The use of high-dose PPIs in poorly controlled asthmatic patients without symptoms of GERD does not improve asthmatic control even in those with an abnormal 24-hour pH score.

Objective: To determine whether the use of high-dose proton-pump inhibitors (PPIs) in poorly controlled asthmatic patients who do not have symptoms of gastroesophageal reflux disease (GERD) improve asthmatic control. Materials/

Methods: This was a 19-center, double-blind, randomized, parallel study of esomeprazole 40 mg twice daily versus a placebo for 24 weeks in patients (≥18 years of age) with poorly controlled asthma despite moderate to high doses of inhaled steroids. Patients entered a 2- to 8-week run-in period to obtain baseline data (spirometry with challenge of methacholine and a bronchodilator) and pH testing. Once in the study, patients kept a diary of daily spirometry, symptoms, and use of medications. The primary outcomes were poor asthma control, defined by changes in FEV₁; unscheduled visit for asthma control; need for a course of oral prednisone. Secondary outcomes included the use of beta-agonists, questionnaires regarding asthma symptoms and GERD type and quality of life measurements, spirometry (before and after beta-agonists, methacholine challenge), and 24-hour pH to identify GERD.

Results: 402 patients entered the study (most were female, with poor asthma control, and low normal FEV₁); 85% did not have symptoms of GERD and 15% had low symptom GERD scores, although 40% had abnormal 24-hour pH monitoring scores. Both groups had similar adherence to taking active or placebo agents. The study revealed that for both study groups, poorly controlled asthma was noted in 42% with the criterion being no use of beta-agonists, but 61% poorly controlled according to the criteria of increased use of beta-agonists. In both groups, 18% required an urgent care visit or a course of oral prednisone. All other criterion tested and recorded (nocturnal awakening, asthma symptoms and control, quality-of-life and GERD questionnaires, decrease in FEV₁), were similar in both groups. A slight improvement in asthma was noted in both groups over the 6 months of the study that was not significantly different from each other. Subgroup analysis did not identify any factor that favored improvement with esomeprazole.

Conclusions: Despite the fact that 40% of poorly controlled asthmatics without symptoms of GERD had abnormal 24-hour pH monitoring scores, long-term, high-dose PPI (esomeprazole) did not significantly improve asthma symptoms when compared to placebo.

Reviewer's Comments: One would have thought that pH positive asymptomatic patients would have improved with PPI therapy, but this was not the case. The data suggest, that in asymptomatic, poorly controlled asthmatics with normal 24-hour pH scores (60% of patients in this study), PPIs should not be administered. Two other randomized controlled studies in symptomatic patients did show some positive effect of PPI use, especially in patients with symptomatic GERD and nocturnal asthma symptoms or in asthmatics taking multiple medications to treat the asthma. (Reviewer-Roy K.H. Wong, MD).

© 2009, Oakstone Medical Publishing

Keywords: Esomeprazole, GERD, Asthma, 24-Hour pH Monitor

Print Tag: Refer to original journal article
Small Bowel Thickening and Lymphadenopathy Do Not Necessarily Indicate Malignancy

Benign Small Bowel Thickening and Lymphadenopathy: A Manifestation of Celiac Disease.

Martel J, Sussman DA, et al:


Although a thickened small bowel wall and lymphadenopathy may suggest lymphoma, it can also be seen in celiac disease in the absence of malignancy.

**Background/Objective:** Thickening of the small bowel wall accompanied by lymphadenopathy is generally considered suggestive of a lymphoma or other malignancy. The case reports published in this article suggest that these findings may actually be the initial manifestation of a benign entity—celiac disease (CD). Three cases are presented in this report. **Case Reports:** The first case is that of a 40-year-old white female who presented with intermittent, "crampy" abdominal pain localized to the left lower quadrant. Neither food nor bowel activity affected the pain. No weight loss or systemic symptoms were present although she had always had 2 loose bowel movements per day. A CT scan of the abdomen and pelvis revealed mesenteric lymphadenopathy a thickened small bowel wall and areas of intermittent intussusception in the mid to distal jejunum. On exploratory laparoscopy, multiple nodes were biopsied and a segment of the jejunum was resected. Pathology revealed atypical small bowel mucosa with villous blunting and lymphoplasmacytic infiltration of lymph nodes, suggesting CD. CD serologies confirmed the diagnosis. Two months after initiation of a gluten-free diet, a CT scan revealed complete resolution of the lymphadenopathy. The second case was that of a 76-year-old white male who had a 40-pound weight loss over a 4-month period accompanied by chronic diarrhea. Biopsies obtained at esophagogastroduodenoscopy (EGD) revealed partial flattening of the villi with acute and chronic inflammation; CD antibodies were positive. The patient was noncompliant with a gluten-free diet and a CT scan revealed mesenteric lymphadenopathy and focal concentric thickening of the small bowel loops. Enteroscopically obtained biopsies revealed complete blunting of the villi and increased intraepithelial lymphocytes consistent with CD. After a brief course of corticosteroids and strict adherence with a gluten-free diet, the patient had complete resolution of his symptoms. Repeat CT scan revealed normal small bowel loops and a decrease in lymphadenopathy. The third case was that of a 37-year-old white male with a history of testicular cancer that was in remission. He was seen initially for rectal bleeding thought to be due to a fissure. It was noted that he had intermittent diarrhea for the previous 2 years and a prior CT scan showed lymphadenopathy. He had no other gastrointestinal or systemic symptoms. Follow-up CT scan revealed increasing adenopathy and thickened small bowel wall. CD antibodies were positive and a small bowel biopsy was compatible with CD. After treatment with a gluten-free diet for a few months, a CT scan revealed decreased size of the lymph nodes and reversion of the small bowel thickening.

**Reviewer's Comments:** These 3 cases demonstrate that mesenteric lymphadenopathy and small bowel thickening are not always indicative of malignancy and may well lead to the benign diagnosis of CD. (Reviewer-Michael L. Phillips, MD).

