrial fibrillation who were hospitalized between March 1998 and April 1999 in all 50 US states. The study outcome was osteoporotic fractures, identified by an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for a fracture of the hip, spine, or wrist. RESULTS: Compared with 7587 patients who were not prescribed warfarin, the adjusted odds ratio (OR) of fracture was 1.25 (95% confidence interval [CI], 1.06-1.48) in 4461 patients prescribed long-term warfarin therapy (> or = 1 year). The association between osteoporotic fracture and long-term warfarin use was significant in men (OR, 1.63; 95% CI, 1.26-2.10) but nonsignificant in women (OR, 1.05; 95% CI, 0.88-1.26). In 1833 patients prescribed warfarin for less than a year, the risk of osteoporotic fracture was not increased significantly (OR, 1.03). Odds ratios (95% CIs) of independent predictors of osteoporotic fractures were as follows: increasing age, 1.63 (1.47-1.80) per decade; high fall risk, 1.78 (1.42-2.21); hyperthyroidism, 1.77 (1.16-2.70); neuropsychiatric disease, 1.51 (1.28-1.78); and alcoholism, 1.50 (1.01-2.24). Factors with a reduced OR (95% CI) included African American race, 0.30 (0.18-0.51); male sex, 0.54 (0.46-0.62); and use of beta-adrenergic antagonists, 0.84 (0.70-1.00). CONCLUSIONS: Long-term use of warfarin was associated with osteoporotic fractures, at least in men with atrial fibrillation. Beta-adrenergic antagonists may protect against osteoporotic fractures.
11. Gasbarrini A, Franceschi F, Tartaglione R, Landolfi R, Pola P, Gasbarrini G. Regression of autoimmune thrombocytopenia after eradication of *Helicobacter pylori*. *Lancet* 1998; 352(9131):878.
12. Groszmann RJ, Garcia-Tsao G, Bosch J *et al*. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* 2005; 353(21):2254-61.
 Notes: Presenter Katayama; April 6, 2006

Abstract: BACKGROUND: Nonselective beta-adrenergic blockers decrease portal pressure and prevent variceal hemorrhage. Their effectiveness in preventing varices is unknown. METHODS: We randomly assigned 213 patients with cirrhosis and portal hypertension (minimal hepatic venous pressure gradient [HVPG] of 6 mm Hg) to receive timolol, a nonselective beta-blocker (108 patients), or placebo (105 patients). The primary end point was the development of gastroesophageal varices or variceal hemorrhage. Endoscopy and HVPG measurements were repeated yearly. RESULTS: During a median follow-up of 54.9 months, the rate of the primary end point did not differ significantly between the timolol group and the placebo group (39 percent and 40 percent, respectively; $P=0.89$), nor were there significant differences in the rates of ascites, encephalopathy, liver transplantation, or death. Serious adverse events were more common among patients in the timolol group than among those in the placebo group (18 percent vs. 6 percent, $P=0.006$). Varices developed less frequently among patients with a baseline HVPG of less than 10 mm Hg and among those in whom the HVPG decreased by more than 10 percent at one year and more frequently among those in whom the HVPG increased by more than 10 percent at one year. CONCLUSIONS: Nonselective beta-blockers are ineffective in preventing varices in unselected patients with cirrhosis and portal hypertension and are associated with an increased number of adverse events. (ClinicalTrials.gov number, NCT00006398.)

13. Hampton JR, Harrison MJ, Mitchell JR, Prichard JS, Seymour C. Relative contributions of history-taking, physical examination, and laboratory investigation to diagnosis and management of medical outpatients. *Br Med J* 1975; 2(5969):486-9.

Abstract: To evaluate the relative importance of the medical history, the physical examination, and laboratory investigations in the diagnosis and management of medical outpatients some physicians recorded their diagnosis and a prediction of the method of management after reading the patient's referral letter, again after taking the history, and again after performing the physical examination. These diagnoses and predictions were compared with the diagnosis and method of management which had been adopted two months after the patient's initial attendance. A diagnosis that agreed with the one finally accepted was made after reading the referral letter and taking the history in 66 out of 80 new patients; the physical examination was useful in only seven patients, and the laboratory investigations in a further seven. In only one of six patients in whom the physician was unable to make any diagnosis after taking the history and examining the patient did laboratory investigations lead to a positive diagnosis.

14. Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med* 2001; 345(24):1727-33.

Abstract: BACKGROUND: In adults with suspected meningitis clinicians routinely order computed tomography (CT) of the head before performing a lumbar puncture. METHODS: We prospectively studied 301 adults with suspected meningitis to determine whether clinical characteristics that were present before CT of the head was performed could be used to identify patients who were unlikely to have abnormalities on CT. The Modified National Institutes of Health Stroke Scale was used to identify neurologic abnormalities. RESULTS: Of the 301 patients with suspected meningitis, 235 (78 percent) underwent CT of the head before undergoing lumbar puncture. In 56 of the 235 patients (24 percent), the results of CT were abnormal; 11 patients (5 percent) had evidence of a mass effect. The clinical features at base line that were associated with an abnormal finding on CT of the head were an age of at least 60 years, immunocompromise, a history of central nervous system disease, and a history of seizure within one week before presentation, as well as the following neurologic abnormalities: an abnormal level of consciousness, an inability to answer two consecutive questions correctly or to follow two consecutive commands, gaze palsy, abnormal visual fields, facial palsy, arm drift, leg drift, and abnormal language (e.g., aphasia). None of these features were present at base line in 96 of the 235 patients who underwent CT scanning of the head (41 percent). The CT scan was normal in 93 of these 96 patients, yielding a negative predictive value of 97 percent. Of the three misclassified patients, only one had a mild mass effect on CT, and all three subsequently underwent lumbar puncture, with no evidence of brain herniation one week later. CONCLUSIONS: In adults with suspected meningitis, clinical features can be used to identify those who are unlikely to have abnormal findings on CT of the head.

