

Abstracts of Articles Authored or Coauthored by Permanente Physicians, Nurses, and Investigators

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Coffee, cirrhosis, and transaminase enzymes.

Klatsky AL, Morton C, Udaltsova N, Friedman GD. Arch Intern Med 2006 Jun 12;166(11):1190-5.

BACKGROUND: A minority of persons at risk develop liver cirrhosis, but knowledge of risk modulators is sparse. Several reports suggest that coffee drinking is associated with lower cirrhosis risk.

METHODS: We studied 125,580 multiethnic members of a comprehensive prepaid health care plan without known liver disease who supplied baseline data at voluntary health examinations from 1978 to 1985. Subsequently, through 2001, 330 of them were diagnosed with liver cirrhosis. Review of medical records confirmed the diagnosis of cirrhosis and ascertained probable etiology. The association of coffee drinking with cirrhosis was estimated by Cox proportional hazards models with seven covariates. We also did a cross-sectional analysis of baseline aspartate aminotransferase and alanine aminotransferase levels, studied by logistic regression.

RESULTS: In the cohort study, relative risks of alcoholic cirrhosis (199 subjects) for coffee drinking (vs none) were less than 1 cup per day, 0.7 (95% confidence interval [CI], 0.4-1.1); 1 to 3 cups, 0.6 (95% CI, 0.4-0.8; $p < .001$); and 4 or more cups, 0.2 (95% CI, 0.1-0.4; $p < .001$). For 131 subjects with non-alcoholic cirrhosis, relative risks were less than 1 cup, 1.2 (95% CI, 0.6-2.2); 1 to 3 cups, 1.3 (95% CI, 0.8-2.1); and 4 or more cups, 0.7 (95% CI, 0.4-1.3). These relative risks for coffee drinking were consistent in subsets. Tea drinking was unrelated to alcoholic or nonalcoholic cirrhosis. In the cross-sectional analyses, coffee drinking was related to lower prevalence of high aspartate aminotransferase and alanine aminotransferase levels; for example, the

odds ratio of four or more cups per day (vs none) for a high aspartate aminotransferase level was 0.5 (95% CI, 0.4-0.6; $p < .001$) and for a high alanine aminotransferase level, 0.6 (95% CI, 0.6-0.7; $p < .001$), with stronger inverse relations in those who drink large quantities of alcohol.

CONCLUSION: These data support the hypothesis that there is an ingredient in coffee that protects against cirrhosis, especially alcoholic cirrhosis.

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CLINICAL IMPLICATION: These data strongly suggest that some coffee ingredient protects against chronic liver disease, especially alcohol-related damage. While useful primarily as a clue to future studies of factors involved in basic liver disease mechanisms, the finding is yet another piece of evidence that moderate coffee drinking is safe for most persons. Since liver disease is only one of many hazards from heavy alcohol drinking, the data do not give license to heavy alcohol drinkers to persist in their habit and cover it by drinking coffee. -AK

Unintended consequences of caps on Medicare drug benefits.

Hsu J, Price M, Huang J, et al. N Engl J Med 2006 Jun 1;354(22):2349-59.

BACKGROUND: Little information exists about the consequences of limits on prescription-drug benefits for Medicare beneficiaries.

METHODS: We compared the clinical and economic outcomes in 2003 among 157,275 Medicare+Choice beneficiaries whose annual drug benefits were capped at \$1000 and 41,904 beneficiaries whose drug benefits were unlimited because of employer supplements.

RESULTS: After adjusting for individual characteristics, we found that subjects whose benefits were capped had pharmacy costs for drugs applicable to the cap that were lower by 31% than subjects whose benefits were not capped (95% confidence interval, 29 to 33%) but had total medical costs that were only 1% lower (95% confidence interval, -4 to 6%). Subjects whose benefits were capped had higher relative rates of visits to the emergency department (relative rate, 1.09 [95% confidence interval, 1.04 to 1.14]), nonelective hospitalizations (relative rate, 1.13 [1.05 to 1.21]), and death (relative rate, 1.22 [1.07 to 1.38]; difference, 0.68 per 100 person-years [0.30 to 1.07]). Among subjects who used drugs for hypertension, hyperlipidemia, or diabetes in 2002, those whose benefits were capped were more likely to be nonadherent to long-term drug therapy in 2003; the respective odds ratios were 1.30 (95% confidence interval, 1.23 to 1.38), 1.27 (1.19 to 1.34), and 1.33 (1.18 to 1.48) for subjects using drugs for hypertension, hyperlipidemia, and diabetes. In each subgroup, the physiological outcomes were worse for subjects whose drug benefits were capped than for those whose benefits were not capped; the odds ratios were 1.05 (95% confidence interval, 1.00 to 1.09), 1.13 (1.03 to 1.25), and 1.23 (1.03 to 1.46), respectively, for subjects with a systolic blood pressure of 140 mm Hg or more, a serum low-density-lipoprotein cholesterol level of 130 mg per deciliter or more, and a glycated hemoglobin level of 8% or more.