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Keywords: Celiac Disease, Lymphadenopathy, Small Bowel Thickening

Print Tag: Refer to original journal article
Patients who present with bleeding peptic ulcers confirmed on endoscopy should be started on proton-pump inhibitors.

**Background:** Outside of some Asian trials, the role of proton-pump inhibitor (PPI) therapy in the immediate post-endoscopic period after bleeding from peptic ulcer disease has been controlled is less well established. Esomeprazole has never been assessed in this situation.

**Objective:** To see if the PPI esomeprazole is useful in such patients.

**Design:** Double-blind, randomized trial.

**Participants:** Patients who presented with upper gastrointestinal (GI) bleeding and who, on endoscopy, had a single bleeding peptic ulcer and had had any active bleeding controlled.

**Methods:** Patients being seen in 1 of 91 centers in 16 countries and who were eligible were randomized into 1 of 2 groups, esomeprazole (80 mg bolus followed by 8 mg/hour IV for 72 hours) or an identical placebo. The randomization was done via a central computer. The primary outcome was bleeding over the 3 days; secondary outcomes included bleeding over 30 days, mortality, the need for further endoscopy or for surgery, and adverse events. A sample size calculation indicated that 380 patients would be needed in each arm.

**Results:** 767 patients were randomized into the 2 arms, but 3 patients (1 treatment, 2 controls or placebo patients) never received any medication. The remaining 375 and 389 constituted the treatment and control arms, respectively. The 2 groups were well matched with regard to demographic and clinical factors. The 72-hour re-bleeding rate was significantly lower in the treated arm (5.9% vs 10.3%); this absolute reduction persisted for 30 days. The treated patients were less likely to receive blood and to undergo further endoscopic interventions; 2.7% of the treatment arm and 5.4% of the control arm underwent surgery ($P=0.059$). Adverse events occurred equally in both arms except for an increased incidence of infusion site reactions in the treated arm.

**Conclusions:** High-dose esomeprazole given after endoscopic evaluation and therapy for bleeding peptic ulcer disease reduces the risk for recurrent bleeding in the next 3 days.

**Reviewer’s Comments:** A systematic review of 24 randomized trials published in the Cochrane Library in 2006 addressed the use of PPIs and came to the same conclusion. While PPIs appeared to be more effective in Asian populations, the effect was present in other groups. Esomeprazole was not assessed in any of these trials. These data in patients with documented bleeding ulcers cannot necessarily be extrapolated to all patients with upper GI bleeding. A practice of evidence-based medicine requires that an endoscopy must first establish the presence of a bleeding ulcer (or at least one with stigmata of recent bleeding) before treatment should be instituted. (Reviewer-Ronald L. Koretz, MD).

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Keywords: Gastric Ulcer, Duodenal Ulcer, PPIs

Print Tag: Refer to original journal article
What Factors Are Associated With an Increased Fatty Liver Index?

Fatty Liver Is Associated With Insulin Resistance, Risk of Coronary Heart Disease, and Early Atherosclerosis in a Large European Population.
Gastaldelli A, Kozakova M, et al:
Hepatology 2009; 49 (May): 1537-1544

In middle-aged, nondiabetic subjects, increased carotid IMT, CVD risk, and IR are associated with an increased fatty liver index.

**Background:** Nonalcoholic fatty liver disease (NAFLD) is common and can result in liver failure. Those with NAFLD have a high risk of developing type 2 diabetes mellitus (DM) and cardiovascular disease (CVD). Furthermore, those with NAFLD have increased carotid intima medial thickness (IMT). Therefore, NAFLD may not only be a marker, but a mediator of atherosclerosis (AS).

**Objectives:** To evaluate the association of fatty liver (FL), insulin resistance (IR), CVD risk, and early AS.

**Design:** Prospective, cross-sectional analysis of a longitudinal cohort.

**Participants:** 1307 nondiabetic subjects without obesity, hypertension, or dyslipidemia (age range, 30 to 60 years) from 19 European centers recruited between 2002 and 2004 in an effort to study the relationship between insulin sensitivity and CVD (the RISC Study).

**Methods:** In the RISC Study, they evaluated liver enzymes, fasting lipids, IR (by euglycemic-hyperinsulinemic clamp), glucose (using the oral glucose tolerance test [OGTT]), IMT, CVD risk (Framingham score [FS]), and physical activity (by accelerometer). FL was estimated by the fatty liver index (FLI) based on body mass index (BMI), waist circumference, triglycerides, and the gamma-glutamyltransferase (GGT) that has an 84% accuracy rate. Subjects were categorized as those with a FLI <20 (likelihood of no FL is >91%, group 1, n=608), intermediate (FLI 20 to 59; group 2, n=465), and FLI >60 (likelihood of having FL is 78%; group 3, n=234).

**Results:** There were 587 men and 720 women with a mean age of 42 and 45, respectively. Compared to group 1, those with a FLI >60 (group 3) included more men (70% vs 24%) and subjects with impaired oral glucose tolerance (OGT; 23% vs 5%). FLI was not associated with alcohol use. Carotid IMT increased with increased FLI ($r=0.30$) and was higher in group 3 compared to group 1 ($P<0.0001$). FLI was also associated with increased CVD risk ($r=0.48$), LDL cholesterol ($r=0.33$), alanine aminotransferase (ALT; $r=0.48$), aspartate aminotransferase (AST; $r=0.25$), systolic blood pressure ($r=0.39$), increased IR ($r=0.43$), reduced HDL cholesterol ($r=-0.50$), adiponectin ($r=-0.42$), and physical activity ($r=-0.16$) (all $P<0.0001$). These correlations also held in multivariate analysis controlling for age, gender, and center.

**Conclusions:** In middle aged, nondiabetic subjects, increased carotid IMT, CVD risk, and IR are associated with increased FLI.

**Reviewer's Comments:** The current study provides additional data of the increased risk of CVD in those with fatty liver. Because many of these patients may fall under the radar of primary care providers, it is incumbent on us to recognize the increased risk of CVD in patients with NAFLD and educate both patients and providers to reduce the increased cardiovascular mortality in this growing population. (Reviewer-Richard K. Sterling, MD).