15. He J, Gu D, Wu X *et al.* Effect of soybean protein on blood pressure: a randomized, controlled trial. *Ann Intern Med* 2005; 143(1):1-9.
 Notes: Katayama, Nov 05
 Abstract: BACKGROUND: Epidemiologic studies suggest that vegetable protein intake is inversely related to blood pressure. OBJECTIVE: To examine the effect of soybean protein supplementation on blood pressure in persons with prehypertension or stage 1 hypertension. DESIGN: Randomized, double-blind, controlled trial. SETTING: Three communities in the People's Republic of China. PATIENTS: 302 participants 35 to 64 years of age with an initial untreated systolic blood pressure of 130 to 159 mm Hg, diastolic blood pressure of 80 to 99 mm Hg, or both. INTERVENTION: Study participants were randomly assigned to receive 40 g of isolated soybean protein supplements per day or complex carbohydrate control for 12 weeks; 91.4% completed the intervention. MEASUREMENTS: Blood pressure measurements were obtained by using random-zero sphygmomanometers at baseline and at 6 and 12 weeks. RESULTS: At baseline, the mean systolic and diastolic blood pressures were 135.0 mm Hg (SD 10.9) and 84.7 mm Hg (SD 6.9), respectively. Compared with the control group, the net changes in systolic blood pressure and diastolic blood pressure were -4.31 mm Hg (95% CI, -2.11 to -6.51 mm Hg; $P < 0.001$) and -2.76 mm Hg (CI, -1.35 to -4.16 mm Hg; $P < 0.001$), respectively, after the 12-week intervention. The net changes in systolic and diastolic blood pressure reductions were -7.88 mm Hg (CI, -4.66 to -11.1 mm Hg) and -5.27 mm Hg (CI, -3.05 to -7.49 mm Hg), respectively, in persons with hypertension and -2.34 mm Hg (CI, 0.48 to -5.17 mm Hg) and -1.28 mm Hg (CI, 0.52 to -3.07 mm Hg), respectively, in those without hypertension. LIMITATIONS: This trial did not examine whether the blood pressure reduction was due to protein or isoflavones in soybean. CONCLUSIONS: Soybean protein supplementation resulted in a reduction in systolic and diastolic blood pressure. These findings suggest that increased intake of soybean protein may play an important role in preventing and treating hypertension.
16. Huang CJ, Lin HC. Association between adrenal insufficiency and ventilator weaning. *Am J Respir Crit Care Med* 2006; 173(3):276-80.
 Notes: Atsuko Yagi; 14 March 06
 Abstract: RATIONALE: Adrenal insufficiency is a common disorder in critically ill patients with mechanical ventilation and is usually associated with higher mortality and poor clinical outcome. OBJECTIVES: To determine whether stress dose corticosteroid supplementation can improve ventilator weaning and clinical outcome in patients with adrenal insufficiency. METHODS: A prospective, randomized, placebo controlled, double-blinded study was conducted in the intensive care unit of a tertiary teaching hospital. A total of 93 mechanically ventilated patients were enrolled in the ventilator weaning trial. Adrenal function was assessed in all patients. Patients with adrenal insufficiency were randomized to the treatment group (50 mg intravenous hydrocortisone every 6 h) and the placebo group. MEASUREMENTS AND MAIN RESULTS: The successful ventilator weaning percentage was significantly higher in the adequate adrenal reserve group (88.4%) and in the stress dose hydrocortisone treatment group (91.4%) than in the placebo group (68.6%). The weaning period was shorter in the hydrocortisone treatment group than in the placebo group. No significant adverse effects were observed in the corticosteroid treatment group. CONCLUSIONS: For patients with respiratory failure, early identification of adrenal insufficiency and appropriate supplementation with stress dose hydrocortisone increase the success of ventilator weaning and shortens the weaning period.
17. Hviid A, Wohlfahrt J, Stellfeld M, Melbye M. Childhood vaccination and nontargeted infectious disease hospitalization. *JAMA* 2005; 294(6):699-705.
 Abstract: CONTEXT: It has been hypothesized that multiple-antigen vaccines, such as measles-mumps-rubella vaccine, or aggregated vaccine exposure could lead to immune dysfunction, resulting in nontargeted infectious diseases as a result of an "overload" mechanism. OBJECTIVE: To evaluate the relationship between routinely administered childhood vaccines (Haemophilus influenzae type b; diphtheria-tetanus-inactivated poliovirus; diphtheria-tetanus-acellular pertussis-inactivated poliovirus; whole-cell pertussis; measles-mumps-rubella; oral poliovirus) and hospitalization for nontargeted infectious diseases. DESIGN, SETTING, AND PARTICIPANTS:

Population-based cohort comprising all children born in Denmark from 1990 through 2001 (N = 805 206). Longitudinal information was collected on type and number of vaccine doses received and hospitalization with infectious diseases, specifically acute upper respiratory tract infection, viral and bacterial pneumonia, septicemia, viral central nervous system infection, bacterial meningitis, and diarrhea. MAIN OUTCOME MEASURES: Rate ratios for each type of infectious disease according to vaccination status. RESULTS: During 2,900,463 person-years of follow-up, 84,317 cases of infectious disease hospitalization were identified. Out of 42 possible associations (6 vaccines and 7 infectious disease categories), the only adverse association was for Haemophilus influenzae type b vaccine and acute upper respiratory tract infection (rate ratio, 1.05; 95% confidence interval, 1.01-1.08 comparing vaccinated participants with unvaccinated participants). This one adverse association of 42 possible outcomes was within the limits of what would be expected by chance alone and the effect was not temporal or dose-response. When considering aggregated vaccine exposure, we found no adverse associations between an increasing number of vaccinations and infectious diseases. CONCLUSION: These results do not support the hypotheses that multiple-antigen vaccines or aggregated vaccine exposure increase the risk of nontargeted infectious disease hospitalization.

18. Jackson RD, LaCroix AZ, Gass M *et al.* Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006; 354(7):669-83.

Notes: CORPORATE NAME: Women's Health Initiative Investigators.

