# Antioxidants Provide Pain Relief in Chronic Pancreatitis

*A Randomized Controlled Trial of Antioxidant Supplementation for Pain Relief in Patients With Chronic Pancreatitis.*

Bhardwaj P, Garg PK, et al:

Gastroenterology 2009; 136 (January): 149-159

Patients in India with chronic pancreatitis, largely due to unknown cause(s), experience pain relief with an antioxidant formulation.

**Background:** The management of patients with pain from chronic pancreatitis (CP) is a frustrating experience, as there are no well established modalities to treat the pain. It has been hypothesized that the pain is due to oxidant stress secondary to inflammation in the perineural region.
**Objective:** To assess the utility of antioxidants in treating CP pain.
**Design:** Randomized, double-blind, controlled trial.
**Participants:** Patients in India with CP (pancreatic anatomical abnormalities) who had at least monthly episodes of pain or ≥1 hospitalization in the preceding 3 months for CP pain were included.
**Methods:** Patients were randomized to 1 of 2 arms, antioxidants or placebo. The treatment arm consisted of 600 µg organic selenium, 0.54 g ascorbic acid, 9000 IU b-carotene, 270 IU a-tocopherol, and 2 g methionine taken daily. The placebo was identical in appearance and packaging. The randomization scheme was adequate, and there was concealment of allocation. A sample size calculation indicated that 200 patients needed to be entered. The patients were followed monthly for 6 months. Each one completed daily diary records indicating the presence or absence of pain, the use or non-use of analgesics (and, if used, what kind), and the need for hospitalization for pain. The primary outcome was the reduction in the number of painful days monthly. Secondary outcomes included reduction in use of pain medication, reduction in days of activity lost, reduction in the need for hospitalization, percentage of patients becoming pain-free, and various biochemical assessments of antioxidant levels and markers of oxidative stress.
**Results:** 71 study and 76 placebo patients were randomized, but 5 and 15, respectively, were lost to follow-up in each group. An unplanned interval analysis was done at that time because recruitment had been slower than expected, and the trial was stopped when significant differences were observed. The antioxidant recipients had a more dramatic reduction in painful days per month (9.14 to 1.68) than did the placebo recipients (7.21 to 3.36) at 6 months after intervention. Analgesic requirement, need for hospitalization, and man-days lost were also reduced in the study arm, and the biochemical markers were also improved in the antioxidant recipients.
**Conclusions:** Antioxidant supplementation was effective in relieving pain.
**Reviewer's Comments:** While the randomization processes (and possibly the blinding) were adequate, bias may be present with regard to the disproportionate dropout rate in the placebo arm and stopping the trial early. It is not clear that the data in Indian patients (who largely had a disease not seen in the Western world, namely tropical pancreatitis) can be extrapolated. Some data show that the long-term use of antioxidants may result in a slight increase in overall mortality. However, this formulation is not very expensive and does offer a therapeutic option in an area where few others exist. (Reviewer-Ronald L. Koretz, MD).



Keywords: Antioxidants

Print Tag: Refer to original journal article

# Patients With Medically Controlled GERD Have Better Outcomes With Fundoplication

*Minimal Access Surgery Compared With Medical Management for Chronic Gastro-Oesophageal Reflux Disease: UK Collaborative Randomised Trial.*

Grant AM, Wileman SM, et al:

BMJ 2008; 337 (epub ahead of print):

Fundoplication rather than continued medical therapy may offer better symptomatic relief in patients with reflux disease that is medically controlled.

**Background:** Patients with gastroesophageal reflux disease (GERD) have symptoms that can be expected to persist for much of the rest of their lives, even if those symptoms are reasonably well controlled with medication and life-style modifications. One might wonder if surgery should be offered as an alternative.
**Objective:** To compare continued medical therapy with laparoscopic fundoplication.
**Design:** Randomized controlled trial.
**Participants:** Patients with documented GERD (by endoscopy and/or pH studies) who had been receiving >12 months of treatment with proton pump inhibitors (PPIs), or alternative therapy, and who were suitable for either ongoing medical therapy or fundoplication were included. Patients who had strong preferences for one or the other treatment were provided with that therapy, but followed in nonrandomized surgical or medical groups; they were not further considered.
**Methods:** Using an adequate randomization scheme that included concealed allocation, patients were assigned to the medical or surgical group. An original power calculation indicated that 300 patients per arm would be needed, but, because of slow recruitment, that estimate was subsequently revised down to 196 patients per arm. The primary outcome was a validated score (the REFLUX score) that assessed symptoms and adverse effects of treatment. Secondary outcomes included other symptom scores, quality-of-life and health status, morbidity, and mortality. The trial was not blinded. Follow-up was done at 3 and 12 months after the surgery (or a time equivalent to the date of surgery for the medical group). The type of fundoplication was left to the discretion of the surgeon. Medical therapy was performed by the patient's personal physician.
**Results:** The REFLUX scores were more improved in the surgical group, although the scores in the medical arm were still improving at 12 months, while the score in the surgical arm had plateaued. The surgical group was also taking less medication on average after 1 year. Some of the quality-of-life scores were better in the surgical group, although there was evidence of attenuation at 12 months. There was 1 death in the medical group.
**Conclusions:** Surgical therapy resulted in better measures of health status at 1 year.
**Reviewer's Comments:** The investigators cited 2 other randomized trials of medical versus surgical therapy that made the same observation. However, none of these trials could be blinded, so bias could have been introduced. The fact that the differences between the 2 groups may have been narrowing might suggest that some of the surgical benefit was due to a placebo effect, although this may also represent a gradually diminishing effect of the fundoplication or even the natural history of GERD. The investigators are planning to publish a cost-effectiveness analysis and also to follow the patients for 4 more years (because of the diminishing differences). (Reviewer-Ronald L. Koretz, MD).



Keywords: Fundoplication

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# Ablation of Barrett's Esophagus Containing Dysplasia

*Circumferential and Focal Ablation of Barrett's Esophagus Containing Dysplasia.*

Sharma VK, Kim HJ, et al:

Am J Gastroenterol 2009; 104 (February): 310-317

Stepwise circumferential and focal ablation of Barrett's dysplasia using the HALO360 balloon is very effective, resulting in resolution of dysplasia in 95% and 79% of LGD and HGD patients, respectively.

