Pharyngeal electrical stimulation relieves experimental dysphagia in normal individuals and may have application in stroke patients with dysphagia.

**Background:** Dysphagic strokes are associated with demonstrable abnormalities in the motor cortex, namely reduced motor activity. Experimental models of transient dysphagia in humans, accomplished by transcranial magnetic stimulation, are available.

**Objective:** To assess the ability of pharyngeal electrical stimulation (PES) to improve experimental and stroke-induced dysphagia.

**Design:** Minimization-allocated trials in normal volunteers and in stroke patients.

**Participants:** Healthy volunteers for experiment 1; stroke patients with acute dysphagia for experiments 2 and 3.

**Methods:** In experiment 1, healthy volunteers were subjected to transcranial magnetic stimulation with the PES electrode in place; swallowing was assessed by videofluoroscopy that measured various time intervals in the swallowing process. The outcome was the percentage of normal swallows. In experiment 2, patients with very recent strokes and dysphagia were "randomly" exposed to sham or one of 4 different "doses" of PES in a factorial design that assessed 3 versus 5 days and once versus thrice daily treatments. In experiment 3, a different group of patients with recent strokes and dysphagia were "randomized" to true or sham PES. The primary outcome was occurrence of aspiration determined by videofluoroscopy.

**Interventions:** Based on the findings of experiment 2, PES was provided once daily for 3 days.

**Results:** In the healthy volunteers subjected to transient dysphagia, true PES resulted in a higher percentage of normal swallows than did sham PES. Thirty-one patients were enrolled in experiment 3, but only 12 true and 16 sham subjects completed the trial. PES recipients did have less aspiration, better dysphagia severity scores, and shorter durations of hospitalization (21 vs 26 days). There was no difference in mortality, pulmonary infections, or percentage of normal swallows. An assessment of the outcomes was hampered by an unusual method of generating the allocation sequence, possible lack of concealment of allocation, potential breaking of the blind because PES does cause symptoms, inability to perform intent-to-treat analysis, and possible vested interest bias (since the negative data were only available in the discussion or the supplement).

**Conclusions:** PES is a neurostimulation intervention that improved dysphagia occurring after a stroke.

**Reviewer's Comments:** As noted, a number of potential sources of bias did create some problems with the reliability of the conclusions. Although this is a novel potential intervention, more data are required from large, well-designed and executed randomized trials comparing PES to standard interventions. (Reviewer-Ronald L. Koretz, MD).

© 2010, Oakstone Medical Publishing

Keywords: Stroke, Dysphagia, Rehabilitation, Pharyngeal Electrical Stimulation

Print Tag: Refer to original journal article
A Review of PPI-Related Small Intestinal Bacterial Overgrowth

Increased Incidence of Small Intestinal Bacterial Overgrowth During Proton Pump Inhibitor Therapy.

Lombardo L, Foti M, et al:
Clin Gastroenterol Hepatol 2010; 8 (June): 504-508

Small intestinal bacterial overgrowth is significantly more common in long-term users of proton pump inhibitors compared to patients with irritable bowel syndrome and normal controls and can be eradicated with rifaximin in 87% to 91% of cases.

Objectives: To determine the effect of chronic proton pump inhibitor (PPI) therapy on the prevalence of small intestinal bacterial overgrowth (SIBO) by glucose hydrogen breath test (GHBT), the risk factors for the development of SIBO, and the eradication rate following treatment with rifaximin.

Participants/Methods: 450 consecutive patients were enrolled into 3 different groups for this study: group 1, 200 patients with gastroesophageal reflux disease (GERD) treated with PPIs for at least 2 months; group 2 (patient controls), 200 irritable bowel syndrome (IBS) patients as defined by Rome III criteria in absence of PPI treatment for at least 3 years; and group 3, 50 normal controls (NC). GHBT was performed at time zero and at 2 months. Gastrointestinal symptoms were graded for pain severity, frequency and duration, bloating, and constipation/diarrhea. SIBO was treated with rifaximin 400 mg thrice daily for 2 weeks while PPI treatment continued.

Results: Significantly more SIBO was noted in the PPI group (50%) when compared to the IBS group (24.5%; P <0.001; OR, 3.14) and versus the NC group (6%; P <0.001; OR, 16.0). In patients from 41 to 60 years of age (but not at older ages), SIBO was more frequent in the PPI users versus the IBS patients (P <0.01). In PPI users, the prevalence of SIBO was greater in patients using PPIs for ≥13 months versus <13 months (P <0.001; OR, 11). SIBO symptom severity increased over time, from moderate in 11% and severe in 11% of cases within the first year of treatment to moderate in 30% and severe in approximately 40% of cases after the third year of PPI treatment. The involved symptoms included diarrhea in 30% of cases and bloating in 50%, which varied in severity during the period of observation. Constipation and abdominal pain did not increase over time and remained about 10%. Bloating and weight loss were more frequent in the PPI group compared to the IBS group (P <0.001). Macrocytosis/megaloblastic anemia occurred more frequently in the PPI groups versus the IBS group, but the difference was not statistically significant. Eradication of SIBO following rifaximin was 87% and 91% for the PPI group and the IBS group, respectively. Comparing SIBO-eradicated patients versus non–SIBO-eradicated patients, bloating improved/absent in 90% versus 30% of cases, diarrhea in 94% versus 35% of cases, and abdominal pain in 92% versus 20% of cases, respectively. Rifaximin was well tolerated.

Conclusions: SIBO occurs more frequently in long-term PPI users compared to patients with IBS and normal controls not on PPI therapy. Treatment with rifaximin eradicated SIBO in 87% of the PPI group and 91% of the IBS group, with symptom improvement in patients who continued to take PPIs.

Reviewer’s Comments: Profound acid inhibition results in bacterial overgrowth with consequences we may not recognize. Physicians give twice the suggested PPI dose because the cost of a 40 mg pills is the same as the 20 mg pill. Not infrequently, the 40 mg pill is given twice a day if the symptoms do not improve, which means giving quadruple the Food and Drug Administration approved dose. These doses should be reserved for patients with long-segment Barrett’s esophagus or Zollinger-Ellison syndrome and not for those with routine GERD or epigastric pain, as lifelong therapy may be indicated. (Reviewer-Roy K.H. Wong, MD).

© 2010, Oakstone Medical Publishing

Keywords: Small Intestine, Bacterial Overgrowth, PPIs, Rifaximin

Print Tag: Refer to original journal article
Capsule endoscopy produces more diagnoses than barium small bowel x-ray, but this does not translate into improved clinical outcomes.

