Can a Duodenal-Jejunal Sleeve Device Induce Short-Term Weight Loss?

Open Label, Prospective, Randomized Controlled Trial of an Endoscopic Duodenal-Jejunal Bypass Sleeve Versus Low Calorie Diet For Pre-Operative Weight Loss In Bariatric Surgery.

Tarnoff M, Rodriguez L, et al:

Surg Endosc 2009; 23 (March): 650-656

A high risk-of-bias, low methodological quality clinical trial suggests that a 60cm long endoscopically placed duodenal-jejunal sleeve may induce short-term weight loss prior to bariatric surgery in obese individuals.

Background: A new endoscopically and fluoroscopically placed duodenal-jejunal bypass device developed for weight loss is a 60cm fluoropolymer sheath, which expands and anchors in the duodenal bulb via barbs. A prior small uncontrolled trial found short-term weight loss in obese recipients.

Objective: To test the duodenal-jejunal sleeve in a randomized controlled trial.

Design: Open label, claimed randomized, small, non-blinded controlled clinical trial

Participants: 39 subjects who planned to undergo bariatric surgery and needed pre-operative weight loss.

Methods: Selected subjects underwent endoscopic placement of the device. Controls did not receive the device. Both groups underwent baseline counseling regarding diet, exercise, and behavior modification. Primary endpoint was percentage of excess weight lost at 12 weeks.

Results: Sleeve insertion was attempted in 26 subjects, but was successful only in 25. Of subjects, 14 were assigned to the control group. Only half of the endoscopic sleeve subjects appear to have been randomized and the other half were assigned directly. At 12 weeks, 20 device recipients completed the protocol and achieved a statistically significant mean percentage excessive weight loss of 22.1±8% compared with only 5.3±6.6% (P =0.02) in the 4 controls who completed the study. Of subjects, 92% of implanted patients and 21% of controls achieved ≥10% excess weight loss reduction - a significant difference. All sleeves were removed successfully at 12 weeks. There was no evidence of pancreatic-biliary obstruction. The sleeve was removed early in 5 patients - 3 for GI bleeding, 1 for anchor migration, and 1 for sleeve obstruction.

Conclusions: The authors conclude that the duodenal-jejunal bypass sleeve appears to be effective for short-term weight loss. They note that longer-term sham controlled trials are underway.

Reviewer's Comments: The authors note the long learning curve for sleeve deployment. They suggest that the success of the sleeve may be due to the transient abdominal pain and increased satiety produced in many. This trial is a high-risk of bias, low methodological quality trial. High risk-of-bias trials generally find more beneficial outcomes. Methodological deficiencies in this trial include: 1) although claimed to be randomized, it was not; many of the sleeve recipients were assigned to that group directly, for non-described reasons; 2) there was no documentation of concealed allocation; 3) it was not blinded; 4) there was no power or sample size calculation; 5) not all subjects were included in the analysis - just those who completed the trial, making the analysis "per protocol" rather than intention-to-treat. Finally, by not providing any assistance to the diet control group other than a base-line consultation, the authors set up a control group that was bound to fail. (Reviewer-Timothy O. Lipman, MD).

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Keywords: Obesity, Endoscopic Treatment

Print Tag: Refer to original journal article
Brown Fat Exists!

Brown Adipose Tissue--When It Pays to Be Inefficient.
Celi FS:


An editorial describes the physiologic role of brown fat, which is to uncouple oxidative phosphorylation, expend energy, and produce heat.

**Background:** In the treatment of obesity, most efforts have focused on the intake side of the equation - reduce food intake and lose weight. Unfortunately, this approach has not been very effective. Increasing energy expenditure has had even less success - increasing physical activity is difficult to sustain and produces minimal results while pharmacological therapy has not been successful at all. Brown fat, or brown adipose tissue, if it could be utilized, might be a target for increasing energy expenditure. Brown fat has been studied mostly in rodents. Human brown fat, located predominately in the intrascapular area in human neonates, mostly disappears shortly after birth and has been considered vestigial and devoid of a physiologic role in humans. In small animals, brown fat takes up free fatty acids and glucose from the circulation and releases chemical energy in the form of heat by uncoupling oxidative phosphorylation, making the process of respiration quite inefficient. But in this lies the potential benefit - instead of storing energy in normal adipose tissue, brown fat expends energy. Brown fat in small animals and human newborns maintains core temperature.

**Design:** Editorial discussing background and 3 articles regarding brown adipose tissue. **Discussion:** The presence of small deposits of brown fat in adult human cervical regions has been recognized for many years, and actually has been considered a nuisance factor in PET-CT scanning, lighting up otherwise normal tissue. Cold temperatures activate brown fat. The 3 New England Journal of Medicine articles took advantage of the PET-CT findings and cold activation to study brown fat in humans and demonstrate potential long-term clinical relevance. The first study demonstrated that brown fat in normal adult humans can be rapidly activated by cold temperatures. The second study found an inverse correlation between the activity of brown fat and age, body-mass index (BMI), and fasting glucose levels; that is, there was a direct relationship between activation of brown fat and measures of good health. The third study found that the activity of brown fat correlated inversely with the BMI and percentage of body fat and directly with energy expenditure during rest. **Conclusions:** These studies demonstrate a proof of principle: that active brown fat exists in humans, that it can be activated, and that it might be used in the future for environmental or pharmacological interventions, aimed at modulating energy expenditure, in our current obesity epidemic. **Reviewer's Comments:** These studies do not mean that the way to weight loss are cold showers or dips in frigid lakes, especially since obesity per se seemed to inhibit activation of the brown fat. This editorial provides lucid insights into the function, current knowledge, and future potential of studies of brown adipose tissue. (Reviewer-Timothy O. Lipman, MD).
Of Many Probiotics, Only One May Be Beneficial in Tx of IBS

The Utility of Probiotics in the Treatment of Irritable Bowel Syndrome: A Systematic Review.

Brenner DM, Moeller MJ, et al:

Am J Gastroenterol 2009; 104 (April): 1033-1049

A systematic review of randomized controlled trials investigating the utility of probiotics for the irritable bowel syndrome found only one that might be beneficial, but noted overall lack of appropriate study design and failure to report adverse events.