**Objective:** To determine the efficacy and safety of the HALO360 radiofrequency ablation (RFA) system in Barrett's esophagus (BE).
**Methods:** Patients with BE and low-grade dysplasia (LGD) were offered stepwise ablation with the HALO360 system or surveillance. High-grade dysplasia (HGD) patients were screened and evaluated for advanced disease (nodular HGD, adenocarcinoma). If none was identified, they were offered photodynamic therapy (PDT), esophagectomy, surveillance, or HALO system therapy. Patients with nodular disease were treated with endoscopic mucosal resection (EMR) and then offered ablative therapy. Histology was confirmed by 2 pathologists. After determining the length of intestinal metaplasia (IM) and sizing the diameter of the esophagus, the HALO360 was introduced side by side with the endoscope; the appropriate area to be ablated was identified and ablated twice. Following ablation, all patients received esomeprazole 40 mg twice a day until all IM was eradicated. The primary end point was histologic: complete response (CR-IM) = no IM, only squamous; (CR-D) = no dysplasia. The HALO360 circumferential ablation catheter (BARRX Medical) consists of a balloon measuring 4 cm in length; the center 3 cm consists of 60 isolated electrode rings, spaced 250 µm apart that deliver RFA to a depth of 1000 µm (about the level of the muscularis mucosa). The depth of Barrett's epithelium measures approximately 500 µm. Focal ablation can be performed with a flat RFA device mounted on the tip of the endoscope (HALO90).
**Results:** 63 patients (39 LGD, 24 HGD) were studied, with a median BE length of 5 cm, and median follow-up of 21 months. In the LGD group, patients required a median of 1 circumferential and 1 focal ablation. Ultimately, CR-IM response was 87% (had only squamous epithelium) for a CR-D of 95%. In the HGD group, a median of 1 circumferential and 1 focal ablation was required for a CR-IM of 67%, a CR-HGD of 100%, and a CR-D of 79%. No buried glands were noted in >1000 biopsies. Overall, complications included a minor bleed and a stricture. During follow-up, 2 focal nodules underwent EMR, which showed intermucosal cancer with negative margins.
**Conclusions:** Stepwise circumferential and focal ablation of Barrett's dysplasia using the HALO360 balloon is very effective. Complete resolution of dysplasia is noted in 95% and 79% of LGD patients and HGD patients, respectively.
**Reviewer's Comments:** This study is 1 of several RFA HALO360 ablation studies that report impressive CR rates to therapy. The side effect profile is low with 1 mild stricture and 1 self-limited minor bleed. Submucosal glands were not seen in all the biopsies taken attesting to the completeness of the ablative therapy. One could make an argument that it would be less expensive and probably more efficacious to treat LGD with RFA than to undergo yearly surveillance. Long-term follow-up with biopsies is critical to determine the durability of RFA. (Reviewer-Roy K.H. Wong, MD).



Keywords: Ablation

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# Triple Therapy Increases SVR in Genotype 4 Patients

*Improved Virologic Response in Chronic Hepatitis C Genotype 4 Treated With Nitazoxanide, Peginterferon, and Ribavirin.*

Rossignol J-F, Elfert A, et al:

Gastroenterology 2009; 136 (March): 856-862

In genotype 4 patients, a 12-week lead-in with nitazoxanide alone, followed by triple therapy with nitazoxanide, peginterferon, and ribavirin for 36 weeks increases the SVR from 50% to 79% in those receiving peginterferon and ribavirin alone for 48 weeks.

**Background:** Anecdotal reports of declines in hepatitis C virus (HCV) and hepatitis B virus (HBV) in Egyptian patients treated with the antiparasite drug, nitazoxanide, approved for the treatment of *Cryptosporidium parvum* and *Giardia lamblia* in the U.S. has stoked interest in this agent. A small trial of nitazoxanide as monotherapy for HCV genotype 4 in Egypt was promising, and nitazoxanide appears to have in vitro antiviral activity as a protein kinase inducer.
**Objective:** To characterize the safety and efficacy of nitazoxanide when given with peginterferon, with or without ribavirin, in previously untreated Egyptian patients with chronic HCV genotype 4.
**Design/Methods:** This open-label, randomized trial had 3 treatment arms: peginterferon alfa-2a (180 µg weekly) plus 1000 to 1200 mg ribavirin daily for 48 weeks; nitazoxanide 500 mg twice daily for 12 weeks followed by the same dose of nitazoxanide and the addition of peginterferon alfa-2a for 36 more weeks without ribavirin; and nitazoxanide 500 mg twice daily for 12 weeks followed by nitazoxanide in the same dose, with peginterferon and ribavirin for 36 more weeks. HCV RNA levels were measured at weeks 4 and 12 after the start of combination therapy, at the end of treatment, and 24 weeks later.
**Results:** The 3 treatment groups, with a total of 96 patients, were evenly matched at baseline except that the group receiving triple therapy had a significantly lower body mass index than those in the peginterferon + ribavirin group. Week 4, rapid virologic response (RVR) was significantly higher in the triple therapy group compared to the peginterferon + ribavirin control group (64% vs 38%; *P* =0.048). The sustained virologic response (SVR) was also significantly higher in the triple therapy group compared to the control group (79% vs 50%; *P* =0.023). Alanine aminotransferase (ALT) levels returned to normal in most patients. Nine of the 96 patients (9%) discontinued treatment because of adverse events, but no specific nitazoxanide-associated events were reported.
**Conclusions:** The addition of nitazoxanide to peginterferon and ribavirin enhances the response to therapy without increasing toxicity in genotype 4 patients.
**Reviewer's Comments:** This small, unblinded study of genotype 4 patients in Egypt is at first glance very exciting since better therapies for chronic HCV are needed. However, as indicated in an accompanying editorial, while the SVR for the triple therapy group was 79% in this study, the identical figure was observed in an analysis of 3 trials that included a total of 24 genotype 4 patients treated solely with peginterferon alfa-2a and ribavirin. Two small studies do not make for definitive conclusions, hence I remain skeptical. Whether the addition of nitazoxanide to standard of care therapy will improve the SVR or permit shortening of therapy in patients with genotype 1 remains to be determined and is under study. This is a story well worth watching. (Reviewer-Raymond S. Koff, MD).



Keywords: Genotype 4

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# Community Pathologists vs Hepatopathologists in Staging Fibrosis

*A Comparison of Hepatopathologists' and Community Pathologists' Review of Liver Biopsy Specimens From Patients With Hepatitis C.*

Robert M, Sofair AN, et al:

Clin Gastroenterol Hepatol 2009; 7 (March): 335-338

Disagreement by community pathologists and hepatopathologists on the degree of hepatic fibrosis in chronic hepatitis C is most likely when fibrosis is mild (stages 1 and 2) since community pathologists tend to understage fibrosis.