**Background:** Patients with obscure gastrointestinal bleeding (bleeding for which a source could not be identified by upper and lower endoscopy) are usually subjected to other diagnostic procedures to assess the small intestine. Capsule endoscopy makes more diagnoses than small bowel x-rays.

**Objective:** To determine if the use of capsule endoscopy in obscure bleeding impacts clinical outcomes.

**Design:** Randomized trial.

**Participants:** Patients with gastrointestinal bleeding (overt bleeding with anemia or occult bleeding associated with anemia and haemoccult-positive stool) who had undergone nondiagnostic upper endoscopy, colonoscopy, and push enteroscopy.

**Methods:** Eligible patients were randomized (computer-generated sequence with stratification for occult or overt bleeding) into 2 arms, capsule endoscopy or dedicated barium small bowel x-ray. A sample size calculation indicated that 136 patients would be required. The primary outcome was recurrent bleeding; secondary outcomes were the use of other diagnostic or therapeutic interventions, hospitalization for bleeding, and blood transfusion requirements.

**Results:** 66 patients were randomized to the capsule endoscopy group and 70 to the radiologic group; only 47 and 54, respectively, completed the 12-month follow-up. Diagnoses were more commonly made with capsule endoscopy (20) compared to small bowel radiography (5). Recurrent bleeding occurred in 20 patients who underwent capsule endoscopy and 17 patients who had small bowel radiography; 17 endoscopy patients and 15 radiography patients had subsequent interventions, of which almost all were other diagnostic tests. Eight endoscopy patients were hospitalized for bleeding (5 were transfused) and 4 patients in the radiography group were hospitalized (all 4 were transfused). There were 5 deaths in the trial, all in the capsule endoscopy group. No differences were seen when the occult and overt subgroups were separately analyzed.

**Conclusions:** Capsule endoscopy established more diagnoses but had no impact on the subsequent clinical outcomes. Further therapeutic or diagnostic interventions may be required.

**Reviewer's Comments:** In the 1970’s, we learned that simply making a diagnosis did not have any impact on the clinical outcome in patients with overt gastrointestinal bleeding. The advantage to performing endoscopy only became apparent when it became possible to do therapeutic procedures through the instruments. Thus, this finding about capsule endoscopy should not come as any surprise. The conclusion that further diagnostic interventions may be required is contrary to the observations. For patients with overt obscure bleeding, a diagnosis may be necessary because there is a threat of future mortality from massive bleeding. However, for occult bleeding, the only threats to the patient are cancer (which are rare in the small intestine) and anemia; the latter can be managed by chronic iron replacement. A lifetime course of iron therapy is probably cheaper than 1 capsule endoscopy. (Reviewer-Ronald L. Koretz, MD).

© 2010, Oakstone Medical Publishing

Keywords: Obscure Bleeding, Capsule Endoscopy, Small Bowel Radiography

Print Tag: Refer to original journal article
Screening flexible sigmoidoscopy reduces colon cancer incidence and mortality and may reduce all-cause mortality.

**Background:** Colon cancer, which is the third most common cancer in the world, has a high mortality rate, accounting for approximately 600,000 deaths per year. In cases of localized disease, the survival rates are 90%. Those who undergo biennial screening with a fecal occult blood test have a 25% reduced rate of mortality. Flexible sigmoidoscopy can be used to examine the rectum and sigmoid colon where around two-thirds of adenomas and colorectal cancers are located.

**Objective:** To assess the ability of a one-time only flexible sigmoidoscopy around the age of 60 years to reduce the incidence and mortality of colon cancer.

**Design:** Randomized trial.

**Participants:** 325,000 subjects in the U.K. were mailed information about colon cancer and sigmoidoscopy; they were asked if they would undergo a sigmoidoscopy if one was offered. The 170,000 subjects who responded affirmatively were entered into the trial.

**Methods:** The subjects, aged 55 to 64 years, were randomized 2:1 (controls:screened), and those who were allocated to the sigmoidoscopy arm were invited to undergo the procedure. Those who had advanced neoplasms or cancer were entered into surveillance programs, and the remaining individuals, as well as all of the controls, were passively followed through various computer databases. The controls were not informed that they were in a trial. Follow-up was planned for 11 years. The methods of randomization were adequate; a sample size was calculated.

**Results:** Approximately 57,000 people were randomized into the flexible sigmoidoscopy arm and 113,000 became the controls. At the end of the follow-up, the screened group had significantly fewer colon cancers (hazard ratio [HR], 0.67; 95% CI, 0.60 to 0.76) as well as colon cancer deaths (HR, 0.57; 95% CI, 0.45, 0.72). The reduced incidence of colon cancer was restricted to distal lesions. The all-cause mortality tended to be better in the screened group (HR, 0.95), but this was not significant (95% CI, 0.91 to 1.00; \( P =0.0519 \)).

**Conclusions:** A one-only screening flexible sigmoidoscopy around the age of 60 years resulted in a reduction in future colon cancer incidence and mortality.

**Reviewer’s Comments:** Colon cancer screening cannot be cost-effective if it does not save life-years. This is the first trial that has suggested that life-years might be saved; it fails to the remaining trials to validate this finding of a trend for an improvement in all-cause mortality. If life-years are saved, the evidence would strongly support flexible sigmoidoscopy as the test of choice. It is unknown if colonoscopy will be better (because more colonic surface area is examined), worse (because of more adverse events), or no different (if colonoscopy does not protect against proximal cancer, which is a finding of several observational studies). Unless there is enough additional benefit to compensate for the increased cost and risk, colonoscopy would be the test of choice for screening. (Reviewer-Ronald L. Koretz, MD).

© 2010, Oakstone Medical Publishing

Keywords: Colon Cancer, Prevention, Screening, Flexible Sigmoidoscopy

Print Tag: Refer to original journal article
Patients having colonoscopic screening by an endoscopist with adenoma detection rates ≥20% are less likely to develop interval cancer.

**Background:** A variety of "quality indicators" have been proposed for screening colonoscopy, including adenoma detection rate (ADR), cecal intubation rate (CIR), and withdrawal time. There are no good validation data for any of these proposed indicators.

**Objective:** To validate the ADR and CIR as quality indicators for screening colonoscopy.

**Design:** Retrospective review of the medical records of patients undergoing colonoscopic screening.

**Participants:** Subjects aged 40 to 66 years who were at average risk of colon cancer and who underwent screening colonoscopy between October 2000 and December 2004.