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Keywords: NAFLD, Cardiovascular Dz, Insulin Resistance

Print Tag: Refer to original journal article
Retreatment of PEG-IFN/RBV NR with CIFN/RBV is safe and efficacious and can be considered a retreatment strategy, especially in those without advanced fibrosis.

**Background:** Although pegylated interferon (PEG-IFN) and ribavirin (RBV) are considered first line therapy in treating hepatitis C virus (HCV), only 50% of patients achieve a sustained virologic response (SVR). Options for nonresponders (NR) are limited.

**Objectives:** To evaluate the efficacy, tolerability, and safety of daily interferon Alfacon-1 (consensus interferon [CIFN]) with RBV in prior NR to PEG-IFN/RBV.

**Design:** Phase 3, prospective, randomized, open-label, multicenter registration trial.

**Participants:** Prior NR (a <2 log decrease in HCV RNA by week 24 or detectable at week 48) to PEG-IFN/RBV.

**Methods:** Patients were randomized to CIFN 9 μg/day (n=171), 15 μg/day (n=172) plus RBV 1000 to 1200 mg/day, or no therapy (n=172). After 24 weeks, those in the control group were randomized to 9 μg/day (n=74) or 15 μg/day (n=70) plus RBV. Those with a ≥2-log decrease in HCV RNA at week 24 were continued for a total of 48 weeks for end of treatment response (ETR) and at week 72 for sustained virologic response (SVR). RBV was dose reduced to 600 mg/day for anemia and growth factors were not allowed. The final analysis included 245 who received 9 μg/day and 242 who received 15 μg/d plus RBV.

**Results:** The mean age was 50 years, 70% were male, 95% were genotype 1, 65% were Caucasian, and 60% had advanced fibrosis. ETR was observed in 15% of those on 9 μg/d and 18% of those on 15 μg/d. SVR was observed in 7% on 9 μg/d and 11% for those on 15 μg/d. Relapse rates were 52% and 42% for the 9 and 15 μg/d groups, respectively. The highest SVR (32%) was observed in those on 15 μg/d without cirrhosis, who had a partial response (>2-log decrease in HCV RNA) with prior PEG-IFN/RBV treatment. Overall safety and tolerability were similar between groups with 15% to 20% requiring discontinuation.

**Conclusions:** Retreatment with PEG-IFN/RBV in NR with CIFN/RBV is safe and efficacious and can be considered a retreatment strategy, especially in those without advanced fibrosis.

**Reviewer's Comments:** Given the difficult-to-treat population, the 7% to 10% SVR rate results of the Daily-Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy (DIRECT) trial is not unexpected. Although a subgroup (mild fibrosis and partial response to prior therapy) had reasonable SVR rates, patients with the most to gain from treatment (those with advanced fibrosis) had the lowest SVR. Therefore, retreatment with CIFN/RBV may not advance our ability to reduce the overall morbidity and mortality from HCV. Because preliminary data suggests that novel specifically targeted antiviral therapies for HCV (STAT-C) when combined with PEG-IFN/RBV in prior NR have higher SVR rates than those observed in the DIRECT trial, use of CIFN will have a limited role in the future. However, until these newer drugs are approved, CIFN/RBV retreatment can be considered in selected populations. (Reviewer-Richard K. Sterling, MD).
Experts and community gastroenterologists significantly differ in several UC uncertain management issues, ranging from surgical referral for LGD to the belief that maintenance mesalamine prevents colon cancer.

**Background:** There are many areas of uncertainty in the management of ulcerative colitis (UC) patients. **Objectives:** To measure variations in decision making between experts and community gastroenterologists in the management of UC patients. **Design:** National vignette survey. **Participants:** 25 experts and 150 community gastroenterologists. **Methods:** An online survey using 3 case vignettes was utilized to evaluate UC management scenarios. The first vignette described an outpatient with a history of proctitis with a flare partially responsive to 2.4 g oral mesalamine. The second had left-sided colitis, low-grade fever, and symptomatic flare; the third patient was an inpatient with UC flare persisting despite 6 days of IV steroids. Level of agreement was measured within 4 areas of controversy (surveillance and management of dysplasia, use of mesalamine, appropriateness of testing for Crohn’s disease (CD), and management of steroid-refractory inpatient UC). **Results:** Experts were more likely to recommend colectomy for unifocal low-grade dysplasia (LGD; 75% vs 47.5%; \( P = 0.02 \)) and multifocal LGD (100% vs 77%; \( P = 0.003 \)) and were more likely to use narrow band imaging and chromoendoscopy for surveillance. Experts were also more likely (71% vs 53%) to use larger doses (4.8 g) of mesalamine to induce remission and 4-times more likely to use long-term maintenance mesalamine in the belief that it prevents colon cancer. In the evaluation for possible CD, experts were more likely to use abdominal CT scans (33% vs 15%; \( P < 0.001 \)), and were less likely to obtain inflammatory bowel disease (IBD) serology (ANCA, ASCA, omp-C) (8.3% vs 24.1%; \( P = 0.001 \)). In patients with steroid refractory UC, both experts and nonexperts equally favored the use of infliximab over cyclosporine (62% vs 26%; \( P < 0.0001 \)). **Conclusions:** In UC management, there are many areas of uncertainty, and experts and community gastroenterologists differ significantly in patient management in several of these controversial areas. **Reviewer’s Comments:** The final chapter on UC has not been written. Our knowledge is incomplete and as a result, management approaches are variable. This study documents several areas of uncertainty in which experts and community gastroenterologists differ in their approach to patient management. I was pleased to find support for my own views (use of high-dose mesalamine, belief that mesalamine decreases inflammation thereby decreasing colon cancer, rare use of IBD serology, referral of patients with confirmed LGD to surgery, and preference for anti-tumor necrosis factor biologics as first choice over cyclosporine in steroid refractory UC) have expert support. Needless to say, although confident in our views, we are not always right. (Reviewer—Allen L. Ginsberg, MD).
In a large scale, 2-year, randomized controlled trial of different macronutrient composition diets to achieve weight loss, the macronutrient composition (protein, carbohydrate, or fat) did not influence weight loss achieved.