Background: Despite the widespread prevalence of Irritable Bowel Syndrome (IBS), treatment remains problematic because few therapies have been documented as effective. There has been recent interest in the use of probiotics - living microorganisms with purported health benefits when ingested - for the treatment of IBS.

Objective: To perform a systematic review of the randomized controlled trials (RCTs) of probiotics for the treatment of IBS to determine the efficacy, safety, and tolerability of these agents.

Design: Systematic review.

Methods: 4 databases as well as meeting abstracts, article references, and guidelines were searched for articles in English which met the following criteria: RCTs with 1) adult study populations meeting defined criteria for IBS; 2) use of a placebo comparator; and 3) appropriate outcomes.

Results: 16 RCTs met selection criteria. It was hoped to perform meta-analyses, but these were not possible given significant heterogeneity in study design, variance in primary and secondary end points, and lack of dichotomous outcomes. Of 16 identified papers, included were 6 combination probiotic products and 7 individual probiotics. The review gives individual descriptions of the 16 identified papers. One probiotic, Bifidobacterium infantis 35624 (patented name: Bifantis and sold as Align® by Proctor and Gamble, Cincinnatti, OH), in 2 appropriately designed studies, showed significant improvement in the composite score for abdominal pain and discomfort, bloating and distension, and/or bowel movement difficulty compared with placebo. The authors found that most RCTs did not follow appropriate study design and did not report adequately on adverse events.

Conclusions: The authors conclude that there is inadequate data to comment on the efficacy of probiotics for IBS, and future studies need appropriate design methodology. One probiotic, B infantis 35624, may successfully treat the symptoms of IBS over a 4-week period.

Reviewer's Comments: I have reviewed previously both of the cited studies of B infantis 35624 for Practical Reviews. In August 2005, I noted that the first study was small, underpowered, with multiple endpoints, and no primary hypothesis. For the second study, reviewed March 2007, I found the results modest and wondered, even if true, what should be done after 4 weeks - continue the probiotic or stop, since it was only a 4-week study. I think that there is little to no good clinical science supporting the use of probiotics for IBS. If patients are interested in probiotics, and reportedly they are, Bifodobacterium infantis 35624 may provide benefit, without knowing if there is any harm. The bottom line: the concept of probiotic use for IBS remains intriguing, but lacks proof. Neither I nor this review's authors have any financial interest in Bifodobacterium infantis 35624. (Reviewer-Timothy O. Lipman, MD).

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Keywords: Probiotics, Irritable Bowel Syndrome

Print Tag: Refer to original journal article
The recommended use of corticosteroids in the management of severe alcoholic hepatitis remains controversial.

Background: Alcoholic hepatitis continues to be a major health problem in the United States. It is generally considered to be the precursor of alcoholic cirrhosis and contributes importantly to premature mortality due to end-stage liver disease and hepatocellular carcinoma. Liver transplantation is almost invariably deferred in patients who have not been abstinent for the preceding 6 months.

Objective: To review medical progress in the pathogenesis and management of alcoholic hepatitis.

Methods: Expert opinion review of the current approach to alcoholic hepatitis. Disclosure: Drs. Lucey, Mathurin, and Morgan report that alcoholic hepatitis may be present in 20% of patients with alcoholism. The well-known common clinical and laboratory features, which include jaundice, aspartate aminotransferase (AST) levels >2 times alanine aminotransferase (ALT) levels, but not >300 IU/mL, polymorphonuclear leukocytosis, elevated international normalized ratio (INR), and elevated creatinine levels, the latter signaling the onset of hepatorenal syndrome in some patients, are reviewed. Liver biopsy is not required for diagnosis but cholestasis which is often present is not seen in nonalcoholic steatohepatitis (NASH), which may otherwise resemble alcoholic hepatitis. The putative roles of lipopolysachharide-endotoxin, oxidative stress, TNF-α and Fas-mediated apoptosis are described. Management of alcoholic hepatitis begins with abstinence, treatment of complications, 1.5g/kg body weight protein feedings (even in the face of hepatic encephalopathy), and vitamin supplementation. Use of prednisolone in a dose of 40mg daily for 28 days is recommended for patients with Maddrey's discriminant function (DF) of ≥32 or a MELD score of ≥21 in patients without sepsis, gastrointestinal bleeding, or hepatorenal syndrome. Use of pentoxifylline also is recommended when corticosteroids cannot be used but this is based on a single study which has yet to be confirmed. Neither infliximab nor etanercept can be recommended. For patients who do not respond to management and have been drinking up to the time of diagnosis, the authors suggest re-evaluation of deferral for liver transplantation. Conclusion: Alcohol abstinence is the key to recovery.

Reviewer's Comments: Use of the Maddrey DF remains controversial, at least in part because in the original Maddrey study, mortality within 48 days after completion of the study in the corticosteroid-treated group was ignored in concluding that the DF was useful. Had those deaths been included, the DF would have been non-predictive. Thus, continuing emphasis on the DF seems anachronistic at best and unsupported at worst. The authors also seem to underestimate the association of alcoholic hepatitis with cirrhosis. In my experience at a Veteran's Administration Medical Center, about 70% of patients with alcoholic hepatitis had underlying cirrhosis and it was this group most likely to succumb to the acute disease. (Reviewer-Raymond S. Koff, MD).

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Keywords: Alcoholic Hepatitis, Corticosteroids, Pentoxyfilline, TNF-α

Print Tag: Refer to original journal article
C282Y/H63D Compound Heterozygotes, Iron Overload-Associated Disease

HFE C282Y/H63D Compound Heterozygotes Are at Low Risk of Hemochromatosis-Related Morbidity.

Gurrin LC, Bertalli NA, et al:

Hepatology 2009; 50 (July): 94-101

In individuals who are HFE C282Y/H63D compound heterozygotes iron-overload related disease is rare.

**Background:** In a previously published population-based cohort study, iron overload disease has been identified in 28% of Australian men and just 1.2% of women who are C282Y homozygotes. The C282Y/H63D compound heterozygous state was found in 2.4% of the population tested but the risk of disease has not been prospectively studied.