**Methods:** All potentially eligible subjects were identified through a retrospective review of endoscopy records from a nationwide colon cancer screening program in Poland. Those who did not have colon cancer identified at the time of the screening examination and who had had an adequate bowel preparation were candidates for the study. Regional and national cancer registries were assessed for each of these individuals for 5 years after the screening colonoscopy. Patients who had been diagnosed with colon cancer within that period of time were labeled as having "interval cancer." The colonoscopy reports were reviewed for comments that the cecum had been intubated and for evidence of polypectomy; pathology records were assessed to confirm the diagnosis of an adenoma. Characteristics of the subjects and the endoscopists were also assessed. The primary outcomes were the rates of interval cancer in the categories of ADR (<11%, 11.0% to 14.9%, 15% to 19.9%, or ≥20%) and CIR (<85%, 85% to 89.9%, 90% to 92.9%, 93% to 94.9%, or ≥95%). Using the highest rates as baselines, hazard ratios were calculated for the other categories.

**Results:** Approximately 50,000 subjects were identified, but about 5000 were excluded for various reasons, leaving slightly >45,000 individuals as the study subjects. No significant differences in the hazard ratios were observed for any of the CIRs. The hazard ratios for each of the different ADR categories that were <20% were all 10 to 13, all significantly higher than for the ADR ≥20% but not different from each other.

**Conclusions:** ADR was a predictor of the risk for interval cancer.

**Reviewer's Comments:** This study did show an association between a higher ADR and a reduced risk for subsequent cancer; in that regard, ADR was validated as a "quality indicator." However, the study did not show that having a colonoscopy by endoscopists with an ADR ≥20% would guarantee less colon cancer, since association cannot establish causation. As noted by the investigators, there may have been incomplete reporting of colon cancer, although it is unclear how such a bias would affect the data. (Reviewer-Ronald L. Koretz, MD).

© 2010, Oakstone Medical Publishing

Keywords: Colon Cancer Screening, Adenoma Detection Rate, Cecal Intubation Rate

Print Tag: Refer to original journal article
Low-volume magnesium citrate and split-dosing preparations yield a better colonic preparation and better patient satisfaction when compared to a single-dose, high-volume polyethylene glycol preparation for colonoscopy.

**Objective:** To determine which of 3 colonoscopy cleansing regimens provides better colonoscopy cleansing and better patient satisfaction.

**Design/Methods:** This prospective, randomized, single-blinded controlled study compared 3 bowel cleansing regimens: group 1 received 4 L of polyethylene glycol (PEG) starting at 10 PM the night before the procedure; group 2 received a split-dose PEG regimen, 2 L at 8 PM the night before the procedure and 2 L at 5 AM on the day of the procedure; group 3 (split-dose and low-volume regimen) received magnesium citrate 250 mL at 8 PM the night before the procedure and 2 L of PEG at 5 AM the day of the procedure. PEG was consumed at a rate of 200 mL/10 minutes. Colonoscopies were performed between 8:30 and 11 AM, and each procedure was allocated 30 minutes. The endoscopist was blinded to the type of solution the patients took. The primary outcome was satisfactory (excellent or good) bowel preparation between groups according to the Aronchick scale. Secondary outcomes included patient tolerance, satisfaction, and preference (willingness to repeat the preparation). Procedures were performed by 27 gastrointestinal fellows, all with experience of >150 colonoscopies.

**Results:** Patient compliance was high in all 3 regimens (92%, 91%, and 96% for group 1, 2, and 3, respectively). Significantly more patients in group 3 had a satisfactory bowel preparation compared to patients in group 1 (75% vs 51%; \(P < 0.001\)), with no significant difference between group 3 and group 2 (75% vs 76%; \(P = 0.896\)). Only in group 1 was inadequate patient preparation noted (n=7), with only bowel preparation as a significant factor for this difference. Reasons for poor compliance included large volume to ingest (44%, mainly groups 1 and 2), bad taste (33%, mainly group 3), and abdominal pain and nausea (15%). When patients were asked if they would repeat the same preparation if necessary, significantly more people said "yes" in group 3 (93%) compared to group 2 (62%; \(P < 0.001\)) and group 1 (48%; \(P < 0.001\)). Overall satisfaction was graded highest in group 3 (43%) versus group 1 (23%; \(P < 0.010\)) versus group 2 (35%; \(P < 0.133\)).

**Conclusions:** This study indicates that the low-volume magnesium citrate 250 cc plus PEG 2 L and split-dosing preparation results in a better colonic preparation and better patient satisfaction when compared to a single-dose, high-volume (4 L) preparation for morning colonoscopies. In addition, more patients were willing to have a repeat colonoscopy with the low-volume preparation.

**Reviewer's Comments:** This study addresses a recurring patient complaint of too much to drink for colon preparation. This preparation looks like a good alternative to our present armamentarium. (Reviewer-Roy K.H. Wong, MD).

© 2010, Oakstone Medical Publishing

Keywords: Magnesium Citrate, Split Dose, Low Volume, Compliance, Tolerance

Print Tag: Refer to original journal article
Early use of transjugular intrahepatic portosystemic shunt in Child-Pugh class B and C cirrhotics with acute variceal bleeding reduces the risk of persistent bleeding/re-bleeding and improves survival.

**Background:** Current therapy of acute variceal bleeding with vasoactive drugs, band ligation, or sclerotherapy is unsuccessful in controlling bleeding in 20% of patients. Transjugular intrahepatic portosystemic shunt (TIPS) has been used as rescue therapy when medical and endoscopic treatment fails.

**Objective:** To determine if early use of TIPS with an extended polytetrafluoroethylene stent would reduce persistent bleeding or re-bleeding in high-risk patients.

**Design/Methods:** In this multicenter European study, cirrhotic patients with Child-Pugh class B and C disease and acute variceal bleeding were treated with vasoactive drugs and endoscopic therapy within 12 hours of admission. Within 72 hours of randomization, which occurred 24 hours after admission, patients were assigned to TIPS or to continued medical and endoscopic therapy and repeated band ligation until variceal eradication. If bleeding persisted or re-bleeding occurred, TIPS was employed as rescue therapy. A severe re-bleeding episode requiring >2 units of blood or 2 less severe episodes was defined as treatment failure. Portal-pressure gradients were measured, and if needed, shunt dilatation or angioplasty was performed. Failure to control acute variceal bleeding or to prevent significant re-bleeding within 1 year was the primary end point.

**Results:** Among 359 patients with acute variceal bleeding, only 63 (18%) were eligible for randomization. Baseline characteristics of the 32 assigned to TIPS and the 31 assigned to non-TIPS treatment were similar. Portal-pressure gradients declined from a mean of 20.2 mm Hg to 6.2 mm Hg after TIPS although in 2 TIPS patients, it remained above 12 mm Hg. Re-bleeding occurred in just 1 (3%) of the early TIPS-treated patients versus 14 (45%) of the non-early TIPS patients. At 1 year, the probability of remaining free of re-bleeding was 97% in the early TIPS group and 50% in the non-TIPS group, and survival was significantly higher at 1 year in the early TIPS group at 86% versus 61%. Hepatic encephalopathy developed in 28% of the early TIPS patients versus 40% of those receiving medical and endoscopic therapy (a nonsignificant difference).