CONCLUSIONS: A cap on drug benefits was associated with lower drug consumption and unfavorable clinical outcomes. In patients with chronic disease, the cap was associated with poorer adherence to drug therapy and poorer control of blood pressure, lipid levels, and glucose levels. The savings in

drug costs from the cap were offset by increases in the costs of hospitalization and emergency department care.

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Monitoring of drugs with a narrow therapeutic range in ambulatory care.

Raebel MA, Carroll NM, Andrade SE, et al. *Am J Manag Care* 2006 May;12(5):268-74.

OBJECTIVES: To describe the proportion of patients receiving drugs with a narrow therapeutic range who lacked serum drug concentration monitoring during a one-year period of therapy and to identify patient characteristics associated with lack of monitoring.

STUDY DESIGN: Retrospective cohort.

METHODS: Ambulatory patients (n = 17,748) at ten health maintenance organizations who were receiving ongoing continuous drug therapy with digoxin, carbamazepine, divalproex sodium, lithium carbonate, lithium citrate, phenobarbital sodium, phenytoin, phenytoin sodium, primidone, quinidine gluconate, quinidine sulfate, procainamide hydrochloride, theophylline, theophylline sodium glycinate, tacrolimus, or cyclosporine for at least 12 months between January 1, 1999, and June 30, 2001, were identified. Serum drug concentration monitoring was assessed from administrative data and from medical record data.

RESULTS: Fifty percent or more of patients receiving digoxin, theophylline, procainamide, quinidine, or primidone were not monitored, and 25% to 50% of patients receiving divalproex, carbamazepine, phenobarbital, phenytoin, or tacrolimus were not monitored. Younger age was associated with lack of monitoring for patients prescribed digoxin (adjusted odds ratio, 1.86; 95% confidence interval, 1.39-2.48) and theophylline (adjusted odds ratio, 1.58; 95% confidence interval, 1.23-2.04), while older age was associated with lack of monitoring for patients

prescribed carbamazepine (adjusted odds ratio, 0.59; 95% confidence interval, 0.44-0.80) and divalproex (adjusted odds ratio, 0.50; 95% confidence interval, 0.38-0.66). Patients with fewer outpatient visits were also less likely to be monitored ($p < .001$).

CONCLUSIONS: A substantial proportion of ambulatory patients receiving drugs with narrow intervals between doses resulting in beneficial and adverse effects did not have serum drug concentration monitoring during one year of use. Clinical implications of this finding need to be evaluated.

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CLINICAL IMPLICATION: We document widespread absence of drug concentration monitoring among ambulatory patients prescribed narrow therapeutic range drugs. Monitoring is recommended for these drugs because life-threatening toxicity can result when concentrations are elevated, therapeutic efficacy can be lost when concentrations are low, and correlations between dosages administered and concentrations achieved can be poor. Monitoring drug concentrations is considered a quality measure associated with avoiding preventable drug-related morbidity and disease exacerbations by NCQA (eg, HEDIS). These study results can be used by practitioners to identify and monitor individual patients and to improve monitoring rates through guidelines targeted toward patient risk groups. —MR

Acute appendicitis: is there a difference between children and adults?

Lee SL, Ho HS. *Am Surg* 2006 May;72(5):409-13.

Historically, the lack of classic symptoms and delay in presentation make diagnosing acute appendicitis more difficult in children, resulting in a higher perforation rate. Despite this, the morbidity of acute appendicitis

is usually lower in children. We evaluated the current differences in clinical presentation, diagnostic clues, and the outcomes of acute appendicitis between the two age groups. A retrospective review of 210 consecutive cases of pediatric appendectomy and 744 adult cases for suspected acute appendicitis from January 1995 to December 2000. Pediatric patients were defined as being 13 years and younger. Pediatric patients were similar to adult patients with respect to duration of pain before presentation (2.4 ± 4.3 days vs 2.5 ± 7.3 days), number of patients previously evaluated (22.0 vs 17.7%), number of imaging tests (computed tomography or ultrasound; 32.9 vs 40.2%), and number of patients observed (16.7 vs 17.2%). However, pediatric patients required less time for emergency room evaluation (4.0 ± 2.7 hours vs 5.7 ± 4.9 hours, $p = 0.0001$). In children and adults, a history of classic, migrating pain had the highest positive predictive value (94.2 vs 89.6%), followed by a white blood cell count $\geq 12 \times 10^9/L$ (91.5 vs 84.3%). The overall negative appendectomy rate was 10.0% for children and 19.0% for adults ($p = 0.003$); the perforation rate was 19.0% and 13.8%, respectively ($p > 0.05$). The perforation rate in children was not associated with a delay in presentation (perforated cases, 2.9 ± 3.3 days compared with nonperforated cases, 2.3 ± 4.6 days). Mortality and morbidity, including wound infection rate and intra-abdominal abscess rate, were similar. Contrary to traditional teaching, diagnosing acute appendicitis in children is similar to that in adults. A history of migratory pain together with physical findings and leukocytosis remain accurate diagnostic clues for children and adults. Perforation rate and morbidity in children is similar to those in adults. The outcomes of acute appendicitis in children are not associated with a delay in presentation or delay in diagnosis. ♦