**Background:** With continuing improvements in response rates, some clinicians now reserve liver biopsy for nonresponders to current therapy for chronic hepatitis C virus (HCV). Nevertheless, liver biopsy is still utilized by others who believe that only patients with periportal or higher degrees of fibrosis are candidates for treatment. As a consequence, the interpretation of the fibrosis stage is key in the decision-making process for these clinicians. Since most liver biopsies are read by general pathologists in the community, the degree of interobserver variability between community pathologists and hepatopathologists is worthy of study.
**Objective:** To assess the effect of interobserver variability in fibrosis staging between community-based, nonacademic general pathologists versus hepatopathologists and to assess the affect of biopsy size.
**Participants/Methods:** Chronic HCV patients identified in New Haven and Alameda counties comprised the study population. Liver biopsy slides from these patients, initially read by 53 community pathologists were re-read by 1 of 2 academic hepatopathologists blinded to the diagnosis. Interobserver variability on fibrosis stage between the hepatopathologists was assessed on an external sample and interobserver variability between community pathologists and hepatopathologists was examined using the study population. Biopsy length was characterized as either <1.5 cm or ≥1.5 cm. Kappa values were utilized to evaluate interobserver variability for stages of fibrosis, stratified by length of biopsy.
**Results:** The 2 hepatopathologists agreed completely for no fibrosis or cirrhosis and disagreed by no more than 1 stage for stage 1 to 3 in 40% of 10 slides. In the study population (391 cases), the community pathologists and hepatopathologists agreed on the stage in 50% of biopsy specimens. In 37%, the disagreement was 1 stage, 2 fibrosis stages in 12%, and 3 or 4 fibrosis stages in <1% of cases. Based on the hepatopathologists readings, 7% of patients had stage 0 (no fibrosis), 23% had stage 1 (portal fibrosis); 36% had stage 2 (periportal fibrosis), 16% had stage 3 (bridging fibrosis), and 18% had stage 4 (cirrhosis). Overall agreement on fibrosis was considered fair (kappa index, 0.409), excellent for stage 4, but poor for stages 0 through 2. Longer biopsies improved kappa scores. In biopsies read as stage 2 by hepatopathologists, 50% were understaged by the community pathologists. As a result, between 20% and 25% of patients with stage ≥2 fibrosis would not be considered candidates for treatment if the community pathologists' readings were accepted.
**Conclusions:** Community pathologists tend to understage hepatic fibrosis in patients with chronic HCV.
**Reviewer's Comments:** In addition to the problem of sampling error, interobserver variability remains an important issue when assessing liver biopsies in chronic HCV. Although longer biopsies reduce the variability somewhat, use of stage 2 fibrosis as a criterion for treatment is weakened by these real-world findings. (Reviewer-Raymond S. Koff, MD).



Keywords: Interobserver Variability

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# An Aperitif Does Not Increase One's Appetite by Enhancing Gastric Emptying

*Aperitif Effects on Gastric Emptying: A Crossover Study Using Continuous Real-Time 13C Breath Test (BreathID System).*

Inamori M, Iida H, et al:

Dig Dis Sci 2009; 54 (April): 816-818

An aperitif, which is believed to enhance one's appetite, does not do so by increasing gastric emptying.

**Background/Objective:** It is widely believed that an aperitif taken before a meal stimulates the appetite. The present study was conducted to determine if an aperitif taken before a meal enhances gastric emptying.
**Design/Participants:** A randomized 2-way crossover study was performed on 10 healthy volunteer males who were between the ages of 20 and 34 years and who were not habitual drinkers.
**Methods:** The study consisted of performing 13C breath tests on the subjects after they drank 50 mL of *umeshu*, a Japanese plum liquor containing 7 mL of alcohol (14%,) with or without a liquid meal (200 kcal/200 mL) containing 100 mg of 13C acetate.
**Results:** In the group who consumed the aperitif plus the liquid meal, their time needed to empty 50% of a labeled meal ($T_{1/2}$) was significantly increased (132 minutes; range, 113 to 174 minutes) versus (112 minutes; range, 92 to 134 minutes) in the control group; $P$ =0.0069). The $T_{lag}$ (very similar to the percentage dosage recovery peak time [minutes]) was also significantly increased (80 minutes; range, 63 to 94 minutes) versus (55 minutes; range, 47 to 85 minutes) in the controls ($P$ =0.0069) as was the time to peak ($T_{peak}$) (81 minutes; range, 62 to 96 minutes) versus (54 minutes; range, 34 to 84 minutes) in the controls ($P$ =0.0069).
**Conclusions:** These results demonstrate that an aperitif taken before a meal leads to delayed gastric emptying compared to a control group who have not taken an aperitif.
**Reviewer's Comments:** Although an aperitif taken before a meal may well help stimulate the appetite as this paper has demonstrated, if that premise is true, it is not because the aperitif leads to enhanced gastric emptying, but by some other mechanism. One must also wonder if the results found in this study would hold up if other aperitifs were tested. In addition and perhaps more importantly, since this study was performed on an Asian population who undoubtedly have different physiologic responses to alcohol, would the results of this study be the same if it were performed on other ethnic groups. (Reviewer-Michael M. Phillips, MD).



Keywords: Gastric Emptying

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# DMC for Colorectal Cancer Screening

*High Detection Rates of Colorectal Neoplasia by Stool DNA Testing With a Novel Digital Melt Curve Assay.*

Zou H, Taylor WR, et al:

Gastroenterology 2009; 139 (February): 459-470

Digital melt curve assay is highly sensitive for detecting colon neoplasms and is improved over other screening techniques for the detection of advanced adenomas.

**Objective:** To determine the sensitivity of stool DNA testing using a digital melt curve (DMC) assay in identifying colorectal carcinoma (CRC) and *KRAS*-positive colorectal adenomas (>1 cm).
**Methods:** Archival stool from patients of 2 previous study groups where CRC was identified in average-risk screened patients were analyzed utilizing the DMC technique. Group I was composed of 31 patients with CRC and target mutations to *KRAS*, *APC*, *BRAF*, and *TP53*. Group II included 8 patients with adenomatous polyps >1 cm with *KRAS* mutations. The assay was able to rapidly scan target genes with a high sensitivity and quantitative capacity of polymerase chain reaction (PCR). Comparisons were made against the PreGenPlus (stool DNA test), Hemoccult, and HemoccultSensa stool cards.
**Results:** The DMC assay was very sensitive, identifying target genes at a concentration of 0.1% (total mutation/total wild type). DMC testing identified at least 1 target mutation in 90% (28 out of 31) of cancers. The stool target mutations were identical to the tumor mutations of the same patient. Detection rates were independent of tumor size, site, or stage. In *KRAS* (+) adenomas, the overall detection rate was 59%, and 80% (8 out of 10) for adenomas >2 cm, 47% (8 out of 17) for those <2 cm, 100% (5 out of 5) for those with high-grade dysplasia (HGD), and 55% for those with low-grade dysplasia (LGD). Advanced adenoma rates of detection were 7% with Hemoccult, 15% with HemoccultSensa, and 26% with PreGenPlus versus 59% by DMC *KRAS* assay ($P$ <0.05).
**Conclusions:** DMC analysis for CRC is high (90%) and is not affected by tumor size, stage, or location. Identification of advanced adenomas is 59%, with sensitivity affected by polyp size and dysplasia grade. DMC assay is significantly more specific and sensitive than PreGenPlus, Hemoccult, and HemoccultSensa.
**Reviewer's Comments:** This interesting study indicates that previous problems associated with stool DNA analysis are being overcome; ie, a vast number of gene mutation rates and associated gene targets can be identified in a single assay (DMC ) with high sensitivity even when mutations rates only represent <0.1% of the entire genes identified in the stool (mutation genes/wild-type DNA). The negative aspects of this study are that the patient-population studied was small and there were no normal controls. Also, more cancer patients need to be studied, which will increase the total number of target genes needed in the assay to identify all cancers. Other questions: How much stool is required from each patient? How easy is it to obtain stools? What is the cost of the test and the number of false positives and false-negatives in a large study population? (Reviewer-Roy K.H. Wong, MD).