**Background:** It remains unclear as to which macronutrient diet composition can achieve maximum long-term weight loss with metabolic benefits. Studies of protein content, carbohydrate content, and/or fat content have led to conflicting results and are plagued by problems of short duration, small sample sizes, few men included, lack of data on adherence to the diet, and limited generalizability.

**Objective:** To test the effects of the 3 principal macronutrients (protein, carbohydrate, and fat) over a 2-year period, with the recognition that in prior trials, maximum weight loss occurred in the first 6 to 12 months, and weight regain occurred in the second year.

**Design:** Randomized, blinded, controlled, 2-center trial.

**Participants:** 811 overweight adults.

**Interventions:** Subjects were randomized to 1 of 4 diets: (1) low-fat/average-protein; (2) low-fat/high-protein; (3) high-fat/average-protein; and (4) high-fat/high protein. The investigators indicated that in this 2 by 2 factorial design, they were able to test for a range of carbohydrate intake (35% to 65% of total energy). All diets were designed to induce a calorie deficit of 750 kcal per day. A power calculation indicated that 800 subjects would need to be enrolled to detect a weight loss difference of 1.67 kg after 2 years, assuming a 40% drop-out rate. The investigators claimed that they achieved blinding of participants by the use of similar foods for each diet. The primary end point was change in body weight over 2 years. Analysis was by intention-to-treat.

**Results:** The macronutrient composition of the diet had no effect on weight loss, which averaged about 6 kg at 6 months. Most participants started to regain weight by a year. At the end of 2 years, weight loss overall was approximately 3 to 3.5 kg. Weight loss was slightly increased in those who actually completed the trial. About 15% of participants achieved around a 10% reduction in weight. All diets improved lipid-related risk factors and fasting insulin levels. Craving, hunger, and satisfaction with the diets were similar among groups. When looked at closely, the macronutrient goals were only partially achieved, as most subjects reverted to pre-study dietary habits. Adherence to the counselling program predicted successful weight loss, leading the investigators to suggest that behavioral factors are more important than macronutrient composition in achieving weight loss.

**Conclusions:** Any type of diet, when taught with enthusiasm, persistence and support can produce weight loss.

**Reviewer's Comments:** I find the results somewhat depressing; after a major effort with motivated subjects and intensive behavioral support, the vast majority are left with minimal weight loss after 2 years. Different approaches are going to be necessary to achieve a dent in the current obesity epidemic. (Reviewer-Timothy O. Lipman, MD).

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Keywords: Obesity, Dietary Therapy, RCT

Print Tag: Refer to original journal article
Restricting IV fluids in the perioperative period and allowing patients to eat shortly after surgery improves the postoperative course following colonic respective surgery.

**Background:** Several small randomized trials have indicated that a "fast-track" program (no preoperative bowel preparation, restricted perioperative IV fluids, adequate nonnarcotic analgesia, early ambulation, and feeding postoperatively) will improve the clinical course after colon surgery.

**Objective:** To undertake an adequately powered trial to test the utility of a fast-track program.

**Design:** Unblinded, randomized controlled trial.

**Participants:** Patients undergoing open elective colonic resective surgery in one of the participating Swiss hospitals.

**Methods:** Preoperative bowel preparation was not employed, and all of the patients received epidural postoperative analgesia and early ambulation. Those randomized to the fast-track arm received one-half of the IV fluids (1 mL/kg per hour saline solution preoperatively and 5 mL/ kg per hour intraoperatively) given to the control group. They were allowed to drink oral fluids immediately after surgery and had the IV fluids stopped on day 1 postoperatively, at which time they began to consume food and a supplement. The control group continued to receive 2000 mL/day IV fluids for the first 2 postoperative days and began oral fluids and nutrition on that day. The primary outcome was the 30-day complication rate. A sample size calculation indicated that 231 patients needed to be entered into each arm. An interim analysis was planned after one-third of the patients had been entered; if a difference with a $P$ value <0.0019 was observed, the trial was to be stopped. The randomization scheme and concealment of allocation were adequate; the trial was not blinded.

**Results:** At the time of the interim analysis, there had been 16 complications in 76 patients in the fast-track arm and 37 in 75 controls ($P$ value claimed to be 0.0014), and the trial was stopped. The patients in the fast-track arm also had a shorter duration of hospitalization at 5 vs 9 days.

**Conclusions:** The fast-track program reduces the complication rate and shortens the duration of hospitalization.

**Reviewer’s Comments:** The trial was not blinded, so observer bias could have at least inflated the difference in the incidence of complications. The trial was actually stopped prematurely, as the statistical tests are not designed to evaluate the total number of complications, but rather the number of patients with complications. There were multiple complications in some of the patients, as the total number of patients with complications in the 2 arms were 13 and 28 ($P$ =0.006). The trial was designed to do the definitive large study to prove a point. However, it does appear that it was stopped prematurely. (Reviewer-Ronald L. Koretz, MD).

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Keywords: Colonic Resective Surgery, Fast-Track Program

Print Tag: Refer to original journal article
A randomized trial suggested that nurses can perform UGI endoscopy and FS as well as doctors.

**Background:** Some single-center reports suggest that nurses who are trained to do flexible sigmoidoscopy (FS) are equally competent as doctors in this procedure. Very little similar information exists for upper gastrointestinal (UGI) endoscopy.

**Objective:** To compare the performances of nurses and doctors who both do upper endoscopy and flexible sigmoidoscopy.

**Design:** Randomized controlled trial.

**Participants:** 67 doctors and 30 nurses at 23 hospitals in the United Kingdom who do endoscopy as part of their daily activity were included. The patients were those who were referred for one or the other procedure because of symptoms.