**Objective:** To identify prevalence of elevated iron indices and iron overload disease in these compound heterozygotes compared to “wild type” individuals with neither HFE gene mutation.

**Participants/Design:** 41,514 persons recruited in the Melbourne cohort study between 1990 and 1994.

**Methods:** Of subjects, 31,192 were HFE genotyped beginning in 2004. All 203 participants identified with C282Y homozygosity, a random sample of 180 with compound heterozygosity, and 330 without mutations were followed for an average of 12 years to a mean age of 65 years and were clinically examined for disease features, tested for iron indices, namely serum ferritin (SF) and transferrin saturation (TS), and evidence of iron overload disease. Iron overload disease was defined, as previously, by the presence of 1 of the following: hepatocellular carcinoma (HCC), cirrhosis or hepatic fibrosis, abnormality of the second and third metacarpophalangeal joints, or by physician’s diagnosis of hemochromatosis with either provisional or documented iron overload. The influence of comorbid factors, such as body mass index (BMI), alcohol consumption, and menopausal status, on aminotransferase levels was examined.

**Results:** Age, BMI, and alcohol consumption were similar in compound heterozygotes compared to wild-type. Mean SF and TS were higher at baseline and follow-up in men and postmenopausal women who were compound heterozygotes but SF in premenopausal women did not differ from that found in the wild type subjects. On the other hand, SF increased significantly in premenopausal women in both groups on follow-up but did not change importantly in men or postmenopausal women. Prevalence of hemochromatosis disease features was generally similar in compound heterozygotes and wild type subjects. Of 82 male compound heterozygotes only 1 had documented iron overload disease compared to none of 95 females compound heterozygotes. Only 1 of the 330 wild type subjects had iron overload-related disease.

**Conclusions:** In compound heterozygotes, iron-overload disease is rare.

**Reviewer’s Comments:** This study provides strong support for the notion that although C282Y/H63D compound heterozygosity is present in 2.4% of an Australian or northern Europe-borne population, iron overload disease is rarely found. Of interest, in their previous study of C282Y homozygotes, the 45% of men and 8% of women with SF levels >1000 μg/L had an increased risk of disease. In this analysis of compound heterozygotes, only 2 persons had such levels. This low prevalence of high ferritin levels may be associated with the rarity of iron overload disease. (Reviewer-Raymond S. Koff, MD).

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Keywords: HFE Genotypes, Iron Overload Disease

Print Tag: Refer to original journal article
The V444A polymorphism is a significant risk factor for intrahepatic cholestasis of pregnancy while the ABCB11 mutations occur less frequently.

**Objective:** To explore the role of the ABCB11 gene coding for the bile salt export protein pump (BSEP) which may be abnormal in intrahepatic cholestasis of pregnancy (ICP).

**Design:** Prospective, controlled cohort study.

**Participants:** Patients in 2 cohorts (n=158 and 333) with ICP were analyzed for mutations and polymorphisms. Also recruited were 261 controls without ICP.

**Interventions:** DNA was obtained from blood samples sequenced by standard molecular methods to look for 5 common mutations in the ABCB11 gene (E297G, N591S, D482G, D676Y and G855R) and genotyping of the V444A polymorphism. Structural analysis of BSEP and Sav1866 (a multidrug resistance protein homologous to BSEP) were determined with software programs based upon the proteins' sequences.

**Results:** E297G mutation was found in 4 patients, N591S in 2 patients, and D482G in 1 patient. D676Y and G855R mutations were not found in any patients. The V444A polymorphism was found to be associated with ICP with the CC homozygotes have the strongest risk (Odds Ratio [OR] 2.8, \( P < 0.0001 \)).

**Conclusions:** The V444A polymorphism is a significant risk factor for ICP while the ABCB11 mutations occur less frequently. These mutations are felt to result in changes in the protein folding of the BSEP protein.

**Reviewer’s Comments:** An interesting molecular study that explores a condition seen uncommonly by adult hepatologists and gastroenterologists (<1% of births). Because of the rarity of this condition, it is not cost effective to screen pregnant women routinely for these genetic abnormalities. ICP does seem to be familial in certain cases, so in those circumstances, molecular analysis with genotyping might be efficacious. (Reviewer-Ingram M. Roberts, MD).

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Keywords: Intrahepatic Cholestasis, Pregnancy

Print Tag: Refer to original journal article
Heredity appears to play a significant role in the development of nonalcoholic fatty liver disease.

**Background:** The most common chronic liver disease in the United States is nonalcoholic fatty liver disease (NAFLD). Although the etiology of this disease is not known it is believed to be multifactorial with a significant component being genetic predisposition.

**Objective:** To test the hypothesis that NAFLD is highly heritable.

**Participants/Methods:** A group of 33 overweight children with biopsy proven NAFLD and 11 overweight children who did not have NAFLD served as probands for this study. First, second, and third degree relatives were studied with magnetic resonance imaging (MRI) to quantify the liver fat fraction. A liver fat fraction of ≥5% was considered to be a fatty liver. Subjects with causes of fatty liver other than NAFLD were excluded from the study. Narrow-sense heritability estimates for fatty liver (dichotomous) and fat fraction (continuous) were calculated using variance components analysis adjusted for covariate effects.

**Results:** Siblings and parents of overweight children who did not have NAFLD had an incidence of fatty liver of 17% and 37%, respectively. In relatives of those children who had NAFLD there was a significantly higher incidence of fatty liver with 78% of parents and 59% of siblings having NAFLD. There was a significantly stronger correlation of liver fat fraction to BMI in families of children with NAFLD than in those who did not have NAFLD. Adjusted for age, sex, race, and BMI, heritability of fatty liver was 1.000 and of liver fat fraction was 0.386.

**Conclusions:** Family members of overweight children with NAFLD appear to be at high risk for the development NAFLD. Based on the results of this study it would appear that familial factors are a major determinant of whether an individual has NAFLD. The results of this study would suggest the need for more studies examining the complex relationship between genes and environment in the development and progression of NAFLD.