Abstract: BACKGROUND: The efficacy of calcium with vitamin D supplementation for preventing hip and other fractures in healthy postmenopausal women remains equivocal. METHODS: We recruited 36,282 postmenopausal women, 50 to 79 years of age, who were already enrolled in a Women's Health Initiative (WHI) clinical trial. We randomly assigned participants to receive 1000 mg of elemental calcium as calcium carbonate with 400 IU of vitamin D3 daily or placebo. Fractures were ascertained for an average follow-up period of 7.0 years. Bone density was measured at three WHI centers. RESULTS: Hip bone density was 1.06 percent higher in the calcium plus vitamin D group than in the placebo group (P<0.01). Intention-to-treat analysis indicated that participants receiving calcium plus vitamin D supplementation had a hazard ratio of 0.88 for hip fracture (95 percent confidence interval, 0.72 to 1.08), 0.90 for clinical spine fracture (0.74 to 1.10), and 0.96 for total fractures (0.91 to 1.02). The risk of renal calculi increased with calcium plus vitamin D (hazard ratio, 1.17; 95 percent confidence interval, 1.02 to 1.34). Censoring data from women when they ceased to adhere to the study medication reduced the hazard ratio for hip fracture to 0.71 (95 percent confidence interval, 0.52 to 0.97). Effects did not vary significantly according to prerandomization serum vitamin D levels. CONCLUSIONS: Among healthy postmenopausal women, calcium with vitamin D supplementation resulted in a small but significant improvement in hip bone density, did not significantly reduce hip fracture, and increased the risk of kidney stones. (ClinicalTrials.gov number, NCT00000611.).

19. Kimura M, Comstock GW, Mori T. Comparison of erythema and induration as results of tuberculin tests. *Int J Tuberc Lung Dis* 2005; 9(8):853-7.

Notes: Gremillion, 17 March 06

Abstract: SETTING: Schoolchildren, tuberculosis (TB) patients, and hospital employees in Tokyo, Japan. OBJECTIVE: To compare erythema and induration resulting from tuberculin tests among TB patients, normal children, and hospital employees with and without evidence of atopy.

DESIGN: The distributions of diameters of erythema and induration were compared among three groups: 951 TB patients, 6139 first-grade and 6185 seventh-grade children, and 97 volunteer employees classified as atopic or non-atopic on the basis of skin tests and serum immunoglobulin E (IgE) concentrations. RESULTS: Erythema and induration were highly correlated. The distribution of erythema diameters was unimodal, and the distribution of induration diameters was bimodal.

Erythema was considerably greater than induration among persons classified as being atopic.

CONCLUSION: Both erythema and induration appear to be adequate indices of tuberculin sensitivity. However, because most of the world uses induration as the index and virtually all studies of tuberculin sensitivity rely on induration, there are advantages in the use of induration. It would be desirable to initiate a large prospective study to see whether erythema or induration is the

better predictor of subsequent tuberculous disease, and to confirm our finding that erythema is more likely to be confounded by atopy than induration.

20. Kotani K, Osaki Y, Kurozawa Y, Kishimoto T. A survey of restaurant smoking restrictions in a Japanese city. *Tohoku J Exp Med* 2005; 207(1):73-9.
Notes: Gremillion , 17 March 06
Abstract: Japan has been behind the times in terms of promoting smoking control. The health-promotion law, which included the aim of preventing environmental tobacco smoke (ETS) in public places, was newly introduced in Japan in 2003. The community-based survey on the present state of restaurant smoking restrictions and restaurant owners' concern of smoking is important as it is a reflection of the community's desire to prevent ETS. Data on the smoking restrictions in 163 restaurants in Yonago, one Japanese community, and the owners' smoking-related awareness were collected just one month after the law was enacted. This study revealed that only 6 (3.6%) restaurants were under sufficient conditions: 3 with totally smoke-free and 3 with complete non-smoking sections. The styles (e.g., Western-, Japanese- and Chinese-styles) and kinds of restaurants (e.g., family restaurants and tearooms) were not related to the state of smoking restrictions. Rates of smokers were relatively high among owners, and smoking owners significantly provided insufficient smoking restrictions. 26.4% of owners knew about the new law. However, there were no restaurants that started their smoking restrictions due to the law. Owners' knowledge of the law did not correlate with smoking restrictions. The owners especially feared the negative effects on business due to smoking restrictions. These survey findings suggested little protection from ETS in a sample of restaurants and a large gap in restaurant smoking restrictions compared to other countries. More widespread adoption of the health-promotion law in restaurants is an issue.
21. Kuriyama S, Hozawa A, Ohmori K *et al.* Green tea consumption and cognitive function: a cross-sectional study from the Tsurugaya Project 1. *Am J Clin Nutr* 2006; 83(2):355-61.
Abstract: BACKGROUND: Although considerable experimental and animal evidence shows that green tea may possess potent activities of neuroprotection, neurorescue, and amyloid precursor protein processing that may lead to cognitive enhancement, no human data are available. OBJECTIVE: The objective was to examine the association between green tea consumption and cognitive function in humans. DESIGN: We analyzed cross-sectional data from a community-based Comprehensive Geriatric Assessment (CGA) conducted in 2002. The subjects were 1003 Japanese subjects aged $> \text{ or } = 70$ y. They completed a self-administered questionnaire that included questions about the frequency of green tea consumption. We evaluated cognitive function by using the Mini-Mental State Examination with cutoffs of < 28 , < 26 , and < 24 and calculated multivariate-adjusted odds ratios (ORs) of cognitive impairment. RESULTS: Higher consumption of green tea was associated with a lower prevalence of cognitive impairment. At the < 26 cutoff, after adjustment for potential confounders, the ORs for the cognitive impairment associated with different frequencies of green tea consumption were 1.00 (reference) for $< \text{ or } = 3$ cups/wk, 0.62 (95% CI: 0.33, 1.19) for 4-6 cups/wk or 1 cup/d, and 0.46 (95% CI: 0.30, 0.72) for $> \text{ or } = 2$ cups/d (P for trend = 0.0006). Corresponding ORs were 1.00 (reference), 0.60 (95% CI: 0.35, 1.02), and 0.87 (95% CI: 0.55, 1.38) (P for trend = 0.33) for black or oolong tea and 1.00 (reference), 1.16 (95% CI: 0.78, 1.73), and 1.03 (95% CI: 0.59, 1.80) (P for trend = 0.70) for coffee. The results were essentially the same at cutoffs of < 28 and < 24 . CONCLUSION: A higher consumption of green tea is associated with a lower prevalence of cognitive impairment in humans.
22. Landrigan CP, Rothschild JM, Cronin JW *et al.* Effect of reducing interns' work hours on serious medical errors in intensive care units. *N Engl J Med* 2004; 351(18):1838-48.
Abstract: BACKGROUND: Although sleep deprivation has been shown to impair neurobehavioral performance, few studies have measured its effects on medical errors. METHODS: We conducted a prospective, randomized study comparing the rates of serious medical errors made by interns while they were working according to a traditional schedule with extended (24 hours or more) work shifts every other shift (an "every third night" call schedule) and while they were working according to an intervention schedule that eliminated extended work shifts and reduced the number of hours worked