**Methods:** Patients who were referred to 1 of the hospitals for UGI endoscopy or FS were randomized, using a central computer, to 1 of the 2 groups before they were even seen. When they appeared for the procedure, the study was explained to them, included revealing the arm into which they had been assigned, and they were asked to participate. Those who did so had the procedure videotaped, provided baseline demographic information, and filled out quality-of-life (QOL) assessments. They were interviewed the next day and information was sought at months 1 and 12. The primary outcome was their QOL at 1 year; a sample size calculation indicated that complete information would be needed on 1300 patients. Secondary outcomes included QOL scores at the different times, patient satisfaction the next day, further GI diagnoses, assessments of the quality of the procedure (by blinded assessors viewing the videotapes), and information about the procedure itself.

**Results:** 4128 patients were randomized, and 1888 agreed to participate; a total of 555 patients were lost to follow-up. For the most part, no significant differences were seen with regard to patient outcome. The quality of the examinations of the esophagus and stomach, but not the duodenum and distal colon, was better in the nurse examinations. The nurses performed more biopsies and employed combination local anesthetic and sedation more often. They also provided more information to the patients, who in turn were more satisfied on the next day. Only a few patients in each arm had other diagnoses made in the subsequent year, suggesting that no important pathology was missed by either group.

**Conclusions:** Nurses can safely and effectively perform UGI endoscopy and FS.

**Reviewer’s Comments:** The randomization scheme may have introduced subtle bias into the study, especially differences in inherent psychologic factors that may have influenced QOL determinations. It was not specified who the "doctors" were; they may not have been trained gastroenterologists, who would have provided the gold standard examination with regard to quality.  (Reviewer-Ronald L. Koretz, MD).

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Keywords: Upper Endoscopy, Nurse Delivered

Print Tag: Refer to original journal article
"Weekend Effect" Exists for Patients Admitted With Bleeding Peptic Ulcers

Weekend Versus Weekday Admission and Mortality from Gastrointestinal Haemorrhage Caused by Peptic Ulcer Disease.
Shaheen AAM, Kaplan GG, Myers RP:
Clin Gastroenterol Hepatol 2009; 7 (March): 303-310

There is an epidemiologic association between being admitted on the weekend, compared to being admitted on a weekday, for bleeding peptic ulcers and death.

**Background:** A number of observational studies have found an association between being admitted on a weekend and having a higher mortality rate (weekend effect). Because bleeding ulcer disease is a common reason for admission, carries a significant mortality rate and requires interventions in the first few days, it would be a good model for exploring this relationship.

**Objective:** To detect a difference in mortality rates between weekend and weekday admission for bleeding ulcer disease and to explore possible explanations for such an association, in particular the availability of endoscopy.

**Design:** Retrospective review of a large hospitalization database.

**Participants:** Patients admitted for bleeding ulcers.

**Methods:** The Healthcare Cost and Utilization Project Nationwide Inpatient Sample database was reviewed to identify patients admitted between 1993 and 2005 with bleeding gastric or duodenal ulcers. This database includes information regarding hospitalization in approximately 20% of non-federal acute care hospitals. Each entry includes a patient identifier, demographic data, hospital transfer status, acuity of admission, up to 15 primary and secondary diagnoses, up to 15 procedures, insurance status, hospital charges, length of stay, and characteristics of the hospital. Data from all those who were admitted emergently or urgently and had undergone endoscopy were eligible. The primary outcome was mortality, both cumulative and for each of the first 7 days. Information regarding demographic features, hospital characteristics, year of admission, comorbidities, receipt of blood (a surrogate for severity of bleeding), and the timing and performance of endoscopy or surgery to treat the bleeding were abstracted.

**Results:** Over 237,000 admissions to >3000 hospitals were identified. Patients admitted on the weekend had longer and more costly admissions and were more likely to undergo surgery. They were also more likely to have had a therapeutic procedure. Endoscopy occurred after a longer delay. Factors associated with mortality included older age, white race, lack of insurance, urban hospitalization (especially in the northeast U.S.), hospitalization between 1993 and 1999 rather than between 2000 and 2005, the presence of comorbidities, and weekend hospitalization. The adjusted odds ratio for a weekend hospitalization was among the lowest odds ratios found (1.08). When the delay in endoscopy was factored into the model, no difference was seen with regard to the risk of a weekend admission death.

**Conclusions:** While weekend admission was associated with an increased mortality risk, the responsible factor(s) remain undefined; the lack of an early endoscopy is not likely to be responsible.

**Reviewer's Comments:** Association cannot establish causation. The factors responsible for the weekend effect are likely related to characteristics unique to the patient or hospital. (Reviewer-Ronald L. Koretz, MD).

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Keywords: Gastric Ulcer, Duodenal Ulcer, Endoscopy

Print Tag: Refer to original journal article
Weekend Effect Exists for Patients Admitted With UGI Bleeding

Outcomes of Weekend Admissions for Upper Gastrointestinal Hemorrhage: A Nationwide Analysis.

Ananthakrishnan AN, McGinley EL, Saeian K:
Clin Gastroenterol Hepatol 2009; 7 (March): 296-302

Patients admitted on the weekend with upper gastrointestinal bleeding have a greater likelihood of dying.

**Background:** A recognized association exists between being admitted on a weekend, in comparison to a weekday, and having a higher risk of dying for a number of disease states, a phenomenon known as the "weekend effect." It is less well established for patients with upper gastrointestinal (UGI) bleeding.

**Objective:** To determine if the weekend effect holds true for UGI bleeding, to assess the difference in the use of endoscopy in patients admitted on a weekday versus a weekend, and to look for an association with the hospital teaching status.

**Design:** Retrospective review of a large database of hospitalizations.

**Participants:** Patients admitted to one of the hospitals participating in the Healthcare Cost and Utilization Project Nationwide Inpatient Sample database.

**Methods:** The database is described in the accompanying abstract. Patients admitted in 2004 and diagnosed as UGI bleeders were identified and separated into those with variceal and non-variceal causes. The primary outcomes were in-hospital mortality, length of stay, and total charges. Data extracted included demographic features, the performance and timing of endoscopy, primary outcomes, comorbidities, in-hospital complications, and other interventions (surgery, transjugular intrahepatic portosystemic shunt).