**Reviewer's Comments:** This interesting paper showed that the parents and siblings of children with NAFLD are at increased risk for the development of NAFLD suggesting that heredity plays a significant role in the development of this disease. (Reviewer-Michael M. Phillips, MD).

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Keywords: Nonalcoholic Fatty Liver Disease, Heritability

Print Tag: Refer to original journal article
Smoking appears to increase the risk of severe fibrosis in chronic hepatitis C but not in chronic hepatitis B.

**Background:** Recent studies have suggested a relationship between smoking, insulin resistance, steatosis, and fibrosis in patients with chronic hepatitis C (CHC), while no data are presently available regarding a relationship with chronic hepatitis B (CHB).

**Objective:** To evaluate the association, if any, between the above factors on liver fibrosis in a cohort of patients with CHC and CHB.

**Participants/Methods:** 271 consecutive patients with CHB (n=95) or CHC (n=170) who had liver biopsies were retrospectively evaluate to determine if such a relationship exists. Smoking histories were obtained by means of questionnaires and anthropometric measurements were collected as were laboratory data and histologic lesions were reviewed.

**Results:** In patients with CHC severe fibrosis was independently associated with a high body mass index (BMI) (odds ratio [OR] 1.180, 95% CI, 1.028 to 1.354; $P=0.019$), heavy smoking (OR 3.923, 95% CI, 1.356 to 11.348; $P=0.012$), higher alanine aminotransferase (ALAT) levels (OR 1.010, 95% CI, 1.003 to 1.017; $P=0.005$) and alkaline phosphatase (ALP) levels (OR 1.165, 95% CI, 1.286 to 96.970; $P=0.029$). In addition, steatosis was independently associated with high gamma-glutamyl transpeptidase (GGT) values, heavy smoking, and presence of necroinflammation. No association was found between smoking habits and fibrosis or steatosis in patients with CHB.

**Conclusions:** In CHC, heavy smoking is associated with severe fibrosis but this association could not be found in CHB. It was also noted that heavy smoking is significantly associated with steatosis in CHC and this could be the link between smoking and fibrosis progression.

**Reviewer's Comments:** This interesting paper presents evidence of a connection between heavy smoking and the increased risk of advanced fibrosis in CHC. Since it is postulated that smoking leads to increased steatosis which leads to fibrosis it would seem prudent to urge patients with CHC to stop smoking and improve their metabolic parameters to avoid an accelerated rate of fibrosis. (Reviewer-Michael M. Phillips, MD).
Budesonide is Effective in Treating Lymphocytic Colitis: A Randomized Double-Blind Placebo-Controlled Study.
Miehlke S, Madisch A, et al:
Gastroenterology 2009; 136 (June): 2092-2100

Budesonide is more effective than placebo in inducing clinical and histologic remission in patients with lymphocytic colitis.

Background: Lymphocytic colitis is a distinct form of microscopic colitis. An increase in intraepithelial lymphocytes (≥20 IEL/100 epithelial cells) and chronic inflammation in the lamina propria is present, however, the subepithelial collagen layer is normal in contrast to collagenous colitis. Both are characterized by chronic non bloody diarrhea and normal endoscopic findings. Budesonide has been shown to be effective as treatment for collagenous colitis but has not been well studied in lymphocytic colitis.

Objectives: To determine the clinical remission rate in patients with lymphocytic colitis after treatment with budesonide for 6 weeks.

Design: Randomized, double-blind, placebo-controlled trial. Patients: 42 patients, (median age 61 years) with histologically confirmed lymphocytic colitis and >3 watery or loose stools per day.

Methods: Budesonide (Budenofalk®), 3mg, packed in enteric coated pH dependent release granules in capsules and placebo capsules were obtained from Dr Falk Pharma GmbH. Patients were randomized to receive 9mg (3 capsules) budesonide or placebo daily for 6 weeks. Stool frequency and consistency were recorded at baseline, 3 and 6 weeks and colonoscopy with multiple biopsies was performed at baseline and 6 weeks. Primary endpoint was ≤3 BM on average within the previous 7 days and a reduction of ≥1 BM compared with baseline. Non responders at 6 weeks were treated with open label 9mg budesonide for an additional 6 weeks.

Results: At 6 weeks 18 of 21 (86%) of budesonide treated patients were in clinical remission compared to 10 of 21 (48%) of the placebo group (P =0.01). Open label therapy resulted in clinical remission in 7 of 8 previous placebo failures. Histologic remission was achieved in 73% of the budesonide group compared to 31% of the placebo group (P =0.03). Responders were followed for a mean of 14 months during which time clinical relapse occurred in 44% after a mean time of 2 months. Of the relapsed patients, 8 were retreated with budesonide and all 8 responded.

Conclusions: Budesonide is effective in inducing clinical and histologic remission in patients with lymphocytic colitis.

Reviewer's Comments: Whether or not Budenofalk is equivalent to Entocort-EC which is commercially available in the United States and Food and Drug Administration approved for treatment of Crohn's disease is unclear. Entocort is coated in granules designed for protection from gastric acid which dissolve at pH >5.5 in the duodenum after which an ethyl cellulose matrix results in slow release into the gut lumen. Budenofalk is shown clearly to be effective in treatment and retreatment of lymphocytic colitis. (Reviewer-Allen L. Ginsberg, MD).

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Keywords: Lymphocytic Colitis, Budesonide

Print Tag: Refer to original journal article
Saccharomyces boulardii is effective in secondary prophylaxis in the prevention of relapse of Clostridium difficile-associated diarrhea.

**Background:** The frequency and severity of Clostridium difficile-associated diarrhea (CDAD) is increasing. Antibiotics limit the ability of bowel flora to inhibit C.diff colonization but despite restricted use of high risk antibiotics, treatment failures and relapse rates continue to rise.