Keywords: Colorectal Neoplasia

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# Prucalopride Improves Symptoms of Chronic Constipation

*Prucalopride (Resolor) in the Treatment of Severe Chronic Constipation in Patients Dissatisfied With Laxatives.*

Tack J, van Outryve M, et al:

Gut 2009; 58 (March 1): 357-365

Prucalopride significantly increases spontaneous complete bowel movements compared to placebo in patients with severe chronic constipation.

**Objective:** To ascertain the safety, efficacy, and change in quality of life in patients with chronic constipation treated with prucalopride.
**Design:** Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial.
**Participants:** 865 patients with severe chronic constipation from 7 countries were screened between March 1998 and July 1999. Ultimately, 713 patients were randomized to comprise the intention-to-treat study population. Severe chronic constipation was defined as ≤2 spontaneous complete bowel movements per week.
**Methods:** Patients were randomized to receive either 2 mg or 4 mg of prucalopride or placebo daily for 12 weeks. The primary study end point was the proportion of study patients achieving ≥3 bowel movements per week and the secondary end point was the proportion of study subjects increasing their bowel movements by once a week or more. A quality-of-life questionnaire was used to characterize a constipation satisfaction score. Laxatives were not allowed during the study period.
**Results:** 19.5% ($P$ <0.01) of patients taking 2 mg of prucalopride and 23.6% ($P$ <0.001) of patients taking 4 mg of prucalopride had ≥3 bowel movements per week versus placebo (9.6% of patients). Also, 83% of patients who were unhappy with previous laxative use noted similar responses to prucalopride therapy. At the 4-mg dose, prucalopride reduced the need for straining at stool versus placebo ($P$ <0.05). Prucalopride was well tolerated and headache and diarrhea were minor adverse effects.
**Conclusions:** Prucalopride improved the symptoms and bowel function in patients suffering from severe chronic constipation.
**Reviewer's Comments:** This was a well-designed study. However, although a statistically significant improvement in symptoms was noted with prucalopride, the clinical significance is uncertain. At the 2-mg dose, only 10% more patients had improvement versus those taking the placebo, and at the 4-mg dose, only approximately 14% had improvement. Prucalopride certainly has efficacy, but the effect is modest at best. Secondly, the study was performed for only 12 weeks, so further studies will be required to examine the long-term efficacy of prucalopride. (Reviewer-Ingram M. Roberts, MD).



Keywords: Chronic Constipation

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# Antidepressants May Have Efficacy for Tx of IBS

*Efficacy of Antidepressants and Psychological Therapies in Irritable Bowel Syndrome: Systematic Review and Meta-Analysis.*

Ford AC, Talley NJ, et al:

Gut 2009; 58 (March): 367-378

The relative risk reduction of the symptoms of IBS for antidepressants is 0.66 by meta-analysis of 32 studies.

**Objective:** To determine the efficacy of antidepressants and psychological therapies versus placebo for the treatment of irritable bowel syndrome (IBS) by systemized review of the literature and meta-analysis.
**Materials:** Only studies in which adult patients with IBS were treated were included in the review and meta-analysis.
**Methods:** Only randomized, controlled studies were reviewed and analyzed. Data were pooled, and the relative risk of the patient remaining symptomatic after treatment was calculated with a 95% confidence interval. Finally, the number needed to treat for the effect was determined from the risk difference reciprocal. The quality of the studies using antidepressants was good, while the quality of the psychological therapy studies was, in general, poor.
**Results:** 571 articles were initially identified, 32 of which were thought to be eligible for inclusion in the analysis. Nineteen studies compared controls versus psychological therapies, 12 compared antidepressants with controls, and 1 study compared psychological therapy plus antidepressants with placebo. The relative risk for symptoms in the antidepressant-treated patients was 0.66, without significant differences between selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants. For psychological therapies, the relative risk was 0.67. The number needed to treat was 4 for both psychological and antidepressant therapy.
**Conclusions:** Antidepressant medications are effective for the treatment of the symptoms of IBS. Although the psychological therapy studies were of lower quality than the antidepressant studies, an effect may still be present for psychological therapy used in the treatment of IBS.
**Reviewer's Comments:** This well-performed study from a group of excellent investigators revealed that antidepressants and psychological therapies reduce the symptoms of IBS. The number needed to treat was only 4, which suggests that many patients may benefit from these treatments in addition to a high-fiber diet, antispasmodics, and laxatives. The effect appeared to be seen with all classes of antidepressants (tricyclic antidepressants and SSRIs). (Reviewer-Ingram M. Roberts, MD).



Keywords: Irritable Bowel Syndrome

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# SDD Improves Survival in Critically Ill Patients

*Decontamination of the Digestive Tract and Oropharynx in ICU Patients.*

de Smet AMGA, Kluytmans JAJW, et al:

N Engl J Med 2009; 360 (January 1): 20-31

SDD and/or SOD in critically ill patients hospitalized in ICUs appear to improve survival.