**Results:** Over 80,000 admissions for non-variceal bleeding and 5988 admissions for variceal bleeding were identified. In both groups, approximately 25% were admitted on the weekend. Patients admitted on the weekdays were slightly more likely to be >65 years old. In the group with non-variceal bleeding, factors associated with mortality included older age, comorbidities, in-hospital complications (especially renal or respiratory failure), and weekend admission. Weekend admission was associated with a decreased likelihood of having an endoscopy. The risk for bleeding associated with a weekend admission persisted after the model was corrected for the performance of endoscopy. In those with variceal bleeding, admission to a teaching hospital on the weekend was associated with a higher likelihood of undergoing endoscopy while those admitted to a nonteaching hospital were less likely to have this procedure. The weekend effect was not observed.

**Conclusions:** The weekend effect was only observed for non-variceal bleeding.

**Reviewer's Comments:** Another study assessing the weekend effect in patients with bleeding ulcers is summarized elsewhere in this issue of *Practical Reviews in Gastroenterology*. It is not clear that the weekend effect was absent in the variceal bleeders. The actual number of patients was small and the mortality rate was higher in the weekend group (11.7% vs 11.0%); in other trials, such small differences have become significant when larger numbers have been analyzed. As was seen in this companion study, the availability of endoscopy was not implicated in the phenomenon. (Reviewer-Ronald L. Koretz, MD).

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Keywords: Non-Variceal Bleeding, Variceal Bleeding, Mortality

Print Tag: Refer to original journal article
Enhanced Symptoms of GERD Associated With GNb3 C825T.

Gastroesophageal Reflux Disease Is Associated With the C825T Polymorphism in the G-Protein b3 Subunit Gene (GNβ3).

de Vries DR, ter Linde JJM, et al:

Am J Gastroenterol 2009; 104 (February): 281-285

GERD is associated with the GNb3 825T allele and an increased signal transduction upon GPCR activation resulting in an enhanced perception or reflux events.

**Objective:** To determine whether increased esophageal sensitivity to acid reflux may be related to polymorphisms (GNb3 C825T) in the G-proteins, which mediate these responses.

**Materials/Methods:** 365 patients were prospectively enrolled with chronic heartburn, regurgitation, or noncardiac chest pain. Patients were considered to have gastroesophageal reflux disease (GERD) if they had an abnormal 24-hour pH score and/or a positive symptom association for heartburn (HB) or regurgitation (ie, symptom index [SI] ≥50% or symptom association probability [SAP] ≥95%). Patients were separated into categories (All GERD patients, GERD pathology acid exposure, GERD physiologic acid exposure, GERD (-) SAP, GERS (+) SAP, GERD only symptoms, functional dyspepsia FD, and irritable bowel syndrome [IBS]). A total of 373 healthy individuals acted as controls. Genotyping was performed to determine GNb3 C825T polymorphisms (C=wild type, T= polymorphism).

**Results:** Overall, the heterozygous genotype GNb3 C825T CT was more prevalent in GERD patients versus healthy controls (OR, 1.43). Specifically, GERD patients with symptoms associated with physiologic reflux (OR, 1.59) and GERD patients with a positive symptom association (OR, 1.5) had a higher likelihood of having this heterozygous genotype. GERD patients without FD or IBS had the highest prevalence for this genotype (OR, 1.66).

**Conclusions:** These studies suggest that the enhanced symptoms of GERD are associated with the GNb3 C825T. It is possible that the increased perception of GERD results from increased signal transduction upon G-protein activation.

**Reviewer’s Comments:** This fascinating study gives insight as to why there may be some individuals with GERD who are very sensitive to acid reflux. These individuals may have the GNb3 C825T polymorphism that may increase signal transduction as a result of G-protein activation, which then results in the lowering of afferent, acid-sensitive sensory thresholds known as transient receptor potentials (TRPV1) in the esophagus. This lowering of the receptor potential results in increased afferent sensory transmission to the central nervous system. Other inflammatory mediators such as, IL8, prostaglandins, and bradykinins can also activate G-proteins and increase sensitivity. (Reviewer-Roy K.H. Wong, MD).

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Keywords: GERD, GNb3 825T allele, C825T Polymorphism

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DNA content abnormalities occur with equal frequency in columnar epithelium with and without goblet cells, which suggests that both type columnar epithelium have a similar propensity for neoplastic change.

**Objective:** To determine whether there is a difference in neoplastic potential between esophageal columnar goblet versus non-goblet-containing tissue utilizing flow cytometry.

**Materials/Methods:** Pathology slides of 68 patients with Barrett’s esophagus were selected. Of these, 22 patients had columnar epithelium without goblet cells (all short segment Barrett’s esophagus [SSBE]) and 46 with goblet cells of varying density (all long segment Barrett’s esophagus [LSBE]). Controls were patient slides of normal gastric mucosa. Using image cytometry, the following measurements were made: DNA index (DI) equal to 0.9 to 1.1 (diploid) or DI >1.1 (aneuploid), with higher numbers representing greater degrees of aneuploidy), DNA content heterogeneity index (HI), and 5N (5N-exceeding cells [5N-EC]) equal to the percentage of cells exceeding 5N.

**Results:** When comparing patient slides of columnar epithelium with and without goblet cells, there was no difference in the cell DNA content or aneuploidy as measured by the DI, HI, or 5N-EC. When compared with the gastric mucosal control biopsies, the columnar tissue had significantly more cell DNA content and aneuploidy.

**Conclusions:** DNA content abnormalities occur with equal frequency in columnar epithelium with and without goblet cells. These findings suggest that columnar epithelium without goblet cells may have similar propensity for neoplastic change as patients with goblet cells.