**Objective:** To review mechanisms of action and clinical studies related to probiotic use for prophylaxis.

**Discussion:** Most of the following data are derived from in vitro and animal model studies. Probiotics have been investigated for efficacy in preventing CDAD in high risk populations (primary prophylaxis) and as therapy in addition to antibiotics to prevent relapse (secondary prophylaxis). Clinical data for secondary prophylaxis as adjunctive therapy to prevent relapse are thin. Two studies found Saccharomyces boulardii treatment for 28 days significantly decreased relapse rate from 45% in the placebo group to 26% in the treatment group ($P = 0.03$) and from 50% to 17% ($P = 0.04$). Two studies each with small numbers found Lactobacillus GG to be ineffective in secondary prophylaxis. Primary prophylaxis clinical data are also meager. Two studies of S. boulardii did not show significant benefit. One study found that the combination of L. acidophilus, Lactobacillus bulgaris, and B. bifidum had a CDAD rate of 11% compared to 40% in the placebo group. A second study found Lactobacillus casei, L. bulgaris and S. thermophilus had a CDAD rate of 0 compared to 17% in the placebo group ($P = 0.01$). Study periods and antibiotic exposure were variable. No placebo controlled primary prophylaxis data for Lactobacillus GG were provided.

**Conclusions:** Probiotics have the potential to decrease colonisation and reduce toxin load and be helpful in primary and secondary prophylaxis. S. boulardii appears effective as secondary prophylaxis in reducing relapse rate.

**Reviewer's Comments:** Controlled clinical data for primary and secondary probiotic prophylaxis of CDAD are meager. The number of patients studied is small, antibiotic exposure is variable, and duration of probiotic therapy is variable. This review provides support for the use of S. boulardii as adjunctive therapy for the prevention of relapse of CDAD. Controlled clinical data for use of Lactbacinilis GG were not found. (Reviewer-Allen L. Ginsberg, MD).

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Keywords: Probiotics, Clostridium Dificile Prophylaxis

Print Tag: Refer to original journal article
Inflammatory bowel disease, specifically ulcerative colitis and Crohn's colitis are independent risk factors for infection with *Clostridium difficile*. Immunosuppressive therapy and corticosteroids further increase the risk of infection.

**Background:** The incidence of *Clostridium difficile* colitis has increased dramatically, doubling in the last 6 years. Antibiotic exposure is a contributing factor in some, but is no longer essential. There has in particular been a marked increase in C diff infection in inflammatory bowel disease (IBD) patients.

**Design:** Review article interview of Dr. Binion. **Review:** Ulcerative colitis and Crohn's colitis patients are at increased risk of C diff colitis. Infected patients have an increased likelihood of hospitalization, longer hospital stays, and greater likelihood of colectomy as well as increased mortality of 4.2%. Ileoanal pouch patients are also at risk of C diff infection of the pouch and small intestine. Of infected IBD patients, 39% had no recent history of antibiotic exposure. Patients on maintenance immunosuppressive therapy were especially at risk. Diagnosis by stool analysis for toxins A and B has limitations often requiring examination of ≥3 specimens. IBD flares and C diff infection have identical symptoms and C diff can trigger IBD flares. Complicating therapy is the fact that necessary steroid and immunosuppressive therapy can worsen C diff infection, interfering with production of antibody to Toxin A. Aggressive, early antibiotic therapy of C diff is essential since untreated C diff can result in worsening, therapeutically refractory IBD. Oral vancomycin at doses as high as 500 mg 4 times per day is replacing metronidazole in sicker patients with metronidazole failures approaching 50%. It is important to maintain an oral diet which may promote the maintenance of healthy bacterial flora reducing C diff colonization. Intravenous metronidazole, which is better tolerated than oral, in combination with oral vancomycin can be useful in difficult cases. Some patients may benefit from probiotics containing *saccharomyces boulardii* and strains of *lactobacillus*. Relapse rates may approach 50% and among these patients, up to half may require colectomy. Lastly, C diff elicits a tumor necrosis factor (TNF) cytokine response in the bowel which potentially may be reversed by anti-TNF biologic medications.

**Reviewer's Comments:** This review is fascinating and fits well with what I am seeing in my practice, and which most certainly must be affecting your practices as well. The most common cause of IBD colitis flare that I document, is infection with C diff (approximately 50%), with at least half of these having no recent antibiotic exposure. I am especially suspicious when a patient in remission for many years flares for no apparent reason. I have also found that 2 to 5 stool specimens may need to be analyzed to confirm the diagnosis of C diff infection. (Reviewer-Allen L. Ginsberg, MD).

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Keywords: Ulcerative Colitis, *Clostridium difficile* Infection

Print Tag: Refer to original journal article
Survival of patients with primary biliary cirrhosis in whom serum albumin and/or bilirubin levels become normal on UDCA treatment is improved compared to patients in whom this response does not occur.

**Background:** Ursodeoxycholic acid (UDCA) is the sole effective treatment for primary biliary cirrhosis (PBC) improving biochemical tests, slowing histologic progression, and improving transplantation-free survival. Reductions in serum alkaline phosphatase in UDCA-treated patients have been linked to an improved prognosis. In a study of Dutch PBC patients treated with UDCA, bilirubin and albumin levels were independent predictors of survival.

**Objective:** To assess correlation of changes in biochemical tests with long-term prognosis in PBC patients treated with UDCA.

**Design:** Multicenter, prospective cohort Dutch study initiated in 1990 with follow-up through 2007.

**Methods:** All patients were treated with 13 to 15 mg/kg per day UDCA and follow-up liver chemistries were measured annually. Patients were classified at entry as having early PBC if both the albumin and bilirubin were normal, moderately advanced PBC if 1 of 2 were abnormal, and advanced PBC if both were abnormal. End points were death, including liver-related death, and transplantation. Observed survival was compared to expected survival in a matched general Dutch population. Biochemical responses were defined as normalization of both bilirubin and albumin levels on treatment when 1 or both were elevated at baseline or normalization of 1 when both were elevated. Other criteria, using reductions of serum alkaline phosphatase alone or in combination with aspartate aminotransferase (AST) and bilirubin were also evaluated.