**Background:** Selective decontamination of the digestive tract (SDD) and/or the selective decontamination of the oropharynx (SOD) of critically ill patients are not recommended in many treatment guidelines.
**Objective:** To assess the efficacy of SDD and SOD, or the oropharynx alone, in improving outcomes of critically ill patients.
**Design:** Prospective, cluster randomized trial with a randomized, crossover design within each cluster.
**Participants:** Patients admitted to an ICU with an expected duration of mechanical ventilation of at least 48 hours or with at least a 72-hour expected duration of stay in the ICU.
**Methods:** SDD consisted of IV cefotaxime and the topical application of tobramycin, colistin, and amphotericin B in the oropharynx and stomach. SOD was limited to the same antibiotic paste, but applying it only to the oropharynx. The control group received no intervention. The investigators feared that such treatment could have an impact on the bacterial environment of the entire unit, and, because of this, undertook a cluster randomized trial in which the unit of randomization was each ICU. In order to ensure that each treatment was accomplished at each unit, the 3 treatments were each used for approximately 2 months, and the order of the treatments was randomized. Antibiotic resistance in each unit was monitored during the course of the study. The primary outcome was mortality. Because of potential imbalances that could have been introduced by the clustering of patients, the analyses were corrected for baseline differences (Acute Physiology and Chronic Health Evaluation II score, intubation status, surgical or medical admission, age, and sex).
**Results:** 5939 patients from 13 ICUs were entered into the trial. There were a number of demographic differences between the 3 groups (standard care, SDD, and SOD); in particular, the standard-care group appeared to be slightly less ill. The absolute mortality rates in the 3 groups were not statistically significant and ranged from 26.6% to 27.5%. When the data were adjusted for the various confounders, odds ratios for death in the SDD and SOD groups as compared with the standard care-group were significantly reduced (0.83 and 0.86, respectively). Bacteremia was less common in the SDD-treated group. Lengths of time on the respirator, in the ICU, or in the hospital were not different. There was no apparent emergence of antibiotic-resistant organisms.
**Conclusions:** Absolute mortality rates were reduced by 3.5% and 2.9% by SDD or SOD.
**Reviewer's Comments:** The randomization scheme did break down, and we do not know what other factors might have been different between the 3 groups. These confounding factors make the results harder to accept. However, at least 3 other truly randomized trials, as well as 2 systematic reviews of older trials, have all observed improved survival rates in those receiving selective decontamination or antibiotic prophylaxis. (Reviewer-Ronald L. Koretz, MD).



Keywords: Digestive Tract Decontamination

Print Tag: Refer to original journal article

# Step-Up Tx of Dyspepsia More Cost-Effective Than Step-Down Tx

*Effect and Cost-Effectiveness of Step-Up Versus Step-Down Treatment With Antacids, $H_2$-Receptor Antagonists, and Proton Pump Inhibitors in Patients With New Onset Dyspepsia (DIAMOND Study): A Primary-Care-Based Randomised Controlled Trial.*

van Marrewijk CJ, Mujakovic S, et al:

Lancet 2009; 373 (January 17): 215-225

Primary care physicians who see patients with new onset dyspepsia can begin therapy with antacids and gradually increase the antacid potency of the medication in those who fail treatment.

**Background:** It is unknown if patients who see primary care physicians with new onset dyspepsia all require proton pump inhibitor (PPI) medication or if initially less potent antacid intervention would be as effective.
**Objective:** To compare the effectiveness and cost-effectiveness of 2 different interventions for new onset dyspepsia, namely step-up (beginning with antacids and progressing through $H_2$-receptor antagonist and PPIs until relief is obtained) versus step-down (beginning with PPIs and progressing in the other direction).
**Design:** Randomized, double-blind trial.
**Participants:** Patients ≥18 years of age with new complaints of dyspepsia (pain or discomfort in the epigastrium judged to be due to problems in the upper gastrointestinal tract), with or without associated regurgitation, heartburn, nausea, or bloating. were included. Alarm symptoms (eg, weight loss, anemia, dysphagia, or bleeding) could not be present.
**Methods:** General practitioners in the Netherlands were provided with boxes containing individually wrapped packages of medications and placebos. If relief was not obtained by 4 weeks, the next step of medications was begun. The principal outcomes were overall relief at 6 months and total costs. The techniques for generating the randomization scheme, concealment of allocation, blinding, intent-to-treat analysis, and sample size calculation were all adequate.
**Interventions:** Aluminium/magnesium oxide (4 times daily), ranitidine (150 mg twice daily), or pantoprazole (40 mg once daily) with respective placebos.
**Results:** 332 of the 341 patients were assigned to the step-up/step-down groups. After the first medication, only 24% and 25%, respectively, of the step-up/step-down groups had adequate relief. After 6 months, adequate relief was achieved in 72% and 70%, respectively. All of the other clinical outcomes were also comparable (not significantly different) between the 2 groups, including quality-of-life scores and adverse events. However, the total costs (medical and indirect) were significantly higher in the step-down group. This economic difference was largely due to the costs of medications; when generic rather than prescription costs were employed, the overall difference in cost was no longer significant, although the cost of the medications remained so.
**Conclusions:** The step-up strategy was more cost-effective than the step-down strategy.
**Reviewer's Comments:** It must be understood that this study was done in patients with their first episode of dyspepsia who were being seen by primary care physicians with their first episode of dyspepsia; the data cannot be extrapolated to dyspeptic patients who are referred to gastroenterologists. However, from the perspective of the primary care physician, there is a rationale to begin treatment in such patients with other, less expensive and less potent, antacid medications. (Reviewer-Ronald L. Koretz, MD).



Keywords: New Onset Dyspepsia

Print Tag: Refer to original journal article

# Hyperdynamic UES and Globus Sensation

*Hyperdynamic Upper Esophageal Sphincter Pressure: A Manometric Observation in Patients Reporting Globus Sensation.*

Kwiatek MA, Mirza F, et al:

Am J Gastroenterol 2009; 104 (February): 289-298

Increased respiratory augmentation or marked differences in UES pressures between inspiration and expiration is noted in patients with globus compared to controls.