per week. Incidents were identified by means of a multidisciplinary, four-pronged approach that included direct, continuous observation. Two physicians who were unaware of the interns' schedule assignments independently rated each incident. RESULTS: During a total of 2203 patient-days involving 634 admissions, interns made 35.9 percent more serious medical errors during the traditional schedule than during the intervention schedule (136.0 vs. 100.1 per 1000 patient-days, $P<0.001$), including 56.6 percent more nonintercepted serious errors ($P<0.001$). The total rate of serious errors on the critical care units was 22.0 percent higher during the traditional schedule than during the intervention schedule (193.2 vs. 158.4 per 1000 patient-days, $P<0.001$). Interns made 20.8 percent more serious medication errors during the traditional schedule than during the intervention schedule (99.7 vs. 82.5 per 1000 patient-days, $P=0.03$). Interns also made 5.6 times as many serious diagnostic errors during the traditional schedule as during the intervention schedule (18.6 vs. 3.3 per 1000 patient-days, $P<0.001$). CONCLUSIONS: Interns made substantially more serious medical errors when they worked frequent shifts of 24 hours or more than when they worked shorter shifts. Eliminating extended work shifts and reducing the number of hours interns work per week can reduce serious medical errors in the intensive care unit.

23. Le Gal G, Righini M, Roy PM *et al.* Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med* 2006; 144(3):165-71.

Notes: Maiko Narita, 17 March 06

Abstract: BACKGROUND: Diagnosis of pulmonary embolism requires clinical probability assessment. Implicit assessment is accurate but is not standardized, and current prediction rules have shortcomings. OBJECTIVE: To construct a simple score based entirely on clinical variables and independent from physicians' implicit judgment. DESIGN: Derivation and external validation of the score in 2 independent management studies on pulmonary embolism diagnosis. SETTING: Emergency departments of 3 university hospitals in Europe. PATIENTS: Consecutive patients admitted for clinically suspected pulmonary embolism. MEASUREMENTS: Collected data included demographic characteristics, risk factors, and clinical signs and symptoms suggestive of venous thromboembolism. The variables statistically significantly associated with pulmonary embolism in univariate analysis were included in a multivariate logistic regression model. Points were assigned according to the regression coefficients. The score was then externally validated in an independent cohort. RESULTS: The score comprised 8 variables (points): age older than 65 years (1 point), previous deep venous thrombosis or pulmonary embolism (3 points), surgery or fracture within 1 month (2 points), active malignant condition (2 points), unilateral lower limb pain (3 points), hemoptysis (2 points), heart rate of 75 to 94 beats/min (3 points) or 95 beats/min or more (5 points), and pain on lower-limb deep venous palpation and unilateral edema (4 points). In the validation set, the prevalence of pulmonary embolism was 8% in the low-probability category (0 to 3 points), 28% in the intermediate-probability category (4 to 10 points), and 74% in the high-probability category (≥ 11 points). LIMITATIONS: Interobserver agreement for the score items was not studied. CONCLUSIONS: The proposed score is entirely standardized and is based on clinical variables. It has sustained internal and external validation and should now be tested for clinical usefulness in an outcome study.

24. Linzer M, Brown JT, Frazier LM, DeLong ER, Siegel WC. Impact of a medical journal club on house-staff reading habits, knowledge, and critical appraisal skills. A randomized control trial. *JAMA* 1988; 260(17):2537-41.

Abstract: The journal club is an established teaching modality in many house-staff training programs. To determine if a journal club improves house-staff reading habits, knowledge of epidemiology and biostatistics, and critical appraisal skills, we randomized 44 medical interns to receive either a journal club or a control seminar series. A test instrument developed by the Delphi method was administered before and after the interventions (mean, five journal club sessions). By self-report, 86% of the house staff in the journal club group improved their reading habits vs 0% in the control group. Knowledge scores increased more in the journal club group than in the control group, and a trend was found toward more knowledge gained as more sessions were attended. Ability to appraise critically a test article increased slightly in each group, but there was no significant difference between the groups. We conclude that a journal club is a powerful motivator

of critical house-staff reading behavior and can help teach epidemiology and biostatistics to physicians-in-training.