**Conclusions:** The use of TIPS early after the onset of acute variceal bleeding in cirrhotic patients with Child-Pugh class B and C disease treated with vasoactive drugs and endoscopic therapy resulted in a marked reduction in re-bleeding and mortality.

**Reviewer’s Comments:** Despite the limited number of patients studied, the results of this trial are quite extraordinary. Not only did early TIPS prevent re-bleeding in 97% of patients followed at 1 year, but it also improved survival at 1 year to an amazing 86%. As indicated in an accompanying editorial, it is possible that the reductions in portal pressure associated with early TIPS and the use of the extended polytetrafluoroethylene stent reduced the likelihood of progressive decompensation which was seen in the patients not receiving early TIPS. Confirmatory studies will be essential. (Reviewer-Raymond S. Koff, MD).

© 2010, Oakstone Medical Publishing

Keywords: Cirrhosis, Variceal Bleeding/Re-Bleeding, TIPS

Print Tag: Refer to original journal article
Ribavirin Enhances Interferon Activity Via Interferon Signaling

*Ribavirin Improves Early Responses to Peginterferon Through Improved Interferon Signaling.*

Feld JJ, Lutchman GA, et al:

Gastroenterology 2010; 139 (July): 154-162

---

Ribavirin appears to enhance the action of peginterferon by augmenting interferon signaling, rather than by hepatitis C virus RNA mutagenesis.

**Background:** In the dozen years since the approval of ribavirin for use in combination with interferon in the treatment of chronic hepatitis C virus (HCV) infection, the mechanisms responsible for its synergistic action have been enigmatic. Early on, inhibition of inosine monophosphate dehydrogenase was demonstrated, as well as inhibition of HCV RNA polymerase, but these actions were deemed insufficient to explain the drug's efficacy when used with interferons. Similarly, there was some evidence that ribavirin had an immunomodulatory effect and, subsequently, lethal mutagenesis was promoted as a potential mechanism. Most recently, up-regulation of interferon-stimulating genes has received attention.

**Objective:** To assess the effect of ribavirin on early viral kinetics, serum cytokines, and mutation rates in hepatitis C patients treated with peginterferon α-2a.

**Methods:** In this study from the National Institutes of Health (NIH), 50 treatment-naïve patients with chronic HCV, genotype 1 were randomized to treatment with peginterferon α-2a (180 µg weekly) and 1000 to 1200 mg of ribavirin daily for 48 weeks or peginterferon α-2a for 4 weeks followed by identical doses of peginterferon and ribavirin for 44 weeks. Quantitative HCV RNA was measured frequently before and through 72 hours after beginning treatment to assess viral kinetics, weekly through week 4, then at week 6 and 8, then monthly through week 24, and then bimonthly. Serum cytokine levels were measured, and an assay for serum ribavirin levels was developed. HCV RNA sequencing was used to identify mutagenesis.

**Results:** The 2 treatment groups, each with 25 patients, were similar in baseline features. The first-phase decline in HCV RNA following the beginning of treatment was similar whether or not ribavirin had been given. Second-phase declines were more rapid in recipients of ribavirin but only in patients with adequate first-phase declines. Among the cytokines measured, induction of interleukin-gamma–inducible protein-10 (IP10) was significantly higher at 12 hours following combination therapy than peginterferon alone and was correlated with viral kinetics and serum ribavirin levels on day 3 in patients with an adequate first-phase decline in HCV RNA. No evidence of mutagenesis was found.

**Conclusions:** Ribavirin appears to enhance the second-phase of HCV RNA decline if the first-phase is adequate, stimulates interferon-gamma–IP10, but does not affect HCV RNA mutagenesis.

**Reviewer's Comments:** If improved interferon signaling is responsible for ribavirin's enhancement of the response to interferon, it would seem possible that other drugs capable of augmenting interferon signaling could be developed. A drug that was as effective as ribavirin but without the toxicity of this agent would be worth pursuing. (Reviewer-Raymond S. Koff, MD).

© 2010, Oakstone Medical Publishing

Keywords: Ribavirin, Peginterferon, Viral Kinetics, Serum Cytokines, Viral Mutagenesis

Print Tag: Refer to original journal article
Radiation exposure is lower during endoscopic retrograde cholangiopancreatography performed by an experienced endoscopist.

**Background:** Radiation exposure during endoscopic retrograde cholangiopancreatography (ERCP) is not trivial and may contribute to future cancer risk.  

**Objective:** To determine what role the endoscopist's experience plays in fluoroscopy time during ERCP.  

**Design:** Retrospective analysis of prospectively collected data.  

**Participants:** Patients undergoing ERCP entered into the ERCP Quality Network database.  

**Methods:** The records of 9052 patients entered into the database from 2007 to 2009 were analyzed to determine factors associated with fluoroscopy time. Over 20 factors were analyzed for using a variety of statistical techniques.  

**Interventions:** ERCP with fluoroscopy.  

**Results:** Compared to endoscopists performing >200 ERCPs/year, those performing <100 ERCPs/year had a 104% increase in fluoroscopy time and those doing between 100 and 200 cases a year had a 27% increase in fluoroscopic time. Interestingly, every 10 years of experience resulted in a 21% decrease in radiation exposure. For high radiation exposure procedures, the increase in fluoroscopy time was 59% for endoscopists performing <100 cases/year and 11% for those doing between 100 and 200 cases/year.  

**Conclusions:** Fluoroscopy times were statistically lower for endoscopists performing >200 cases/year and with more senior status. This may have implications in the reduction of radiation exposure.  

**Reviewer’s Comments:** Clearly, the literature suggests that complicated procedures, a lesser experienced endoscopist, and the presence of a fellow can be associated with higher radiation doses. In addition, other studies have shown that monitoring radiation doses can result in shorter fluoroscopy times. This study reinforces the well-accepted belief that results and outcomes for many procedures are related to procedural volume. This appears to also apply to radiation exposure to our patients undergoing ERCP. (Reviewer-J. Mark Lawson, MD).

© 2010, Oakstone Medical Publishing
Stenting the common bile duct when large stones are present results in a significant reduction in stone size over a 2-month period.

**Background:** Large common bile duct stones ≥20 mm in size are difficult to remove and the use of fragmentation techniques results in prolonged procedure time.

**Objective:** To evaluate the effect of biliary stenting for treatment of common bile duct stones. **Design:** Retrospective trial.