**Objective:** To measure upper esophageal sphincter (UES) pressure during inspiration and expiration in patients with globus sensation, normal controls, and gastroesophageal reflux disease (GERD).
**Design/Participants:** Retrospective analysis of 131 globus patients (31 males and 100 females; age range, 20 to 86 years), 68 normal controls, and 46 GERD patients without globus.
**Methods:** Of the 131 globus patients of whom 24 had only globus symptoms, 85 had heartburn (HB) plus dysphagia, 5 had concurrent HB, and 15 had dysphagia. All patients underwent manometric studies using high-resolution manometry (HRM), which was performed in the supine position and after ten 5-mL water swallows. Mean UES length, pressure, pressure between inspiration and expiration (respiratory augmentation), and relaxation was obtained.
**Results:** Mean UES pressures were similar in all groups of patients studied (47 to 53 mm Hg). However, when comparing the difference in pressures between inspiration and expiration (respiratory augmentation), globus patients with or without esophageal motility disorders had significantly higher pressures that were 3 times than normal or GERD controls (37.3 to 38.5 mm Hg vs 10.6 to 13 mm Hg; mean difference, 27 mm Hg; $P$ <0.0001). These elevated pressure differences were noted in 60% to 63% of globus patients versus 6% to 15% of normal or diseased controls. Age and esophageal motility patterns were not correlated with elevated respiratory augmentation pressures. Interestingly, 13% of all patient groups had maximal respiratory pressures during expiration rather than during inspiration when one normally notes higher pressures. While mean UES nadir deglutitive pressures were similar, they significantly increased with age in globus patients with and without esophageal dysmotility ($P$ <0.003 and 0.03, respectively).
**Conclusions:** Increased respiratory augmentation or marked differences in UES pressures during inspiration and expiration are prevalent in patients with globus. This increase in augmentation pressure is independent of distal esophageal motility disorders. This observation may be the basis of further studies on the pathogenesis and treatment of globus.
**Reviewer's Comments:** This study is significant in that it identifies a manometric parameter that may characterize this disorder. Many feel that this disorder may be related to visceral hypersensitivity. It would be interesting to determine if various therapies decrease this pressure with concomitant relief of the globus sensation. Problems with the study include: that it is retrospective and uniform data were not obtained in all patients; only 10% fulfilled the strict Rome III criteria for globus; there were significant differences in age groups studied; and patients were studied in the supine position rather than in the upright position, which is when globus is noted. Impedance studies to determine if reflux of contents into the esophagus concomitantly affects respiratory pressure would be of interest. (Reviewer-Roy K.H. Wong, MD).



Keywords: Upper Esophageal Sphincter

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# NBI of Reflux Dz

*The Utility of Narrow Band Imaging in Improving the Endoscopic Diagnosis of Gastroesophageal Reflux Disease.*

Fock KM, Teo EK, et al:

Clin Gastroenterol Hepatol 2009; 7 (January): 54-59

Compared to conventional endoscopy, narrow band imaging identifies more micro-erosions and mucosal islands and increases vascularity, thus improving the diagnostic yield for GERD.

**Objective:** To determine the efficacy of narrow band imaging (NBI) in increasing the endoscopic diagnostic accuracy of gastroesophageal reflux disease (GERD).
**Participants/Methods:** 77 GERD patients who were referred for esophagogastroduodenoscopy (EGD) and 31 controls underwent the study. The EGD was performed initially with white light followed by NBI at normal and 1.5X magnification in the area of the squamocolumnar junction (SCJ). Parameters studied included mucosal breaks, micro-erosions, increased vascularity at the SCJ, punctate spots, mucosal pit patterns, and mucosal islands. The Olympus XGIF-H160Y2 endoscope was used.
**Results:** On endoscopy, there were 41 erosive reflux disease (ERD) cases, 36 nonerosive reflux disease (NERD) cases, and 30 normal controls. When comparing conventional endoscopy to NBI, there were significantly more micro-erosions (52.8% vs 23.3%in controls), increased vascularity at SCJ (91.7% vs 36.7% in controls), and mucosal islands (5.6% vs 38.9%) noted with NBI. When comparing NBI erosive disease versus asymptomatic controls, there were more mucosal breaks and micro-erosions (100% vs 23%) and increased vascularity at the SCJ (95.1% vs 36.7%) ($P$ <0.001) noted with NBI. Pit patterns for ERD versus controls was: tubular (52.8% vs 10%); villous 22.2%; straight pattern (19.4% vs 20%), round pattern (5.6 % vs 70%) ($P$ <0.001). In a comparison between NBI in ERD and NERD, there was similar increased vascularity at the SCJ and types of pit patterns, with the only difference being more mucosal breaks and/or micro-erosions (100% vs 52.8%) seen with NBI. In the NBI comparison between NERD versus controls, more micro-erosions (52.8% vs 23.3% in controls; $P$ <0.001), increased vascularity at the SCJ (91.7% vs 36.7% in controls; $P$ <0.001), and mucosal islands (38.9% vs 50%; not significant) were noted with NBI, but the proportion of round pit pattern (5.6% vs 70%; $P$ <0.001) was greater with controls. Interobserver agreement was good for increased vascularity (kappa = 0.95) and micro-erosions (kappa = 0.89), but lower for pit pattern (kappa = 0.59).
**Conclusions:** These studies indicate that more endoscopic findings can be noted with NBI versus conventional endoscopy. NBI identifies more micro-erosions, increased vascularity, and mucosal islands compared with conventional endoscopy. When NBI and ERD are compared with NERD, the findings are similar in vascularity and pit patterns, but ERD has more mucosal breaks. In controls, the round pit pattern is more common than in both NERD and ERD patients.
**Reviewer's Comments:** While these data are very interesting, in actuality, many of these parameters are not simple to identify. Even pit patterns are not consistently categorized in the literature. In my experience, the same patient may have several pit patterns and because of motility, these characteristics are hard to photograph. Are these findings clinically important? Presently, they are of academic interest, but as we continue to use NBI, these findings may become part of our evaluation. (Reviewer-Roy K.H. Wong, MD).



Keywords: Narrow Band Imaging

Print Tag: Refer to original journal article

# Esomeprazole Will Reduce Gastroesophageal Reflux After Beer Consumption

*Esomeprazole Reduces Gastroesophageal Reflux After Beer Consumption in Healthy Volunteers.*

Franke A, Hepp C, et al:

Scand J Gastroenterol 2008; 43 (December): 1425-1431

Take esomeprazole before drinking beer if you have GERD.

**Background:** It is well known that alcohol increases gastroesophageal reflux in normal volunteers and in patients with gastroesophageal reflux disease (GERD). Therefore, most physicians counselling patients with GERD advise against the consumption of alcoholic beverages, especially beer. Although proton pump inhibitors (PPIs) are frequently prescribed for GERD, their effect on reflux following the consumption of alcohol has not been studied.
**Objective:** To determine the effect of esomeprazole on GERD following the consumption of beer.
**Design/Participants:** Placebo-controlled, double-blind, cross-over study performed on 16 healthy male volunteers.
**Methods:** The volunteers were treated in a cross-over design with 20 mg of esomeprazole or placebo daily for 7 days after which they consumed 500 mL of beer within 5 minutes. Gastroesophageal reflux was determined by a pH-telemetry over a period of 3 hours. Gastric emptying was also measured by ultrasonography and blood concentration of alcohol; cholecystokinin and gastrin were also measured.
**Results:** Gastroesophageal reflux was dramatically and significantly reduced in those receiving esomeprazole compared to those receiving placebo (93% vs 2.6%; *P* =0.001). Gastric emptying, blood ethanol level, and cholecystokinin were unchanged by esomeprazole treatment. Plasma gastrin levels were significantly higher in those receiving esomeprazole (98.6 ± 19.7 pg/mL) versus in those receiving placebo (22.7 ± 3.8 pg/mL; *P* =0.0003). Beer consumption had no effect on plasma gastrin levels in those taking esomeprazole or placebo.
**Conclusions:** In healthy volunteers, esomeprazole significantly reduces gastroesophageal reflux compared to placebo following the consumption of beer. Esomeprazole does not impair gastric emptying after beer consumption, although its use is associated with a significant rise in plasma gastrin levels. It would appear that when a proton pump inhibitor (PPI) is used, moderate beer consumption does not worsen gastroesophageal reflux.
**Reviewer's Comments:** When treating a patient with symptomatic GERD, it is still probably wise to suggest that they stop all alcohol consumption at least until they become asymptomatic. After that if they continue the use of a PPI, it would seem that based on the results of this study, that moderate alcohol consumption would not lead to an exacerbation of their symptoms. (Reviewer-Michael M. Phillips, MD).