25. Liu Z, Chen G, Chen H. [Clinical analysis of 50 cases of pulmonary complications associated with Tsutsugamushi disease]. *Zhonghua Jie He He Hu Xi Za Zhi* 2002; 25(8):478-80.
Abstract: OBJECTIVE: To study the clinical features of pulmonary complications associated with tsutsugamushi disease. METHODS: Two hundred and thirty two patients with tsutsugamushi disease were retrospectively analyzed by chest X-ray, ultrasonography and lung function test. The differential diagnosis of tsutsugamushi disease associated lung complications from mycoplasma pneumonia, streptococcal pneumonia and tuberculosis was discussed. RESULTS: Pulmonary complications were present in 21.6% (50/232) of the patients with tsutsugamushi disease. Of them 42% were initially misdiagnosed as other pulmonary diseases. The characteristic radiographic manifestation was exudative lesions. The lesions were bilateral in 36 cases (72%), and unilateral in 14 cases (28%). Pleural effusion was present in 16 cases. Chloromycetin was effective in all the cases. CONCLUSIONS: Pulmonary complications were common in tsutsugamushi disease. The prognosis was good if diagnosed and treated properly at an early stage.
26. Lockley SW, Cronin JW, Evans EE *et al.* Effect of reducing interns' weekly work hours on sleep and attentional failures. *N Engl J Med* 2004; 351(18):1829-37.
Abstract: BACKGROUND: Knowledge of the physiological effects of extended (24 hours or more) work shifts in postgraduate medical training is limited. We aimed to quantify work hours, sleep, and attentional failures among first-year residents (postgraduate year 1) during a traditional rotation schedule that included extended work shifts and during an intervention schedule that limited scheduled work hours to 16 or fewer consecutive hours. METHODS: Twenty interns were studied during two three-week rotations in intensive care units, each during both the traditional and the intervention schedule. Subjects completed daily sleep logs that were validated with regular weekly episodes (72 to 96 hours) of continuous polysomnography ($r=0.94$) and work logs that were validated by means of direct observation by study staff ($r=0.98$). RESULTS: Seventeen of 20 interns worked more than 80 hours per week during the traditional schedule (mean, 84.9; range, 74.2 to 92.1). All interns worked less than 80 hours per week during the intervention schedule (mean, 65.4; range, 57.6 to 76.3). On average, interns worked 19.5 hours per week less ($P<0.001$), slept 5.8 hours per week more ($P<0.001$), slept more in the 24 hours preceding each working hour ($P<0.001$), and had less than half the rate of attentional failures while working during on-call nights ($P=0.02$) on the intervention schedule as compared with the traditional schedule. CONCLUSIONS: Eliminating interns' extended work shifts in an intensive care unit significantly increased sleep and decreased attentional failures during night work hours.
27. Martin GS, Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. *Crit Care Med* 2005; 33(8):1681-7.
Notes: Presenter; Riosuke Myamoto; April 6, 2006
Abstract: OBJECTIVE: Hypoproteinemia is a common condition in critically ill patients, associated with the development of acute lung injury and acute respiratory distress syndrome and subsequent worse clinical outcomes. Albumin with furosemide benefits lung physiology in hypoproteinemic patients with acute lung injury/acute respiratory distress syndrome, but the independent pharmacologic effects of these drugs are unknown. DESIGN: Randomized, double-blinded, placebo-controlled multicentered trial. SETTING: Eleven medical, surgical, and trauma intensive care units including 190 beds within two university hospital systems. PATIENTS: Forty mechanically ventilated patients with acute lung injury/acute respiratory distress syndrome, whose serum total protein concentrations were <6.0 g/dL were included. Patients were excluded for hemodynamic instability or significant renal or hepatic failure. INTERVENTIONS: Subjects were equally randomly allocated to receive furosemide with albumin or furosemide with placebo for 72 hrs, titrated to fluid loss and normalization of serum total protein concentration. MEASUREMENTS AND MAIN RESULTS: The primary outcome was change in oxygenation from baseline to day 1, with secondary physiologic and clinical outcomes. There were no

differences in baseline characteristics of the subjects in relation to group assignment. Albumin-treated patients had greater increases in oxygenation (mean change in Pao₂/Fio₂: +43 vs. -24 mm Hg at 24 hrs and +49 vs. -13 mm Hg at day 3), serum total protein (1.5 vs. 0.5 g/dL at day 3), and net fluid loss (-5480 vs. -1490 mL at day 3) throughout the study period (all p < .05). Fluid bolus administration to control patients reduced net negative fluid balance; control patients more frequently developed hypotension and had fewer shock-free days, which translated to differences in organ failure at study end. CONCLUSIONS: The addition of albumin to furosemide therapy in hypoproteinemic patients with acute lung injury/acute respiratory distress syndrome significantly improves oxygenation, with greater net negative fluid balance and better maintenance of hemodynamic stability. Additional randomized clinical trials are necessary to examine mechanisms and determine the effect on important clinical outcomes, such as the duration of mechanical ventilation.

28. Merten GJ, Burgess WP, Gray LV *et al.* Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA* 2004; 291(19):2328-34.
Notes: Reviewed by Manubu, 24 March 2006
Abstract: CONTEXT: Contrast-induced nephropathy remains a common complication of radiographic procedures. Pretreatment with sodium bicarbonate is more protective than sodium chloride in animal models of acute ischemic renal failure. Acute renal failure from both ischemia and contrast are postulated to occur from free-radical injury. However, no studies in humans or animals have evaluated the efficacy of sodium bicarbonate for prophylaxis against contrast-induced nephropathy. OBJECTIVE: To examine the efficacy of sodium bicarbonate compared with sodium chloride for preventive hydration before and after radiographic contrast. DESIGN, SETTING, AND PATIENTS: A prospective, single-center, randomized trial conducted from September 16, 2002, to June 17, 2003, of 119 patients with stable serum creatinine levels of at least 1.1 mg/dL (> or =97.2 micromol/L) who were randomized to receive a 154-mEq/L infusion of either sodium chloride (n = 59) or sodium bicarbonate (n = 60) before and after iopamidol administration (370 mg iodine/mL). Serum creatinine levels were measured at baseline and 1 and 2 days after contrast. INTERVENTIONS: Patients received 154 mEq/L of either sodium chloride or sodium bicarbonate, as a bolus of 3 mL/kg per hour for 1 hour before iopamidol contrast, followed by an infusion of 1 mL/kg per hour for 6 hours after the procedure. MAIN OUTCOME MEASURE: Contrast-induced nephropathy, defined as an increase of 25% or more in serum creatinine within 2 days of contrast. RESULTS: There were no significant group differences in age, sex, incidence of diabetes mellitus, ethnicity, or contrast volume. Baseline serum creatinine was slightly higher but not statistically different in patients receiving sodium bicarbonate treatment (mean [SD], 1.71 [0.42] mg/dL [151.2 [37.1] micromol/L) for sodium chloride and 1.89 [0.69] mg/dL [167.1 [61.0] micromol/L) for sodium bicarbonate; P = .09). The primary end point of contrast-induced nephropathy occurred in 8 patients (13.6%) infused with sodium chloride but in only 1 (1.7%) of those receiving sodium bicarbonate (mean difference, 11.9%; 95% confidence interval [CI], 2.6%-21.2%; P = .02). A follow-up registry of 191 consecutive patients receiving prophylactic sodium bicarbonate and meeting the same inclusion criteria as the study resulted in 3 cases of contrast-induced nephropathy (1.6%; 95% CI, 0%-3.4%). CONCLUSION: Hydration with sodium bicarbonate before contrast exposure is more effective than hydration with sodium chloride for prophylaxis of contrast-induced renal failure.
29. Michalsen A, Klotz S, Ludtke R, Moebus S, Spahn G, Dobos GJ. Effectiveness of leech therapy in osteoarthritis of the knee: a randomized, controlled trial. *Ann Intern Med* 2003; 139(9):724-30.
Notes: Reviewed by Dr. Gremillion Feb 2004
Abstract: BACKGROUND: Leech therapy was commonly used in traditional medicine for treating localized pain. Clinically significant pain relief after leech therapy for osteoarthritis of the knee has been demonstrated by preliminary data. OBJECTIVE: To evaluate the effectiveness of leech therapy for symptomatic relief of osteoarthritis of the knee. DESIGN: Randomized, controlled trial. SETTING: Outpatient department for integrative medicine of an academic teaching hospital. PATIENTS: 51 patients with osteoarthritis of the knee (leech therapy: 24 patients, mean age [+/-SD], 62.5 +/- 10.2 years; topical diclofenac therapy: 27 patients, mean age [+/-SD], 65.5 +/- 6.7