**Results:** Median follow-up was 9.7 years; just 4% were lost to follow-up. Of patients, 60% had early PBC and 65% had Ludwig stage 1 or 2 histologic disease. Liver-related death or transplantation occurred in 18% of the early PBC group, in 37% of moderately advanced PBC, and in 91% with advanced PBC. Survival in early PBC was not different from that of the general population but it was significantly worse for those with moderately advanced or advanced disease. Survival in early PBC for patients with an albumin-bilirubin response was comparable to that for non-responders and better for survival without UDCA as predicted by Mayo risk score. For patients with moderately advanced and advanced PBC, those with biochemical responses to UDCA showed higher survival rates than those without responses (also using improvements in alkaline phosphatase, AST and bilirubin) but not when alkaline phosphatase reductions alone were considered a response.

**Conclusions:** The authors conclude that the outcomes of PBC in biochemical responders to UDCA is improved in comparison to non-responders, and that responses, defined by a return to normal of albumin and/or bilirubin levels, have better prognostic utility than responses defined by reductions in alkaline phosphatase levels alone.

**Reviewer’s Comments:** This study suggests that improvements in albumin and bilirubin levels are superior to reductions in alkaline phosphatase levels as prognostic indicators in UDCA-treated PBC patients. Unfortunately, management of non-responders is problematic since there is no alternative treatment to UDCA. (Reviewer-Raymond S. Koff, MD).

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**Keywords:** Primary Biliary Cirrhosis, Ursodeoxycholic Acid, Biochemical Responses, Survival

**Print Tag:** Refer to original journal article
Both Preoperative Perinuclear Antineutrophil Cytoplasmic Antibody and Anti-CBir1 Expression in Ulcerative Colitis Patients Influence Pouchitis Development After Ileal Pouch-Anal Anastomosis.

Fleshner P, Ippoliti A, et al:

Clinical Gastroenterology and Hepatology 2008; 6 (May): 561-568

Ulcerative colitis patients with high levels of perinuclear antineutrophil cytoplasmic antibody have an increased risk of chronic pouchitis.

Background: Perinuclear antineutrophil cytoplasmic antibody (pANCA), found in over 50% of ulcerative colitis (UC) patients, is an autoantibody with cross reactivity to a number of commensal bacterial antigens. Anti-CBir1 reacts to flagellin of Clostridium species and is found in the sera in 50% of Crohn's disease (CD) patients but only in 6% of UC patients.

Objective: To assess whether there is an association of preoperative levels of pANCA and anti-CBir1 with the incidence of pouchitis in UC patients after ileal pouch-anal anastomosis (IPAA).

Participants: 238 consecutive patients with UC or indeterminate colitis requiring colectomy for refractory disease or dysplasia.

Methods: Postoperatively, patients were assessed for pouchitis with examinations including pouchoscopy every 3 months for the first year and then yearly. Preoperative sera were tested for pANCA and anti-CBir1 using an enzyme-linked immunoabsorbent assay. Patients were sub stratified into high levels (>100 EU/mL) and low levels (<100 EU/mL). Patients were assessed blindly without knowledge of seromarker results.

Results: During a median follow-up of 47 months, 72 patients (30%) developed pouchitis. Of those pANCA+, 36% developed pouchitis compared to 16% of those pANCA- (P = 0.005). Of those anti-CBir1+, 46% developed pouchitis compared to 26% of those anti-CBir1- (P = 0.02). Of those positive for both pANCA and anti-CBir1, 54% developed pouchitis. Chronic pouchitis, defined as requiring continuous antibiotic treatment for symptom relief or who were refractory to antibiotic treatment was significantly more common in patients with high preoperative levels of pANCA (29%) than with low levels (11%, P = 0.03).

Conclusions: The presence preoperatively of pANCA and anti-CBir1 each increase the risk of development of pouchitis. Patients with high levels of pANCA were more likely to develop chronic pouchitis.

Reviewer's Comments: These findings are interesting; however, they should not influence the surgical plan since at least half of those with these serologic markers do not develop pouchitis. (Reviewer-Allen L. Ginsberg, MD).

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Keywords: Pouchitis, Perinuclear Antineutrophil Cytoplasmic Antibody, Anti-CBir1

Print Tag: Refer to original journal article
Long-term treatment with infliximab had a good safety profile and is generally well tolerated.

Objective: To determine the safety and adverse effect profile of patients treated with long-term infliximab.

Design: Retrospective cohort study.

Participants: 734 patients from a single institution with inflammatory bowel disease treated with infliximab and 666 control patients not treated with infliximab. Patients were studied over a period from December 1994 through December 2008.

Methods: All medical records were reviewed and adverse effects recorded. A serious adverse effect was defined as one that led to hospitalization, was fatal or life-threatening, or resulted in disability. Serious infections were defined in a similar fashion. Acute infusion reactions were defined as adverse effects that began within 1 hour of infusion or serum sickness-like symptoms that occurred 1 day to 2 weeks after the infusion.

Results: Patients and controls were monitored for a median time of 58 months. Of patients, 13% in the infliximab group and 19% of patients in the control group developed serious adverse effects ($P=0.45$). Rate of malignancy, infection, and mortality was not different between groups. Two patients with negative baseline purified protein derivatives (PPDs) developed tuberculosis but no patients of 16 with baseline positive PPDs receiving chemoprophylaxis developed active tuberculosis during the course of the study. Patients also receiving steroids while on infliximab were at increased risk for infection ($P=0.018$). The side effect seen most frequently with infliximab was a psoriasiform rash in 20% of patients.

Conclusions: Infliximab was well-tolerated for up to 5 years of therapy with a small proportion of patients developing serious adverse effects. Reviewers Comments: Unfortunately, the control group in this study may have not been appropriate. Age at diagnosis of Crohn's disease, gender, age at end of treatment and years of follow-up were all significantly different compared to the group of patients taking infliximab. This may make the conclusion that there was no difference in mortality, malignancies, or infections between the control and experimental infliximab group invalid. (Reviewer-Ingram M. Roberts, MD).

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Keywords: Infliximab, Crohn's disease, Ulcerative Colitis

Print Tag: Refer to original journal article
Background: Relative costs and benefits with regard to nurses, compared to doctors, performing upper gastrointestinal (UGI) endoscopy and flexible sigmoidoscopy are unknown.