**Participants:** Patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) at a single medical center who had common bile duct stones and were treated with a 7F double pigtail plastic stent insertion without stone removal at the initial procedure reviewed. Forty patients met inclusion criteria and included patients with stones ≥20 cm or with ≥3 stones.

**Methods:** ERCP with double pigtailed 7F stent insertion was performed. Two months later, a sphincterotomy was performed, and stone extraction was attempted using a mechanical lithotripter or balloon catheter.

**Interventions:** ERCP with stent insertion followed 2 months later by sphincterotomy and stone removal.

**Results:** Mean patient age was 77.8 years. There was a marked decrease in stone number after 2 months of stenting (P <0.0001). Larger stones became smaller and small stones disappeared, with the median stone index measurements dropping from 4.6 to 2.0 (P <0.0001). Complete stone removal was accomplished at the time of second ERCP in 93% of cases. Complications after the second ERCP included cholangitis in 13% and pancreatitis in 5%.

**Conclusions:** Bile duct stenting for 2 months resulted in reduction of stone number and size without significant risk.

**Reviewer's Comments:** Biliary stenting is certainly a reasonable option when faced with large or multiple stone that are difficult to remove, particularly in a frail patient. The mechanism for the decrease in stone number and size is open to debate and may be related to stone-stent friction or changes to the bile composition. (Reviewer-J. Mark Lawson, MD).

© 2010, Oakstone Medical Publishing

Keywords: Common Bile Duct Stones, Biliary Stenting

Print Tag: Refer to original journal article
Use high-resolution transabdominal ultrasonography to look for complications of Crohn's disease.

**Background:** When treating patients with Crohn's disease, it is often necessary to determine if they have developed complications frequently associated with this disease, such as strictures, fistulas, and abscesses. CT scans can ascertain the presence of most of these problems with a fair degree of accuracy, but the patient is exposed to a significant dose of radiation, especially when one considers the fact that imaging studies often need to be done repeatedly as a follow-up or with ensuing episodes of symptoms. In an attempt to circumvent repeated exposure to ionizing radiation for these chronically ill patients, non-radiation imaging is needed.

**Objective:** To evaluate the diagnostic accuracy of high-resolution transabdominal ultrasound (US) in diagnosing these complications of Crohn's disease.

**Participants/Methods:** 58 patients with known Crohn's disease were studied with high-resolution ultrasonography (US) between April 2003 and July 2009. There were 31 women and 27 men studied, who had a mean age of 36.3 years (range, 13 to 81 years). Only patients with previously documented Crohn's disease were studied, and 20 of the patients were studied on a second occasion for different symptoms. Thus, a total of 78 studies were made on the 58 patients. Within 2 weeks of the US study, other imaging studies, such as MRI, CT, enteroclysis, or endoscopy and biopsy were performed.

**Results:** 28 patients had bowel stenosis (36% of the 78 studies); 20 were in the small bowel and 8 were in the colon. Of the 28 stenoses, 24 were correctly found by US (sensitivity, 86%). Four strictures found by a CT study could not be found by US. In 5 patients, the diagnosis of a stenosis was falsely positive (specificity, 90%). Twenty-three patients (29% of the 78 studies) presented with fistulas, both interenteric and to other organs. Eighteen of the 23 fistula were correctly identified by US (sensitivity, 78%). Five fistulas could not be identified by US because they were in the perirectal area. The diagnosis of interenteric fistula was erroneous in 3 patients (specificity, 95%). In 10 patients, an abscess was found (13% of 78 studies). Nine of the 10 abscesses were correctly diagnosed by US (sensitivity, 90%). One diagnosis of an abscess was a false positive (specificity, 99%).

**Conclusions:** This study has demonstrated that with experienced examiners, high-resolution transabdominal US has excellent diagnostic accuracy in patients with Crohn's disease who have developed strictures, fistula, or abscesses.

**Reviewer's Comments:** This report suggests that the use of high-resolution transabdominal US (which exposes patients to no radiation and requires no intravenous contrast) should be encouraged as the initial diagnostic tool when complications of Crohn's disease are suspected. (Reviewer-Michael M. Phillips, MD).

© 2010, Oakstone Medical Publishing

Keywords: Diagnostic Studies, Ultrasound, Disease Complications

Print Tag: Refer to original journal article
Patients with Sjögren's syndrome have a 25% to 33% incidence of pancreatic dysfunction.

**Background:** Sjögren's syndrome is an autoimmune disease considered to affect all exocrine glands. Although it is well known that salivary and lachrymal glands are involved in this syndrome, other exocrine dysfunction has not been established.

**Objective:** To evaluate the exocrine and endocrine function in a group of patients with established Sjögren's syndrome.

**Participants/Methods:** 12 patients with a diagnosis of Sjögren's syndrome, with no known pancreatic disease, were randomly selected for this study. None were smokers or consumed excessive alcohol. They were examined with regard to the morphology and the endocrine and exocrine function of their pancreas. The group was studied with secretin-stimulated magnetic resonance cholangiopancreatography (MRCP), a Lundh test, oral glucose tolerance test, and blood studies.

**Results:** Morphologic changes were found in 25% of patients by means of secretin-stimulated MRCP, and 2 patients had chronic pancreatitis-like changes. Four (33%) of the patients studied had diminished exocrine function of the pancreas, with either significantly reduced amylase and/or lipase in the pancreatic juice.

**Conclusions:** The present study has demonstrated that patients with Sjögren's syndrome have 25% to 33% incidence of pancreatic dysfunction, which is much higher than in a background population. Patients with Sjögren's syndrome, who have appropriate symptoms, should be investigated for pancreatic dysfunction and chronic pancreatitis.

**Reviewer's Comments:** This article demonstrated that in a significant number of patients with Sjögren's syndrome, there is structural damage to the pancreas, which expands our knowledge of the exocrinopathy associated with this disease. It has been estimated that 5% to 6% of patients diagnosed with chronic pancreatitis have the newly recognized autoimmune or autoimmune-related pancreatitis (AIP). As salivary gland dysfunction is frequently seen in AIP, this condition may be part of the spectrum of autoimmune diseases that includes Sjögren's syndrome. (Reviewer-Michael M. Phillips, MD).

© 2010, Oakstone Medical Publishing

Keywords: Sjögren's Syndrome, Pancrease, Function, Morphology

Print Tag: Refer to original journal article
Oral Valganciclovir Effectively Treats CMV Infection in Severe UC

Oral Valganciclovir for Colonic Dilatation in Ulcerative Colitis Associated With Human Cytomegalovirus Infection.
Criscuoli V, Plano S, et al:
Inflamm Bowel Dis 2010; 16 (May): 727-728

Valganciclovir is effective in the treatment of cytomegalovirus infection in patients with ulcerative colitis.