**Reviewer’s Comments:** These findings are contrary to what has been taught. Additionally, it is interesting that in this study, patients with columnar epithelium without goblets cells had only SSBE. We also know that patients with SSBE have less esophageal acid exposure patients with LSBE. Although never proven completely, there is a suggestion that LSBE patients have a greater risk of adenocarcinoma. (Reviewer-Roy K.H. Wong, MD).

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Keywords: Metaplastic, Columnar Epithelium Aneuploidy, Goblet Cells

Print Tag: Refer to original journal article
Increased Risk of CD Relapse in Young Patients With Small Intestinal Stricturing Dz

Prospective Study of Long-Term Results and Prognostic Factors After Conservative Surgery for Small Bowel Crohn's Disease.

Sampietro GM, Corsi F, et al:
Clin Gastroenterol Hepatol 2009; 7 (February): 183-191

Risk factors for surgical recurrence in small bowel CD are young age, upper jejunoileal location, stricturing disease, and small bowel wall thickening 12 months after surgery.

Objectives: To evaluate the perioperative morbidity and mortality, long-term rate of surgical recurrence, and related risk factors after conservative surgery for small bowel Crohn's disease (CD).

Design: Prospective analysis. Patients: 393 of 503 consecutive CD patients who had small bowel surgery between 1993 and 2007 were included, while patients with colonic disease were excluded.

Methods: Postoperative complication rates and cumulative surgical recurrence rates were calculated. Statistical analysis of clinical variables, such as age at diagnosis, disease location, disease type (stricturing versus penetrating), gender, family history, smoking, extraintestinal manifestations, type of preoperative therapy, C-reactive protein, hemoglobin, and serum albumin, looking for a prognostic association was performed.

Results: 318 small bowel resections and 367 stricturoplasties were performed with no deaths and a complication rate of 5.6% (22/393). None of the variables studied was prognostic for postoperative complications. The cumulative 10-year surgical recurrence rate was 35%. Increased risk of recurrence was found in younger age persons (HR, 2.4; P =0.03), upper jejunoileal location (HR, 2.5; P =0.004), stricturing behavior (HR, 2.2; P =0.01), and small bowel wall thickening 12 months after surgery (HR, 4.5). Immunomodulator therapy did not reduce the risk of long-term surgical recurrence.

Conclusions: Young patients with upper small intestinal stricturing disease are at increased risk of CD relapse.

Reviewer's Comments: Following intestinal resection or stricturoplasty, the cumulative 10-year rate of recurrence is 35%, with higher risks in younger patients with high jejunoileal stricturing disease. Immunomodulators did not reduce the risk of recurrence; however, we are given no data on dosage of 6MP used or of levels of the therapeutic moiety, 6TGN. More aggressive therapy with dose escalation and 6MP metabolite monitoring as well as earlier use of anti-tumor necrosis factor biologics seems warranted in these patients who are at higher risk of recurrence and additional hospitalization and surgery. (Reviewer-Allen L. Ginsberg, MD).

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Keywords: Crohn's Dz, Conservative Surgery

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A transparent hood for the tip of the colonoscopy reduces procedure time.

**Background:** Any technique to reduce the difficulty and time in the performance of a high demand procedure is desirable.  
**Objective:** To evaluate the effectiveness of a transparent hood on the tip of the colonoscope in improving procedure efficiency.  
**Design:** Prospective, randomized, controlled study.  
**Participants:** Consecutive patients undergoing complete colonoscopic evaluation for screening or surveillance.  
**Methods:** Patients were randomized into 2 groups composed of a group having the procedure with a transparent hood on the tip of the scope and a group examined without the hood. Six proceduralists did the procedures using standard techniques. The proceduralists were stratified into moderate and highly experienced groups.  
**Interventions:** Colonoscopy with and without a clear hood attached.  
**Results:** The total study population totalled 592. The mean time to cecal intubation was 10.2 minutes ± 12.5 minutes in the hood group and 13.4 ± 15.8 minutes in the non-hood group (P =0.0241). The grade of patient-perceived discomfort was lower in the hood group, but success of cecal intubation and polyp detection was similar. The shortened cecal intubation time in the hood group was most pronounced in the expert endoscopy group.  
**Conclusions:** A clear hood placed on the tip of the colonoscope reduces cecal intubation time and decreases patient discomfort.  
**Reviewer's Comments:** The hood used in this study only extended 2 mm beyond the tip of the scope and is unlikely to cause any harm. Whether a longer hood would be more helpful is unclear. This may be a technique that is best applied when a difficult colonoscopy is encountered due to a tortuous colon. Further studies will be needed to confirm the best utilization of this device. (Reviewer-J. Mark Lawson, MD).
Colonoscopic perforations remain uncommon, occurring in <0.1%. This rate has not changed over time.

**Background:** Prior studies regarding the incidence of colonoscopic perforation have been limited by small sample size.

**Objective:** To use a large population-based study to evaluate the frequency and risk factors for colonic perforation.

**Design:** Retrospective, population-based, cohort-based study, with nested case-controls.

**Participants:** 277,434 patients undergoing colonoscopy and identified to be ≥18 years of age enrolled in the MED-Cal program from 1995 to 2005.

**Methods:** Using Current Procedural Terminology (CPT) coding, patients were identified from the Medi-Cal database. The first part of the study identified cases of perforation within 7 days of the procedure with comparison to a cohort controls not undergoing colonoscopy for comparative risk. The second part of the study evaluated risk factors for perforation in the affected cohort with comparison to a cohort having uncomplicated colonoscopy.

**Results:** After 277,434 colonoscopies were reviewed, 228 perforations have been identified for a 7-day incidence of 0.082%. Multivariate analysis showed that perforation was statistically more common in patients with advanced age, significant comorbidity, obstruction as an indication, and performance of invasive procedures during the examination.

**Conclusions:** The risk of colonoscopic perforation remains low and has been stable over time.

**Reviewer’s Comments:** In multiple studies, the perforation rate for colonoscopy has hovered in the 0.2% to 0.08% range. Increased risk in the elderly patient with multiple medical problems is no surprise, although the lack of association in this study with polypectomy is. Other papers have noted an increased incidence of perforations in situations where the proceduralists performs <200 cases a year adding to the evidence that experience and training matters. (Reviewer-J. Mark Lawson, MD).