years). INTERVENTION: A single treatment with 4 to 6 locally applied leeches (leech therapy group) or a 28-day topical diclofenac regimen (control group). MEASUREMENTS: Mean of the pain, function, and stiffness subscores of the Western Ontario and McMaster Universities Osteoarthritis Index and physical sum score of the Medical Outcomes Study 36-Item Short-Form Health Survey with group comparisons at days 3, 7, 28, and 91. RESULTS: The primary end point, pain at day 7, was reduced from a mean (+/-SD) of 53.5 +/- 13.7 to 19.3 +/- 12.2 after leech therapy compared with 51.5 +/- 16.8 to 42.4 +/- 19.7 with topical diclofenac (estimated group difference, -23.9 [95% CI, -32.8 to -15.1]; P < 0.001). Although the difference between group pain scores was no longer significant after day 7, differences for function, stiffness, and total symptoms remained significant in favor of leech therapy until the end of study and for quality of life until day 28. Results were not affected by outcome expectation. CONCLUSIONS: Leech therapy helps relieve symptoms in patients with osteoarthritis of the knee. The potential of leech therapy for treating osteoarthritis and the pharmacologic properties of leech saliva remain to be clarified.

30. Morimoto T, Fukui T, Lee TH, Matsui K. Application of U.S. guidelines in other countries: aspirin for the primary prevention of cardiovascular events in Japan. *Am J Med* 2004; 117(7):459-68.
 Abstract: PURPOSE: Clinical guidelines developed in the United States are used frequently in other countries without assessment of their appropriateness in non-U.S. populations. We explored the relevance of recent U.S. guidelines for the use of aspirin for the primary prevention of cardiovascular events in the Japanese population. METHODS: From a systematic search of published data, estimates were derived for rates of coronary heart disease, hemorrhagic stroke, and major gastrointestinal bleeding for the Japanese population and for subgroups with different risk factors. Odds ratios derived from meta-analyses were used to assess the potential benefits and risks of aspirin use. RESULTS: The estimated incidence of coronary heart disease in middle-aged men in Japan is lower than in the United States (1.57 vs. 6.0 per 1000 person-years), while that of hemorrhagic stroke is higher (1.14 vs. 0.37 per 1000 person-years). Because of higher baseline rates of hemorrhagic diseases, the expected reduction in cardiovascular events with aspirin use would be offset by a greater increase in hemorrhagic complications for women and most men in Japan, except for those with both hypertension and diabetes. To achieve the same 2:1 ratio of coronary heart disease events avoided to hemorrhagic events caused that is implied by the 3% threshold for 5-year coronary disease risk in U.S. guidelines, a 6% to 14% risk threshold, depending on patient age, seems appropriate for recommending aspirin in Japanese patients. CONCLUSION: The thresholds of antiplatelet therapy for Asian populations should be two to five times higher than those for the U.S. population because of higher risks of hemorrhagic complications. The assumptions and implications of U.S. guidelines should be evaluated before use in other countries.
31. Njamnshi AK, Blackett KN, Mbuagbaw JN, Gumede F, Gupta S, Wiysonge CS. Chronic Chlamydia pneumoniae infection and stroke in Cameroon: a case-control study. *Stroke* 2006; 37(3):796-9.
 Abstract: BACKGROUND AND PURPOSE: To determine the relationship between chronic Chlamydia pneumoniae infection and stroke in Cameroon. METHODS: Sixty-four consecutive stroke patients 26 to 80 years of age were enrolled at 2 tertiary hospitals in Yaounde, Cameroon, between March 2000 and December 2001 and matched for age and sex to 64 controls. We measured IgG (1/64) and IgA (1/16) titers against C pneumoniae in both patients and controls using a validated microimmunofluorescence technique. RESULTS: There was no significant difference between cases and controls with respect to hypertension (P=0.2), smoking (P=0.53), alcohol intake (P=0.8), body mass index (P=0.49), waist-to-hip ratio (P=0.14), and diabetes (P=0.76). IgA antibodies were detected in 50 (78.1%) patients and 27 (42.2%) controls (odds ratio [OR] 4.29; 95% CI, 1.84 to 11.56; P=0.0002), and IgG antibodies in 41 (64.1%) patients and 35 (54.7%) controls (OR, 1.46; 95% CI, 0.68 to 3.22; P=0.29). For confirmed thrombotic stroke, the association with IgA antibodies became stronger (OR, 21.0; 95% CI, 3.38 to 868.45; P<0.0001), but there was still no association with IgG antibodies (OR, 1.86; 95% CI, 0.69 to 5.50; P=0.18). CONCLUSIONS: Our study shows a strong statistical association between (IgA, and not IgG, as a serological marker of) chronic C pneumoniae infection and stroke for the first time in a resident indigenous African population. These findings, if confirmed, may have important policy implications (in terms of antibiotic use in stroke prevention) in sub-Saharan Africa.