Background: Fulminant colitis and toxic megacolon are dreaded complications of ulcerative colitis (UC). Immunosuppressive medications such as corticosteroids, aminopurines, and methotrexate as well as biologic anti-tumor necrosis factor agents can increase susceptibility to infection with Clostridium difficile or cytomegalovirus (CMV). Colitis patients infected with these pathogens often become refractory to medical therapy and may require life-saving colectomy. American College of Gastroenterology Practice Guidelines for the management of patients with severe colitis unresponsive to maximal immunosuppressive therapy recommend efforts to diagnose CMV infection with sigmoidoscopy biopsies and viral cultures, and also recommend the treatment of infected patients with ganciclovir. Nevertheless, most patients with colonic dilatation and CMV infection must be treated surgically. Valganciclovir is an orally administered prodrug of ganciclovir that has been shown to be effective and well tolerated in the treatment of CMV retinitis in patients with AIDS. It provides greater systemic bioavailability, is usually well tolerated, and is easily administered.

Case Report: A 69-year-old woman with UC of 10 years' duration presented with severe disease flare with 10 loose bloody bowel movements per day, abdominal pain, tenderness, fever (temperature, 38.7°C), and hypoalbuminemia (2.3 g/dL). This flare occurred despite ongoing treatment with azathioprine for steroid dependence. She failed to improve despite therapy for 4 days with IV methylprednisolone and total parenteral nutrition, and developed colonic dilatation seen on abdominal x-rays and CT scan. Sigmoidoscopy without air insufflation revealed multiple large ulcers as well as severe colitis. Biopsies revealed CMV nuclear inclusions. Valganciclovir (450 mg twice a day) orally was administered for 14 days, resulting in rapid clinical response with complete clinical remission at 7 days. Steroids were gradually tapered.

Conclusions: Superimposed CMV infection must be considered as the cause of severe flare and colonic dilatation in UC patients. This patient responded dramatically to therapy with valganciclovir.

Reviewer's Comments: I am a believer. Within the past year I also had a UC patient with severe colitis and dilatation who was refractory to 6-MP and steroids and was about to lose his colon. CMV was identified by sigmoidoscopy biopsy; in addition, C. difficile toxins were identified in multiple stool specimens. The patient responded dramatically to treatment with valganciclovir and vancomycin. He is in remission a year later on infliximab. (Reviewer-Allen L. Ginsberg, MD).

© 2010, Oakstone Medical Publishing

Keywords: Ulcerative Colitis, CMV Infection, Valganciclovir

Print Tag: Refer to original journal article
A prospective analysis of data on fruit and vegetable intake and cancer risk in participants of the European Prospective Investigation into Cancer and Nutrition suggests only a modest, if any, protective effect of fruits and vegetables.

**Background:** A daily intake of fruits and vegetables is recommended to prevent cancer and other chronic diseases. However, there is no conclusive evidence that the recommended intake of fruits and vegetables reduces cancer risk. Most studies have assessed only one or a few types of cancers, rather than all cancer risk.

**Objective:** To assess the association between overall cancer risk and the intake of total fruits and vegetables.

**Design:** Data were analyzed from a large-scale prospective cohort study.

**Participants:** The European Prospective Investigation into Cancer and Nutrition (EPIC) was conducted between 1992 and 2000 in 23 European centers.

**Methods:** Participants self-reported validated, country-specific food frequency and lifestyle questionnaires. Cancer incidence and mortality rates were derived from national and other registries. Multivariate Cox regression models estimated cancer hazard ratios (HR). The primary outcome measures were the association between overall cancer risk and the consumption of total fruits, total vegetables, and total fruits and vegetables combined.

**Results:** Data from 478,478 eligible men and women aged 25 to 70 years at study entry were analyzed. Median follow-up was 8.7 years, and 30,604 incident cancers were identified. A high intake of total fruits and vegetables as well as a high intake of total vegetables demonstrated significant, albeit small, decreases in associated cancer risk (HR, 0.97; 95% CI, 0.96 to 0.99, and HR, 0.98; 95% CI, 0.97 to 0.99, respectively). The inverse association was stronger in heavy alcohol drinkers and was restricted to cancers associated with tobacco and alcohol.

**Conclusions:** A high intake of fruits and vegetables is associated with a small reduction in cancer risk, especially in persons with a high alcohol intake and in alcohol- and smoking-associated cancers.

**Reviewer's Comments:** The inverse association between fruit and vegetable intake and cancer risk, although statistically significant, is so small that its clinical validity is called into question. While fruit and vegetable intake may have other health benefits, this study does support a benefit with respect to cancer reduction. (Reviewer-Timothy O. Lipman, MD).

© 2010, Oakstone Medical Publishing

Keywords: Fruits, Vegetables, Cancer Risk

Print Tag: Refer to original journal article
In a longitudinal prospective Dutch cohort, toenail selenium status was found to be inversely associated with esophageal squamous cell carcinoma.

**Background:** Observational studies suggest that selenium is inversely associated with prostate cancer and possibly lung and gastric cancers. Selenium is of interest in relation to cancer because of the anti-oxidant capacity of the selenium-dependent glutathione peroxidase enzymes. Data on the possible associations between upper gastrointestinal cancers and selenium status are sparse.

**Objective:** To study the association between toenail selenium and the risk of esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma (EAC), and gastric cardia adenocarcinoma (GCA).

**Design:** Prospective case-cohort approach.

**Participants:** Selected subjects in the Netherlands Cohort Study on diet and cancer were included. This study involved 120,852 Dutch men and women, aged 55 to 69 years, who were enrolled starting in 1986.

**Methods:** At baseline, all cohort members completed a lifestyle and food-frequency questionnaire and submitted toenail clippings. A random subset of 3500 participants was used for estimation of person-years at risk and for the general cohort analysis. Cancer cases were found through several registries.

**Results:** Follow-up was 16.3 years. Complete selenium data were available for 71 ESCC cases, 129 EAC cases, 127 GCA cases, and 2426 subcohort members without cancer. Multivariate analysis found a significant inverse association between selenium status and ESCC (RR, 0.80; 95% CI, 0.67 to 0.96) and a borderline inverse association with GCA (RR, 0.91; 95% CI, 0.80 to 1.02). No association was found with EAC, but a subgroup analysis for EAC found inverse associations for women, never smokers, and low anti-oxidant consumers.

**Conclusions:** Selenium status as measured once in toenail analysis is inversely associated with risk for selected upper gastrointestinal cancers. These associations need confirmation.