Keywords: Beer Consumption & GERD

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# Length of Barrett's Epithelium Is Key Factor in Adequacy of Ablation of HGD

*Patient Predictors of Histopathologic Response After Photodynamic Therapy of Barrett's Esophagus With High-Grade Dysplasia or Intramucosal Carcinoma.*

Yachimski P, Puricelli WP, Nishioka NS:

Gastrointest Endosc 2009; 69 (February): 205-212

The factor most associated with resolution of HGD Barrett's epithelium after PDT therapy is length ≤3 cm.

**Background:** Due to the morbidity and mortality associated with surgical therapy of Barrett's associated high-grade dysplasia (HGD) alternative therapies are being explored.
**Objective:** To evaluate clinical variables that might predict the likelihood of a response to photodynamic therapy (PDT) for patients with Barrett's esophagus.
**Design:** Retrospective cohort study.
**Participants:** 117 patients with Barrett's esophagus and associated HGD, intramucosal carcinoma, or T1 cancer.
**Methods:** Evaluation included endoscopic staging of Barrett's mucosa and/or neoplasia, staging with CT, and endoluminal ultrasonography (EUS). Endoscopic mucosal resection (EMR) of small nodules was also performed where indicated. PDT was given using standard protocols and patients were placed on proton pump inhibitor therapy. Surveillance endoscopy with biopsy was performed 3, 6, 9, and 12 months later.
**Interventions:** PDT therapy and follow up endoscopy.
**Results:** A little over 50% of patients (51%) had HGD and 49% had intramucosal carcinoma. Ablation of HGD or cancer was noted in 70% of patients at 12 months follow up and ablation of Barrett's was noted in 39%. Using multivariate analysis, pre-treatment length of Barrett's esophagus (≤3 cm) was inversely correlated with successful ablation of all Barrett's epithelium.
**Conclusions:** The use of PDT in patients with HGD or intramucosal carcinoma can result in total eradication of Barrett's lining, especially in patients with shorter lengths of Barrett's esophagus.
**Reviewer's Comments:** **Reviewer's Comments:** The increasing long-term experience with effective techniques for ablation of Barrett's esophagus, such as PDT and the newer HALO system, now mandate comparative trials with surgery to determine stratification of risk and treatment protocols that include these less morbid procedures. (Reviewer-J. Mark Lawson, MD).



Keywords: Photodynamic Therapy

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# What Factors Are Associated With Incomplete Small-Bowel CE?

*Risk Factors for Incomplete Small-Bowel Capsule Endoscopy.*

Westerhof J, Weersma R, et al:

Gastrointest Endosc 2009; 69 (January): 74-80

Incomplete small-bowel CE is more common in patients with a history of small-bowel surgery, delayed gastric transit, hospitalization, or borderline bowel preparation.

**Background:** In a significant number of cases, small bowel capsule endoscopy (CE) is incomplete.
**Objective:** To identify the risk factors associated with an incomplete small bowel CE.
**Design:** Retrospective evaluation of data from consecutive CEs.
**Participants:** Patients undergoing CE.
**Methods:** The medical records of patients undergoing CE between September 2003 and August 2007 at a single center were reviewed. Standard instructions specified that patients stop iron therapy, use a low fiber diet, fast after midnight, and drink 4 L of polyethylene glycol (PEG) for bowel preparation; 10 mg of domperidone were given and an antifoam agent was administered.
**Interventions:** CE.
**Results:** Incomplete capsule studies occurred in 19% of cases. Patients with incomplete procedures had longer gastric transit times compared to successful studies (45 vs 21 minutes). Also noted was that risk factors for an incomplete CE examination included prior small-bowel surgery, hospitalization, and moderate or poor bowel preparation.
**Conclusions:** Identification of these risks factors will allow the physician to minimize some of the risk factors associated with an incomplete examination.
**Reviewer's Comments:** The results of this paper suggest that avoiding CE in hospitalized patients may increase the success rate. I am skeptical that bowel preparation and diet measures will result in improved success rates or that reducing gastric transit can be achieved, especially when the use of a pro-motility agent and a rigorous bowel protocol was still associated with a number of failures. One development that might resolve some of these issues is the new technologies that are likely to result in prolonged battery life, such as that seen in the new colon capsule. (Reviewer-J. Mark Lawson, MD).



Keywords: Incomplete Small-Bowel CE

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# Race Is Not Significantly Associated With Extent or Severity of Ulcerative Colitis

*Racial Differences in Disease Extent and Severity in Patients With Ulcerative Colitis: A Retrospective Cohort Study.*

Flasar MH, Quezada S, et al:

Dig Dis Sci 2008; 53 (October): 2754-2760

Race is not significantly associated with the extent of ulcerative colitis disease, nor is the use of steroids when other variables are accounted for.

**Objectives:** To assess disease extent and severity by race in patients with ulcerative colitis (UC).
**Design:** Retrospective cohort study.
**Participants:** 197 patients with UC, who were evaluated as outpatients at the University of Maryland and the Baltimore Veterans Administration from 1997 to 2005.
**Methods:** Patients were identified by ICD-9 codes. All available endoscopy, pathology and clinical notes were reviewed. Patient demographics, association of race with disease extent, association of race with prednisone use, and the need for surgery were assessed.
**Results:** Of the 197 UC patients, 47 (23%) were African American and 150 (77%) were Caucasian. African Americans were significantly less likely than Caucasians to be evaluated at the University of Maryland Hospital (49% vs 70%; *P* =0.008). African Americans and Caucasians were similar in age as well as the proportion <40 years of age at the time of diagnosis. There was a trend toward more limited disease in African Americans, with 23% having proctitis, 23% having left-sided colitis, and 53% having extensive colitis. This compared with 10% having proctitis, 31% having left-sided colitis, and 59% having extensive disease in Caucasians. Females were less likely to have extensive disease (relative risk, 0.64). African Americans were less likely to ever receive steroids (45% vs 62%; *P* =0.065). Being seen at the University of Maryland Hospital was also associated with steroid use (odds ratio, 5.10). Eleven percent of African Americans underwent colectomy compared to 15% of Caucasians.
**Conclusions:** Although there was a trend for African Americans to have less extensive disease and to be less likely to receive steroids, the results were not statistically significant when corrected for other variables.
**Reviewer's Comments:** Although there is a trend toward less extensive disease in African Americans with UC, none of the differences noted are statistically significant. With only 47 African Americans analyzed, this study is underpowered to detect modest differences after correcting for other variables. Caucasians who may have had more extensive disease appeared more likely to have been seen at the University of Maryland Hospital and to have received steroids. Insurance issues, veteran status, racial prejudice, and more limited less severe disease in African Americans may all be contributing factors to be considered. (Reviewer-Allen L. Ginsberg, MD).