Objective: To calculate the cost-effectiveness of nurse- and doctor-performed endoscopy.

Design: Randomized controlled trial.

Methods: Details of this trial are described on another abstract in this issue of PRG. Briefly, patients were randomized into 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. Follow-up information was obtained at day 1 and months 1 and 12. Using established cost estimates and results from the trial, a cost-effectiveness analysis was undertaken.

Results: 4128 patients were randomized; 1888 agreed to participate. Of patients, 269 and 286 were lost to follow-up. For the most part, no significant differences were seen with regard to patient outcome in the groups. Nurses performed more biopsies and used combination local anesthetic and sedation more often, increasing those costs. Baseline cost of doctors was higher. Using raw data, and assuming that small and non-significant differences represented absolute truth rather than chance error, it was calculated that the doctor-performed procedures resulted in a net gain of 0.015 quality-adjusted life-years at a cost of 56 pounds. Since it is widely believed that society can afford to spend 30,000 pounds gain 1 quality-adjusted life-year, doctor-performed procedures were cost-effective. In the text, but not in the conclusions, the authors recognized that there was much uncertainty regarding the actual numbers.

Conclusions: Endoscopy performed by nurses is unlikely to be cost-effective compared to endoscopy performed by doctors.

Reviewer's Comments: As previously noted, clinical data from the trial are problematic because of potential biases that were introduced. Furthermore, no significant differences were found; assuming that non-significant differences are true disregards accepted scientific practices. Data are simply too unreliable to undertake any such calculation. A better approach would have been to take the extremes of the confidence intervals and undertake most-favorable and least-favorable cost-effectiveness analyses. These numbers would have provided the range over which the cost-effectiveness may be likely to lie. Disregarding the fact that the numbers are unreliable in the conclusion section, results in providing a misleading perspective to people such as health care policymakers, who only read the bottom line. (Reviewer-Ronald L. Koretz, MD).

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Keywords: Upper Endoscopy, Flexible Sigmoidoscopy, Nurse-Delivered

Print Tag: Refer to original journal article
The current study suggests that celiac disease patients on a gluten-free diet in remission may be deficient in B vitamins and may improve their global sense of well-being with supplementation.

**Background:** Studies have suggested that celiac disease patients on a gluten-free diet in remission may suffer selected B vitamin deficiency and may have a reduced health-related quality of life.

**Objective:** To evaluate biochemical and clinical effects of B vitamin supplementation for 6 months in adults with celiac disease on a strict gluten free-diet and in remission for ≥8 years.

**Design:** Randomized, double-blind placebo-controlled clinical trial.

**Participants:** Adults from 4 Swedish hospitals with original diagnosis based upon histology and evidence of remission.

**Methods:** Plasma total homocysteine (tHcy) levels as well as serum B₁₂ and folate levels were obtained at baseline and at 6 months. Psychological well-being was assessed by the Psychological General Well-Being (PGWB) index, a composite of 6 subscales: anxiety, depressed mood, positive well-being, self-control, general health, and vitality. Subjects were randomized to receive daily pyridoxine, folic acid, and B₁₂ or placebo for 6 months.

**Results:** Of 210 patients assessed for eligibility, 65 were randomized; 57 completed the trial and were analyzed per protocol. Baseline tHcy was significantly higher in the total subject population compared to population based controls (11.7μmol/L vs 10.2μmol/L), indicating insufficient B vitamin nutriture. Plasma tHcy dropped significantly in the supplemented group as compared with the placebo control group. There was no major difference in the PGWB index for both groups at the end of 6 months, but in those with a reduced PGWB index at baseline (about half of each group and indicating reduced psychological well-being), the PGWB index increased significantly in the supplemented group.

**Conclusions:** Adult celiac patients in remission may suffer from abnormal B vitamin levels and reduced psychological well-being; these abnormalities may be improved with B vitamin supplementation.

**Reviewer’s Comments:** This is an interesting study which supports prior data suggesting micronutrient deficiency in celiac patients on a gluten-free diet. However, this is a high risk-of-bias, low methodological quality study, which makes the conclusions less firm. Quality issues include a questionable power calculation and sample size determination, failure to account for all patients entered into the trial (per protocol analysis), analysis of multiple end points without statistical correction, and post-hoc analysis of population subsets (those with reduced psychological well-being scores at baseline). High risk-of-bias studies tend to overestimate treatment benefits. Nonetheless, analysis of celiac disease patients on a gluten-free diet in remission for B vitamin status and supplementation of those who are deficient is probably a reasonable, potentially beneficial, low-risk clinical strategy. (Reviewer-Timothy O. Lipman, MD.)
Healthy Lifestyle Associated With Reduced Risk for Pancreatic Cancer

A Combined Healthy Lifestyle Score and Risk of Pancreatic Cancer in a Large Cohort Study.

Jiao L, Mitrou PN, et al:

Arch Intern Med 2009; 169 (Apr 27): 764-70

In a large scale prospective observational cohort, a healthy lifestyle (no smoking, modest alcohol use, normal weight, healthy diet, and exercise) was associated with a significantly reduced risk of developing pancreatic cancer.

**Background:** Some modifiable lifestyle factors (smoking, obesity) have been associated consistently with increased risk for pancreatic cancer, but others (diet, physical activity) have had inconsistent associations. Since early detection and therapy of pancreatic cancer are problematic, modification of risk factors may have the current best chance of reducing the burden of disease.

**Objective:** To determine if a combination of healthy lifestyle factors is associated with a reduced risk of pancreatic cancer.

**Design:** Prospective, large-scale observational cohort.

**Participants:** Eligible participants in the National Institute of Health-AARP Diet and Health Study, initiated in 1995.

**Methods:** A Food Frequency Questionnaire (FFQ) was mailed to 3.5 million AARP members aged 50 to 71 years residing in 6 states and 2 metropolitan areas. Self-reported information was obtained on smoking, daily alcohol use, dietary intake ("Mediterranean style" diet defined as "healthy"), body mass index (BMI), and physical activity. A "healthy life-style" score was generated for each of the previously named lifestyle factors, ranging from 0 (least healthy) to 5 (most healthy). Cox proportional hazards regression models were used to calculate relative risks (RR).