**Reviewer's Comments:** It is biologically plausible that selenium is cancer protective, and much effort has been generated to demonstrate protective effects over a range of cancers and study methodology. The strengths of the study include its large size, its prospective format, and analysis of a Western, non-Asian population. A major limitation, as noted by the authors, is that only one selenium analysis was performed; data from at least one other study suggest <50% correlation in samples taken 6 years apart. Finally, the authors also note that the multiple statistical tests performed increase the risk of false-positive results; that is, the findings could be due to chance. Nonetheless, the observations are worth pursuing in other studies. (Reviewer-Timothy O. Lipman, MD).

© 2010, Oakstone Medical Publishing

Keywords: Selenium, Esophageal Carcinoma, Gastric Cardia Adenocarcinoma

Print Tag: Refer to original journal article
Severe liver injury, resulting in death or transplantation, can be a consequence of dietary supplements that do not require efficacy, safety testing, or Food and Drug Administration approval before marketing.

**Background:** Because the manufacturers of dietary supplements are not required to provide evidence of either efficacy or safety and because Food and Drug Administration (FDA) approval is not required, drug-induced liver injury due to these agents is generally recognized only after the supplement has been heavily marketed and consumed by an unwary public. A supplement called Muscletech Hydroxycut, touted as a “fat burning” weight loss inducer, was linked to liver injury shortly after its marketing in 2002. After a warning by the FDA in 2009, it was voluntarily withdrawn by the manufacturer.

**Objective:** To clinically characterize the features of Hydroxycut-associated liver injury and to establish a causal association.

**Methods:** Clinical and laboratory information was obtained from the records of 8 patients with suspected Hydroxycut liver injury seen at 8 medical centers and from 9 other potential cases with adequate clinical data obtained from the FDA’s MedWatch database. Liver injury severity was graded and causality was assessed using guidelines developed by the Drug-Induced Liver Injury Network. Four independent reviewers assessed causality. When discrepancies occurred, they were reconciled by teleconference.

**Results:** The mean age of affected patients was approximately 30 years, and all 17 patients required hospitalization. The latent period between beginning Hydroxycut and recognition of liver injury was about 6 weeks but was longer in patients who took the supplement intermittently. No rechallenges were identified, and no evidence of hypersensitivity was found. Severity was judged to be mild in just 1 case. Several patients required transplantation, and one patient died. The pattern of liver injury was predominantly hepatocellular. The causality assessment found that 8 of the 17 cases were definitely associated with Hydroxycut, 5 were highly likely, 2 were probable, and 2 were possibly related. The responsible hepatotoxin in Hydroxycut remains uncertain.

**Conclusions:** Hydroxycut causes severe hepatocellular liver injury.

**Reviewer’s Comments:** Despite the recall of Hydroxycut, the list of dietary supplement, herbs, and other remedies associated with liver injury continues to expand, and more cases of severe, life-threatening liver disease are likely. This will continue until the U.S. Congress permits the FDA to require evidence of both efficacy and safety for approval of these substances, rather than the passive reporting of injury after the fact. (Reviewer-Raymond S. Koff, MD).

© 2010, Oakstone Medical Publishing

Keywords: Dietary Supplement, Liver Injury, Causality

Print Tag: Refer to original journal article
The re-entry of single-patient-use vials is a risk factor for bloodborne hepatitis transmission.

**Background:** Previous studies have suggested that approximately 20% of non-hospital, health care-related outbreaks of hepatitis B virus (HBV) and hepatitis C virus (HCV) can be attributed to the delivery of anesthesia. Syringe re-use for re-entry and the repeated use of single-patient-use vials appears to be the common denominator in these infections. The present report describes the investigation of an outbreak of both HBC and HCV among endoscopy patients attending 2 separate gastroenterology clinics in New York.

**Objective:** Based on the report of a patient who had tested negative for HCV infection 1 week before an upper endoscopy but then developed symptomatic HCV 3 months later, an investigation was performed to determine the extent and mechanism of infection. During the investigation, a second gastroenterology clinic was also linked to infection.

**Methods:** The medical staff were interviewed and tested for evidence of infection. The dates and types of endoscopy and the order in which patients had procedures were determined. Patients who had procedures on days close to the day in which a known or source case had a procedure were identified and tested, if possible. Patients were classified as cases if they had evidence of HBV and/or HCV infection and no other risk factors for hepatitis acquisition. Phylogenetic analyses were undertaken to compare HCV isolates from affected patients.

**Results:** Molecular sequencing and quasi-species analysis confirmed the relatedness of the HCV infections in clusters of patients. A total of 12 infections were identified: 6 cases of HCV, 5 cases of HBV, and 1 case of HBV/HCV co-infection. Neither the staffs of the clinics, the endoscopes, nor the handling of endoscopy equipment could be implicated in hepatitis transmission. A contract anesthesiologist who worked in both clinics was found to have re-used a single-patient-use vial of propofol for many patients, clearly a departure from the aseptic technique. The outbreaks were attributed to this break in aseptic technique.

**Conclusions:** Poor infection control practice during propofol anesthesia associated with endoscopy resulted in 12 cases of hepatitis B and C in this study.

**Reviewer's Comments:** In addition to a careful and continuous review and monitoring of infection control practices in endoscopy centers, with an emphasis on anesthesia delivery, it may be time to re-think how single-use vials are manufactured. It should be possible to develop a single-patient-use vial that cannot be re-entered. Perhaps multiple-patient vials should also be abandoned, since these, too, have been implicated in hepatitis transmission. (Reviewer-Raymond S. Koff, MD).

© 2010, Oakstone Medical Publishing

Keywords: Hepatitis C & B, Contamination, Propofol Vials, Infection Control

Print Tag: Refer to original journal article
**Objective:** To determine the rates of cancer and high-grade dysplasia (HGD) in patients found to have small polyps (6 to 9 mm) and large polyps (≥10 mm) at CT colonography (CTC).

**Participants/Methods:** 5124 consecutive asymptomatic patients undergoing screening CTC were studied. CTCs were read in both 3 dimensions and 2 dimensions. Patients were offered same-day colonoscopy for lesions >5 mm. Only patients with endoscopic or surgical confirmation with histologic samples available were included. Polyps were classified according to size: small (6 to 9 mm) and large (≥10 mm). Large polyps were then subdivided: 10 to 19 mm, 20 to 29 mm, and ≥30 mm.