Keywords: Ulcerative Colitis

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# Sustained Virologic Response in HCV--A 5-Year Follow-Up

*Clinical, Virologic, Histologic, and Biochemical Outcomes After Successful HCV Therapy: A 5-Year Follow-up of 150 Patients.*

George SL, Bacon BR, et al:

Hepatology 2009; 49 (March): 729-738

In patients with an SVR to treatment for chronic HCV, 5-year follow-up liver biopsies demonstrate an improvement in fibrosis in 80% and in inflammation in 92%.

**Background:** It is generally accepted that patients successfully treated for chronic hepatitis C virus (HCV) infection will demonstrate improvement in hepatic histopathology on follow-up biopsies, which are not routinely undertaken in patients who achieve sustained virologic responses (SVRs). However, follow-up studies addressing this question have been relatively small and the follow-up periods have been variable, but often short. It seems likely that improvements in fibrosis might take longer than improvements in hepatic necroinflammation. Hence, failure to find changes in fibrosis score could reflect relatively short follow-up periods.
**Objective:** To assess the long-term histologic, clinical, and virologic features of patients who had SVRs to treatment for HCV.
**Methods:** Patients with SVRs were invited to enroll in a follow-up study, and if the pre-treatment biopsy showed periportal or focal bridging fibrosis or more fibrosis, to have a repeat liver biopsy after the fourth year of follow-up. HCV RNA was measured by polymerase chain reaction (PCR) and transcription-mediated amplification (TMA) assay, the latter on recent serum samples. Coded biopsies were reviewed using the Ishak methods.
**Results:** Of the 150 enrolled patients, 116 had sufficient fibrosis for inclusion; 60 of these patients had follow-up biopsies, and 49 patients had paired biopsy specimens adequate for Ishak rescoring. Fibrosis scores improved in 80%, and 33% had a decreased fibrosis score of 2 points or greater. Among 8 patients with pre-treatment cirrhosis, only 2 had cirrhosis on follow-up biopsy. Two patients with pre-treatment cirrhosis developed hepatocellular carcinoma. Inflammation decreased in 92% of patients with paired biopsies. Normal or near-normal biopsies were found in 20% of patients. PCR for HCV RNA remained negative in all patients although positive TMA results were found in single samples from 7%, a finding of uncertain significance. Despite SVR, 3 patients had persistent elevations of serum alanine aminotransferase (ALT).
**Conclusions:** Histologic outcomes in the fifth year of follow-up are good and virologic relapse is absent. Nonetheless, hepatocellular carcinoma remains a risk in those with pre-treatment cirrhosis.
**Reviewer's Comments:** When a study begins with 150 patients and bases much of its conclusions on just 40 patients, claims that it is the largest follow-up study seem overblown. Nevertheless, there were no real surprises here. In general, histology improves following SVR, including cirrhosis. However, patients with cirrhosis before treatment remain at risk for hepatocellular carcinoma and must continue under active surveillance. Other data (eg, from the HALT-C study) also suggest that some patients with bridging fibrosis are also at risk for hepatocellular carcinoma. This adds to data supporting the notion that virologic relapse is exceedingly rare on prolonged follow-up. (Reviewer-Raymond S. Koff, MD).



Keywords: Successful HCV Therapy

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# Hyperamylasemia in Acute Liver Failure

*The Role of Etiology in the Hyperamylasemia of Acute Liver Failure.*

Coté GA, Gottstein JH, et al:

Am J Gastroenterol 2009; 104 (March): 592-597

Elevations of serum amylase to levels 3 times greater than the upper limit of normal are found in 12% of patients with ALF and just 9% of these have evidence of clinical pancreatitis.

**Background:** Amylase elevations and acute pancreatitis have been recognized in patients with acute liver failure (ALF) for >3 decades, and the role of acetaminophen (APAP) as both a hepatotoxin and pancreatic toxin has received attention in this regard. However, in many patients with elevated serum amylase levels and ALF in the absence of acetaminophen, there is little evidence of pancreatic involvement, suggesting that nonpancreatic sources of amylase, macroamylasemia, or altered metabolism of amylase may be responsible, including renal failure.
**Objective:** To assess the frequency and characteristics of hyperamylasemia (HA) in patients with acute liver failure of multiple etiologies, with an emphasis on comparing APAP and non-APAP-induced disease.
**Design:** Utilizing the database of the Acute Liver Failure Study Group, patients with amylase determinations on admission to hospital were identified retrospectively, and classified into 2 groups of APAP and non-APAP-associated disease. Serum amylase levels above, but no more than 3 times the upper limit of normal, were labelled elevated, while those with higher values were labelled HA. Documented clinical features of pancreatitis with elevated amylase levels were used to define clinical pancreatitis.
**Results:** Of the 1,033 patients in this database, 60% had amylase levels recorded. In 46% APAP was implicated. Elevated amylase levels were found in 34% of APAP cases and HA in 13%. Among non-APAP cases, 30% had elevated levels and 12% had HA. Of all the patients with HA, only 9% had documented pancreatitis. Patients with HA, regardless of etiology, had elevated creatinine levels. Among those with non-APAP etiologies, HA was also linked with multiorgan failure. HA was associated with a poor outcome, but not as an independent effect.
**Conclusions:** HA in ALF is not etiologically specific, but reflects renal and multiorgan failure and is not an independent predictor of survival.
**Reviewer's Comments:** The retrospective nature of this analysis is a major limitation since it is not clear how thoroughly acute pancreatitis was sought in this group of acutely ill patients. Nonetheless, it does suggest that 90% of ALF patients with HA do not have overwhelming clinical evidence of pancreatitis and that renal failure and multiorgan failure are largely responsible. Although the presence of HA appears to signal a poor outcome, it seems to add little to current assessments of the severity of ALF. (Reviewer-Raymond S. Koff, MD).



Keywords: Acute Liver Failure

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