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Keywords: Colonoscopy Perforation

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Pre-LT serum Na does not have a significant impact on post-LT survival but can be associated with longer ICU and hospital stay.

**Background:** Hyponatremia is often seen in cirrhotic patients with portal hypertension and hepatic dysfunction and is correlated with increased mortality. Recently, hyponatremia has been added to the model for end stage liver disease (MELD) score in prioritizing patients awaiting liver transplantation (LT). However, giving priority to those with hyponatremia and its impact on post-LT survival is unknown.

**Objectives:** To investigate the effect of hyponatremia at the time of LT on post-LT morbidity and mortality.

**Design:** Retrospective study.

**Participants:** Those included in the National Institute of Diabetes and Kidney Disease Liver Transplantation Database (NIDDK-LTD) database undergoing LT between 1990 and 1994 from 4 large LT centers and those in the Models for Optimal Liver Transplant Outcomes (MOLTO) who underwent LT between 1994 and 2000 were combined. All subjects were primary LT, >16 years old, and did not have acute liver failure or hepatocellular carcinoma (HCC).

**Methods:** Patients were divided into 3 groups: normal sodium (Na >135 mEq/L); mild hyponatremia (125 to 134 mEq/L); and severe hyponatremia (Na <125 mEq/L). Patients were further classified into the following diagnostic categories: alcoholic; cholestatic; viral; and other liver diseases. The primary outcomes were 30- and 90-day mortality and morbidity (number of days in ICU and hospital, and incidence of central pontine myelinolysis (CPM)).

**Results:** Out of 2175 subjects, 68.7% had normal Na, 615 (28.3%) had mild hyponatremia, and 65 (3%) had severe hyponatremia. The 3 groups were similar in age (50 years) and disease etiology. Those with hyponatremia were more likely male and to have more severe liver disease (higher bilirubin, creatinine, and international normalized ratio [INR]). Serum Na had no impact on 30- or 90-day morbidity. Those with severe hyponatremia had slightly longer ICU and total hospital stay compared to those with normal Na. There were only 10 patients who developed CPM (0.5%), which did correlate with Na concentrations ($P <0.01$).

**Conclusions:** Pre-LT serum Na does not have a significant impact on post-LT survival, but can be associated with longer ICU and hospital stay. Therefore, incorporating serum Na into organ allocation may not adversely affect overall post-LT outcome.

**Reviewer's Comments:** Because pre-LT hyponatremia is associated with increased wait list mortality, especially if MELD scores are <25, many transplant regions give additional MELD points to give these patients priority on the transplant list. Although the current study did not provide morbidity or mortality beyond 90 days following LT, it does support our current practice that additional MELD points for pre-LT hyponatremia is not at the expense of post-LT short-term (up to 90-day) mortality and overall outcomes. (Reviewer—Richard K. Sterling, MD).

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Keywords: Liver Transplantation, Hyponatremia, Outcomes

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**Low Rates of ETVr in Nucleoside-Naïve Patients**

*Long-Term Monitoring Shows Hepatitis B Virus Resistance to Entecavir in Nucleoside-Naïve Patients Is Rare Through 5 Years of Therapy.*

Tenney DJ, Rose RE, et al:

Hepatology 2009; 49 (May): 1503-1514

There are low rates of entecavir resistance in nucleoside-naïve patients during 5 years of therapy.

**Background:** Long-term benefits of oral nucleoside chronic hepatitis B virus (HBV) antiviral therapy are limited by the development of resistance. Barriers to antiviral resistance include potency of suppressing viral replication, a genetic barrier (number of mutations that will result in resistance, and the replication fitness of the virus. Unlike lamivudine (LAM), which has a high rate of resistance (20% annually), newer agents, such as Entecavir (ETV) have lower rates of resistance but long-term data are lacking.

**Objectives:** To describe the results from comprehensive resistance monitoring in patients with chronic HBV who were treated with ETV for up to 5 years.

**Design:** Prospective analysis of a longitudinal cohort.

**Participants:** Patients from 6 phase 2 and 3 trials on the safety and efficacy of ETV.

**Methods:** Monitoring included genotypic analysis of isolates from all patients at baseline and when HBV DNA was detectable by polymerase chain reaction (PCR) (>300 copies/mL) from years 1 to 5 of therapy. In addition, genotyping was performed on isolates from patients with viral breakthrough (>1 log increase in HBV DNA). In vitro phenotypic testing for ETV susceptibility was determined for those with breakthrough and for HBV containing novel substitutions emerging during treatment.

**Results:** During the first year of treatment, 663 nucleoside-naïve patients were monitored. Of these, 81% had undetectable HBV DNA. In the second year, 278 patients remained on therapy of which 232 (83%) remained HBV DNA negative. By year 5, 100/108 (93%) of patients on therapy remained HBV-DNA negative. The cumulative probability of genotypic resistance to ETV (ETVr) and genotypic ETVr associated with viral breakthrough were 1.2% and 0.8%, respectively. In contrast, those who had LAM resistance had a 5-year cumulative probability of genotypic ETVr and ETVr related to viral breakthrough of 51% and 43%, respectively. Only 4 patients who were HBV DNA <300 copies/mL developed ETVr.

**Conclusions:** There are low rates of ETVr in nucleoside-naïve patients during 5 years of therapy. However, those with prior LAM resistance have a high rate of ETVr.

**Reviewer's Comments:** These data support the long-term use of ETV in the treatment of nucleoside-naïve patients with chronic HBV. However, because of the high rate of ETV resistance in those with existing LAM resistance, Tenofovir is the preferred agent in those who have failed LAM. So for now, ETV or Tenofovir should be used as first line therapy for nucleoside-naïve patients and Tenofovir for LAM experienced patients.

(Reviewer-Richard K. Sterling, MD).

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**Keywords:** Hepatitis B Virus Resistance, Entecavir

**Print Tag:** Refer to original journal article