**Results:** Of the 5124 CTCs, 479 (9.34%) underwent colonoscopy, identifying 755 lesions >6 mm with histologic confirmation; 60.1% of lesions were neoplastic. Of the neoplasms, 71.4% were tubular adenomas (TA), 18.3% were tubulovillous adenomas (TVA), 1.7% were villous adenomas (VA), 3.7% were serrated adenomas, 3.3% were HGD, and 4.4% were invasive cancers. According to size, 61.5% (n=464) were 6 to 9 mm, 28.6% (n=216) were 10 to 19 mm, 4.4% (n=33) were 20 to 29 mm, and 5.6% (n=42) were ≥30 mm. In the small-polyp group, the rate of advanced adenomas was 3.9% (18 of 464): 15 TVAs, 1 VA, 1 serrated adenoma with HGD, and 1 TA with HGD (overall HGD, 0.4%). In the large-polyp group, the rates of advanced adenomas and malignancy were higher than in the smaller-polyp group at 61.9% (180 of 291) versus 6.9% (20 of 291), respectively (P <0.001). In the 10 to 19 mm size group (n=216), advanced adenomas represented 60.6% of the lesions (62.6% by size alone), malignant polyps represented 0.9% (n=2), and the rate of HGD was 1.4% (n=3). For polyps 20 to 29 mm, 6.1% (2 of 33) were malignant. Of masses ≥30 mm, 38.1% (16 of 42) were malignant; this represented 80% (18 of 20) of all invasive cancers. The majority of nonneoplastic lesions were hyperplastic (67.7%); 75% measured 6 to 9 mm, and 25% measured ≥10 mm. Approximately 12.3% of polyps were found at colonoscopy but not at CT (78.5% were 6 to 9 mm, 18.3% were 10 to 19 mm, and 3.2% were ≥20 mm). None were malignant or showed HGD.

**Conclusions:** No malignancy was noted in small polyps; HGD was noted in 0.4%. In large polyps (10 to 20 mm), the malignancy rate was 61.9%. Reviewer's Comments: These CTC findings in asymptomatic individuals suggest that follow-up of small polyps could be extended and that immediate colonoscopy may not be necessary. Even in large polyps (1 to 2 cm), the rates of malignancy and HGD were small. (Reviewer-Roy K.H. Wong, MD).

© 2010, Oakstone Medical Publishing

**Keywords:** Cancer, Dysplasia, Colonography, Screening, CT

**Print Tag:** Refer to original journal article
Laparoscopic surgery for elective diverticular disease results in less morbidity and shorter postoperative hospitalization time compared to open surgery; however, it requires a longer operative time.

**Objective:** To determine whether there is a significant difference in the rate of postoperative complications in elective open versus laparoscopic surgery for diverticular disease.  

**Methods:** Prospective preoperative, intraoperative, and postoperative data were collected from a large data bank, the American College of Surgeons National Surgical Quality Initiative Program; 120 private and academic hospitals were included. Patients undergoing open surgery (OS; n=3468) and laparoscopic surgery (LS; n=3502) for diverticular disease between 2005 and 2008 were included.  

**Results:** Patients undergoing LS were younger, had a lower body mass index, had fewer comorbidities, and had a more favorable ASA class. LS patients had fewer superficial and deep wound infections, organ space surgical site infections, pneumonia, pulmonary embolism, sepsis, septic shock, and deep venous thrombosis ($P < 0.0039$ to $0.0001$); however, they also had longer operative times (2.9 hours for OS vs 2.74 hours for LS; $P < 0.001$). The length of stay for LS versus OS patients was shorter (7.8 vs 4.8 days; $P < 0.001$), as was 30-day mortality (0.4 vs 1.1; $P < 0.0004$).  

**Conclusions:** Laparoscopic surgery for elective diverticular disease results in less morbidity than open surgery.  

**Reviewer’s Comments:** The major flaws of this study are that it was not randomized, and that more favorable presurgical attributes were found in the LS group. The authors tried to normalize this difference by using a propensity score and still found that LS decreased the rate of complications independently. The reasons for not favoring a laparoscopic approach have been complicated diverticulitis with fibrosis and inflammation (making dissection difficult), higher conversion rates (>30%), and longer operating times. Surgeons need to gain more laparoscopic experience, which is critical but difficult to obtain (they need to perform approximately 40 LS cases to become proficient, whereas most surgeons may perform 5 colectomies per year). LS may be the preferred surgical approach to treat elective diverticulitis but should not be demanded as most surgeons do not have enough training to perform LS. (Reviewer-Roy K.H. Wong, MD).
The presence of tumor cells in the peripheral blood, mesenteric blood, and possibly bone marrow indicates a poor prognosis with regard to colon cancer recurrence and survival.

Background: With advances in technology, it has become possible to identify tumor cells in the blood. There is evidence that patients with breast cancer who have tumor cells in the blood or bone marrow have poor prognoses. There is no analysis of the prognostic implication of circulating tumor cells in patients with colorectal cancer.

Objective/Design: To undertake a systematic review and meta-analysis to assess the prognostic value of circulating tumor cells in colon cancer.

Methods: Using computerized databases, papers were sought that addressed the association between the detection of colorectal cancer cells in the blood or bone marrow and the rate of cancer recurrence or mortality. The hazard ratio (HR) and 95% confidence interval (CI) from each trial were extracted and combined with a meta-analysis using a random effects model (since heterogeneity was expected). A worse prognosis was indicated by HR >1.00. Subgroup analyses were planned to assess the following: sampling site (peripheral blood, mesenteric/portal vein blood, or bone marrow); sampling time (preoperative, intraoperative, or postoperative); target gene or antigen; number of tested targets; number of positive targets needed to define a positive test; risk of bias (low risk defined as being adequate in 6 parameters); and inclusion or exclusion of patients with overt metastases. (Trials in which all patients had overt metastases were excluded from the analyses.) Sensitivity analyses were conducted by excluding studies with <24 months of follow-up.

Results: 36 studies were identified; 17 of these were at low risk of bias. The primary analysis (all studies) found a poor prognosis with regard to cancer recurrence (HR, 3.24; 95% CI, 2.06 to 5.10) and mortality (HR, 2.28; 95% CI, 1.55 to 3.38). The HRs for all of the various subgroup/sensitivity analyses were >1.00; for most of these, the 95% CI did not cross the line of equivalence. The studies of bone marrow cells did not achieve significance for recurrence (HR, 2.17; 95% CI, 0.94 to 5.03) or mortality (HR, 1.50; 95% CI, 0.52 to 4.32), but there were only a few such reports. There was substantial heterogeneity in most of these analyses. As is true for most systematic reviews, the analysis of trials with a high risk of bias found a higher HR than did the analysis of trials with a low risk of bias; however, even the latter showed the association.

Conclusions: Detecting tumor cells in the blood indicated the presence of poor prognoses in patients with colorectal cancer.

Reviewer’s Comments: The demonstration of this association was not surprising. If the price of such tests is reasonable, this may be a useful prognostic test in clinical medicine, particularly if only a peripheral blood sample is needed. (Reviewer-Ronald L. Koretz, MD.)