32. Peterson MC, Holbrook JH, Von Hales D, Smith NL, Staker LV. Contributions of the history, physical examination, and laboratory investigation in making medical diagnoses. *West J Med* 1992; 156(2):163-5.
Abstract: We report an attempt to quantitate the relative contributions of the history, physical examination, and laboratory investigation in making medical diagnoses. In this prospective study of 80 medical outpatients with new or previously undiagnosed conditions, internists were asked to list their differential diagnoses and to estimate their confidence in each diagnostic possibility after the history, after the physical examination, and after the laboratory investigation. In 61 patients (76%), the history led to the final diagnosis. The physical examination led to the diagnosis in 10 patients (12%), and the laboratory investigation led to the diagnosis in 9 patients (11%). The internists' confidence in the correct diagnosis increased from 7.1 on a scale of 1 to 10 after the history to 8.2 after the physical examination and 9.3 after the laboratory investigation. These data support the concept that most diagnoses are made from the medical history. The results of physical examination and the laboratory investigation led to fewer diagnoses, but they were instrumental in excluding certain diagnostic possibilities and in increasing the physicians' confidence in their diagnoses.
33. Quinn JV, Stiell IG, McDermott DA, Kohn MA, Wells GA. The San Francisco Syncope Rule vs physician judgment and decision making. *Am J Emerg Med* 2005; 23(6):782-6.
Notes: Reviewed March 30, 2006 by Katayama
Abstract: OBJECTIVE: To compare a clinical decision rule (San Francisco Syncope Rule [SFSR]) and physician decision making when predicting serious outcomes in patients with syncope. METHODS: In a prospective cohort study, physicians evaluated patients presenting with syncope and predicted the chance (0%-100%) of the patient developing a predefined serious outcome. They were then observed to determine their decision to admit the patient. All patients were followed up to determine whether they had a serious outcome within 7 days of their emergency department visit. Analyses included sensitivity and specificity to predict serious outcomes for low-risk patients and comparison of areas under the receiver operating characteristic curve for the decision rule, physician judgment, and admission decisions. RESULTS: During the study period, there were 684 visits for syncope with 79 visits resulting in serious outcomes. The area under the receiver operating characteristic curve was 0.92 (95% confidence interval [CI], 0.88-0.95) for the SFSR compared with physician judgment 0.89 (95% CI, 0.85-0.93) and physician decision making 0.83 (95% CI, 0.81-0.87). Physicians admitted 28% of patients in a low-risk group, with a median length of stay of 1 day (interquartile range, 1-2.5 days). The SFSR had the potential to absolutely decrease admissions by 10% in this low-risk group and still predict all serious outcomes. CONCLUSIONS: Physician judgment is good when predicting which patients with syncope will develop serious outcomes, but contrary to their judgment, physicians still admit a large number of low-risk patients. The SFSR performs better than current physician performance and has great potential to aid physician decision making.
34. Quinn JV, Stiell IG, McDermott DA, Sellers KL, Kohn MA, Wells GA. Derivation of the San Francisco Syncope Rule to predict patients with short-term serious outcomes. *Ann Emerg Med* 2004; 43(2):224-32.
Notes: Reviewed March 30, 2006 by Katayama
Abstract: STUDY OBJECTIVE: The causes of syncope are usually benign but are occasionally associated with significant morbidity and mortality. We derive a decision rule that would predict patients at risk for short-term serious outcomes and help guide admission decisions. METHODS: This prospective cohort study was conducted at a university teaching hospital and used emergency department (ED) patients presenting with syncope or near syncope. Physicians prospectively completed a structured data form when evaluating patients with syncope. Serious outcomes (death, myocardial infarction, arrhythmia, pulmonary embolism, stroke, subarachnoid hemorrhage, significant hemorrhage, or any condition causing a return ED visit and hospitalization for a related event) were defined at the start of the study. All patients were followed up to determine whether they had experienced a serious outcome within 7 days of their ED visit. Univariate analysis was performed with chi² and nonparametric techniques on all predictor variables. kappa Analysis was performed on variables requiring interpretation. Variables with kappa more than 0.5 and a P value

less than .1 were analyzed with recursive partitioning techniques to develop a rule that would maximize the determination of serious outcomes. RESULTS: There were 684 visits for syncope, and 79 of these visits resulted in patients' experiencing serious outcomes. Of the 50 predictor variables considered, 26 were associated with a serious outcome on univariate analysis. A rule that considers patients with an abnormal ECG, a complaint of shortness of breath, hematocrit less than 30%, systolic blood pressure less than 90 mm Hg, or a history of congestive heart failure has 96% (95% confidence interval [CI] 92% to 100%) sensitivity and 62% (95% CI 58% to 66%) specificity. If applied to this cohort, the rule has the potential to decrease the admission rate by 10%. CONCLUSION: The San Francisco Syncope Rule derived in this cohort of patients appears to be sensitive for identifying patients at risk for short-term serious outcomes. If prospectively validated, it may offer a tool to aid physician decision making.

35. Sanchez-Quijano A, Pineda JA, Lissen E *et al.* Prevention of post-transfusion non-A, non-B hepatitis by non-specific immunoglobulin in heart surgery patients. *Lancet* 1988; 1(8597):1245-9.
Abstract: To evaluate the effectiveness of immune serum globulin (ISG) in preventing non-A, non-B hepatitis, 291 heart surgery patients who received blood from voluntary donors were randomly assigned to receive either ISG or no additional protection. ISG was given intramuscularly before and 1 week after transfusion. 98 controls and 100 in the ISG group completed the study. Post-transfusion non-A, non-B hepatitis developed in 11 (11.2%) controls but in only 3 (3.0%) of the ISG group ($p = 0.0203$). 8 (72.7%) of control group with hepatitis had symptoms, and in 5 (45.4%) the disease became chronic. The disease was self-limiting in all 3 ISG patients affected, and only 1 of them had symptoms. Among those with non-A, non-B hepatitis aminotransferase levels were higher in the controls than in the ISG patients. Incubation periods longer than 8 weeks correlated with a tendency for the disease to become chronic. ISG recipients had shorter as well as more homogeneous incubation periods. ISG could be a safe, low-cost means for preventing post-transfusion non-A, non-B hepatitis which does not call for the discarding of donated blood.
36. Shah S, Lewis A, Leopold D, Dunstan F, Woodhouse K. Gastric acid suppression does not promote clostridial diarrhoea in the elderly. *QJM* 2000; 93(3):175-81.
Abstract: Gastric acid prevents bacterial colonization of the stomach and suppression of its secretion might predispose to *Clostridium difficile* (CD) diarrhoea. We retrospectively studied elderly patients admitted to medical wards of an acute hospital to determine whether the incidence of CD diarrhoea was greater among those previously treated with gastric acid suppressants. From records of stool CD toxin tests undertaken in 1995 and 1996, we found 126 cases with positive results, and selected 126 controls with negative results. Information about pre-morbid illness, predisposing factors for CD and medication received in the preceding 16 weeks was obtained from case-notes. A greater number of CD positive cases had received antibiotics such as Cefuroxime, ciprofloxacin or macrolides with or without metronidazole, were more severely disabled, required assistance for feeding, or had hypoalbuminaemia before the onset of diarrhoea. A greater number of controls had received lactulose, suggesting either that its laxative effect resembled CD infection prompting frequent stool tests, or that it offered protection against CD in this group. Both groups were similar for the use of proton-pump inhibitors or H₂-receptor antagonists, suggesting that susceptible elderly patients are not more likely to develop CD diarrhoea after receiving gastric acid suppression therapy.
37. Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. *JAMA* 2005; 294(20):2623-9.
Abstract: CONTEXT: The chest pain history, physical examination, determination of coronary artery disease (CAD) risk factors, and the initial electrocardiogram compose the information immediately available to clinicians to help determine the probability of acute myocardial infarction (AMI) or acute coronary syndrome (ACS) in patients with chest pain. However, conflicting data exist about the usefulness of the chest pain history and which components are most useful. OBJECTIVE: To identify the elements of the chest pain history that may be most helpful to the clinician in identifying ACS in patients presenting with chest pain. EVIDENCE ACQUISITION: MEDLINE and Ovid were searched from 1970 to September 2005 by using specific key words and