**Results:** 450,416 participants met eligibility criteria. During a mean 7.2 years of follow-up, 1057 cases of pancreatic cancer developed. Consistent with the findings in other studies, after adjustment for other factors, the individual factors of non-smoking and normal BMI were significantly associated with reduced risk for pancreatic cancer. The most healthy life style compared with the least healthy lifestyle was associated with a significant 58% reduction of developing pancreatic cancer (RR, 0.42; 95% CI, 0.26 to 0.66). The calculated age- and energy-adjusted population attributable risk (PAR) of developing pancreatic cancer was 27% for having a lifestyle score of <5 points. In other words, it is estimated that 27% of pancreatic cancers could have been prevented if individuals had a total healthy lifestyle.

**Conclusions:** A healthy lifestyle including nonsmoking, limited alcohol use, a Mediterranean diet pattern, normal weight, and regular physical exercise is associated with a reduced risk for developing pancreatic cancer.

**Reviewer's Comments:** As is always true with similar large scale prospective observational cohorts, the statistical analyzes are daunting, and the findings only represent associations, not causality. Nonetheless, the present findings confirm and expand upon prior observations. Unless other similar cohorts come up with different findings, pancreatic cancer should be added to the various gastrointestinal cancers whose risk appears to increase with unhealthy lifestyle choices. The unproven assumption is that modification of lifestyle may reduce the risk for pancreatic and other cancers. (Reviewer-Timothy O. Lipman, MD).

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Keywords: Pancreatic Cancer, Healthy Lifestyle

Print Tag: Refer to original journal article
High levels of tissue transglutaminase indicate celiac disease and are associated with diminished bone mineral density in middle aged women.

**Objective:** To determine if the serological marker for celiac disease, tissue transglutaminase autoantibody (tTGAb), is associated with decreased bone mass density (BMD) and an increased frequency of fractures in middle aged women screened for osteoporosis.

**Participants:** 6480 Swedish women whose mean age was 56 years.

**Methods:** Participants completed questionnaires and had a dual X-ray absorptiometry of the wrist. They all had serum samples analyzed for tTGAb with a level of >4 U/ml being used to determine a positive value and a level of >17 U/ml being used as an alternative discrimination of high levels.

**Results:** In 90 (1.4%) women a tTGAb level of > 4 was found and correlated with lower BMD (multiple linear regression coefficient 382.1; 95% CI, --673.6-90.7, P =0.011) and with fracture frequency (r =0.18, P =0.023). The 59 women who had tTGAb ≥17 U/ml had a lower BMD (0.41±0.08 g/cm2 vs 0.44±0.08 g/cm2, P =0.001) and a lower T-score (-1.40±1.28 versus -0.90±1.40, P =0.003) as well as a higher prevalence of osteoporosis (13.4% vs 6.5%, P =0.008) compared with the remaining 6421 women with tTGAb <17 U/ml. It was further noted that the fracture frequency was greater in women with tTGAb levels ≥17 U/ml among whom 19 of 59 (32.2%) had fractures during the study period compared with 1204 of 6421 (18.8%) among women with tTGAb levels of <17U/ml (P =0.009).

**Conclusions:** This study has demonstrated that women aged 50 to 64 years with high levels of tTGAb indicating celiac disease are likely to have lower BMD and higher fracture frequency than women who have normal levels of tTGAb.

**Reviewer's Comments:** Elevated levels of tissue tTGAb suggestive of celiac disease can now be added to the list of risk factors for osteoporosis among which are: old age, female gender, loss of ovarian function, low physical activity, low body mass index, smoking, low calcium intake and long term use of systemic corticosteroids. (Reviewer-Michael M. Phillips, MD).

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Keywords: Celiac Disease, Osteoporosis, Fractures

Print Tag: Refer to original journal article
Weight loss is the most common symptom and hypoalbuminemia is the most common laboratory finding in patients with AL amyloidosis.

**Background:** Immunoglobulin light-chain (AL) amyloidosis can affect many organs but the present study attempts to describe the symptoms, biochemistry and outcomes of patients with AL affecting the gut.

**Objective:** To elucidate gastrointestinal clinical manifestations of the admittedly rare disease AL amyloidosis.

**Design:** Retrospective analysis of all patients admitted to the gastrointestinal division of the Rigshospitalet in Copenhagen Denmark over a period of 7 years beginning in January 2000 with malabsorption related to AL amyloidosis was made.

**Participants:** 11 patients, 4 of whom were women whose ages ranged from 50 to 69 years.

**Methods/Results:** All patients had biopsy-proven gastrointestinal involvement with AL amyloidosis. Of patients, 3 had no gastrointestinal symptoms prior to their diagnosis of amyloidosis but developed symptoms after diagnosis. The delay between onset of symptoms and the diagnosis of AL amyloidosis was 7 months with a range of 0 to 24 months. The most common symptom was weight loss in 10 subjects averaging 7kg (range 0 to 25) followed by diarrhea seen in 5 subjects. Steatorrhea (2 mild, 1 moderate and 1 severe) was found in 4 of 7 patients examined. Hypoalbuminemia was seen in 9 patients at presentation and 6 had diarrhea. Home parenteral nutrition was used in 3 patients. Conventional chemotherapy was used in 5 patients consisting of melphalan and prednisone and 5 patients had high-dose melphalan therapy and autologous stem-cell transplantation. During the period of observation, 5 patients died at a median of 10 (3 to 36) months after the diagnosis was made. Those who died presented with lower levels of serum albumin and had more involvement of other organs than survivors.

**Conclusions:** Most patients with gastrointestinal AL amyloidosis experience weight loss and all have signs of malabsorption. The prognosis for this disease, even with aggressive therapy, is grave.

**Reviewer’s Comments:** This paper presented an interesting review of what is clearly a rare disease. When the gut is involved in AL amyloidosis the prognosis is poor. (Reviewer-Michael M. Phillips, MD).

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Keywords: Amyloidosis, Gastrointestinal Involvement

Print Tag: Refer to original journal article