Medical Subject Heading terms. Reference lists of these articles and current cardiology textbooks were also consulted. EVIDENCE SYNTHESIS: Certain chest pain characteristics decrease the likelihood of ACS or AMI, namely, pain that is stabbing, pleuritic, positional, or reproducible by palpation (likelihood ratios [LRs] 0.2-0.3). Conversely, chest pain that radiates to one shoulder or both shoulders or arms or is precipitated by exertion is associated with LR (2.3-4.7) that increase the likelihood of ACS. The chest pain history itself has not proven to be a powerful enough predictive tool to obviate the need for at least some diagnostic testing. Combinations of elements of the chest pain history with other initially available information, such as a history of CAD, have identified certain groups that may be safe for discharge without further evaluation, but further study is needed before such a recommendation can be considered reasonable. CONCLUSION: Although certain elements of the chest pain history are associated with increased or decreased likelihoods of a diagnosis of ACS or AMI, none of them alone or in combination identify a group of patients that can be safely discharged without further diagnostic testing.

38. Van den Berghe G, Wilmer A, Hermans G *et al.* Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354(5):449-61.
 Abstract: BACKGROUND: Intensive insulin therapy reduces morbidity and mortality in patients in surgical intensive care units (ICUs), but its role in patients in medical ICUs is unknown. METHODS: In a prospective, randomized, controlled study of adult patients admitted to our medical ICU, we studied patients who were considered to need intensive care for at least three days. On admission, patients were randomly assigned to strict normalization of blood glucose levels (80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]) with the use of insulin infusion or to conventional therapy (insulin administered when the blood glucose level exceeded 215 mg per deciliter [12 mmol per liter], with the infusion tapered when the level fell below 180 mg per deciliter [10 mmol per liter]). There was a history of diabetes in 16.9 percent of the patients. RESULTS: In the intention-to-treat analysis of 1200 patients, intensive insulin therapy reduced blood glucose levels but did not significantly reduce in-hospital mortality (40.0 percent in the conventional-treatment group vs. 37.3 percent in the intensive-treatment group, P=0.33). However, morbidity was significantly reduced by the prevention of newly acquired kidney injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital. Although length of stay in the ICU could not be predicted on admission, among 433 patients who stayed in the ICU for less than three days, mortality was greater among those receiving intensive insulin therapy. In contrast, among 767 patients who stayed in the ICU for three or more days, in-hospital mortality in the 386 who received intensive insulin therapy was reduced from 52.5 to 43.0 percent (P=0.009) and morbidity was also reduced. CONCLUSIONS: Intensive insulin therapy significantly reduced morbidity but not mortality among all patients in the medical ICU. Although the risk of subsequent death and disease was reduced in patients treated for three or more days, these patients could not be identified before therapy. Further studies are needed to confirm these preliminary data. (ClinicalTrials.gov number, NCT00115479.)
39. Wilkinson GR. Drug metabolism and variability among patients in drug response. *N Engl J Med* 2005; 352(21):2211-21.
40. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 2005; 353(19):2034-41.
 Notes: Ai Oishii, 17 arch 06
 Abstract: BACKGROUND: Previous studies have suggested that the obstructive sleep apnea syndrome may be an important risk factor for stroke. It has not been determined, however, whether the syndrome is independently related to the risk of stroke or death from any cause after adjustment for other risk factors, including hypertension. METHODS: In this observational cohort study, consecutive patients underwent polysomnography, and subsequent events (strokes and deaths) were verified. The diagnosis of the obstructive sleep apnea syndrome was based on an apnea-hypopnea index of 5 or higher (five or more events per hour); patients with an apnea-hypopnea index of less than 5 served as the comparison group. Proportional-hazards analysis was used to determine the independent effect of the obstructive sleep apnea syndrome on the composite outcome of stroke or

death from any cause. RESULTS: Among 1022 enrolled patients, 697 (68 percent) had the obstructive sleep apnea syndrome. At baseline, the mean apnea-hypopnea index in the patients with the syndrome was 35, as compared with a mean apnea-hypopnea index of 2 in the comparison group. In an unadjusted analysis, the obstructive sleep apnea syndrome was associated with stroke or death from any cause (hazard ratio, 2.24; 95 percent confidence interval, 1.30 to 3.86; P=0.004). After adjustment for age, sex, race, smoking status, alcohol-consumption status, body-mass index, and the presence or absence of diabetes mellitus, hyperlipidemia, atrial fibrillation, and hypertension, the obstructive sleep apnea syndrome retained a statistically significant association with stroke or death (hazard ratio, 1.97; 95 percent confidence interval, 1.12 to 3.48; P=0.01). In a trend analysis, increased severity of sleep apnea at baseline was associated with an increased risk of the development of the composite end point (P=0.005). CONCLUSIONS: The obstructive sleep apnea syndrome significantly increases the risk of stroke or death from any cause, and the increase is independent of other risk factors, including hypertension.