High Mortality Rate Makes Etanercept Ineffective Tx for Alcoholic Hepatitis

A Randomized, Double-Blinded, Placebo-Controlled Multicenter Trial of Etanercept in the Treatment of Alcoholic Hepatitis.
Boetticher NC, Peine CJ:
Gastroenterology 2008; 135 (December): 1953-1960

Treatment of moderate-to-severe alcoholic hepatitis with etanercept for 3 weeks is linked to increased mortality at 6 months of follow-up when compared to placebo.

**Background:** Despite a slew of studies regarding potential treatments, the optimal management of alcoholic hepatitis has yet to be established. Tumor necrosis factor-α has been implicated in the pathogenesis and clinical features of alcoholic hepatitis and pentoxifylline, a TNF-α release inhibitor, appeared to be beneficial in a study published in 2000. Etanercept (Enbrel®), a TNF-α blocker that binds to unbound TNF-α, is approved for the treatment of rheumatoid arthritis, psoriatic disease, ankylosing spondylitis, and juvenile rheumatoid arthritis. In a small uncontrolled Mayo Clinic pilot study, 2 weeks of treatment with etanercept appeared promising.

**Objective:** To assess the therapeutic efficacy of etanercept.

**Design:** Randomized double-blind controlled trial.

**Methods:** Eligible patients with moderate-to-severe alcoholic hepatitis, defined as MELD >15, with or without cirrhosis, seen at 7 U.S. centers between 2004 and 2007 were randomized to receive subcutaneous injections of 25 mg of etanercept or placebo. Injections were given on days 1, 4, 8, 11, and 18. Patients were monitored on each of those days and at 1, 3, and 6 months. The primary end point was mortality at 1 and 6 months. The prevalence of infection and cause of death were secondary end points.

**Results:** Although 174 patients were evaluated for eligibility, only 48 were randomized: 22 in the placebo arm and 26 in the etanercept arm. At baseline, both groups were well-matched by age, gender, reported alcohol consumption, MELD score, liver enzymes, albumin levels, and clinical features. IL-6 and IL-8 levels were also similar. At 1 month, mortality was higher, but not statistically significantly so, in the etanercept group than in the placebo group (35% vs 23%). However, at 6 months, mortality was significantly higher in the etanercept group at 58% vs 23% for the placebo group ($P=0.017$). Renal failure and hepatic encephalopathy were identified as the major causes of death. Serious adverse events, especially infections, were significantly more common in patients receiving etanercept.

**Conclusions:** Given the higher mortality in the etanercept-treated patients, etanercept is ineffective in the treatment of alcoholic hepatitis.

**Reviewer's Comments:** Based on this still small but striking study, etanercept can now be included in the long list of drugs that had once seemed promising for alcoholic hepatitis in uncontrolled pilot studies or in controlled but inadequately powered trials. At the end of the day, alcoholic hepatitis continues to lack effective therapy. (Reviewer-Raymond S. Koff, MD).

© 2009, Oakstone Medical Publishing

Keywords: Alcoholic Hepatitis

Print Tag: Refer to original journal article
Failure in aseptic technique and standard infection control practices in U.S. health care settings other than hospitals has resulted in multiple outbreaks of HBV or HCV infection in the past 10 years.

**Background:** Health care-related transmission of hepatitis B virus (HBV) or HCV infection is generally believed to be uncommon in the United States, and very few outbreaks have been linked to hospital settings. However, since health care is now delivered in a broad array of non-hospital settings, including endoscopy centers in which infection control practices may be less rigidly followed than in hospitals, patient-to-patient transmission may be more common.

**Objective:** To review outbreaks of HBV and HCV occurring in non-hospital health care locations between 1998 and 2008 and to describe the responsible lapses in infection control.

**Methods:** All HBV or HCV outbreaks reported to the Centers for Disease Control and Prevention, whether published or not, relevant communications with state and local health authorities, and PubMed were searched and examined. The outbreak setting, number of persons at risk, number screened and number of incident cases, and the responsible mechanisms permitting hepatitis transmission were identified.

**Results:** Among the 33 identified outbreaks reviewed, 18 were due to HBV and affected 173 individuals, and 16 were due to HCV and affected 275 individuals. The implicated health care facilities included hemodialysis centers, nursing home and assisted-living facilities, pain clinics, hematology and oncology clinics, nuclear imaging facilities, physician offices, and in 2 instances, endoscopy clinics. Delivery of anesthesia was implicated in 6 of 33 outbreaks. Provider-to-patient transmission and transmission of HIV were not observed. Syringe reuse or multiple use of single-use vials or saline bags, and reuse of fingerstick devices and blood glucose monitors were the responsible mechanisms.

**Conclusions:** The authors reason that these outbreaks were preventable since they were all caused by lapses in standard infection control practices. They call for better surveillance, education, supervision, and awareness.

**Reviewer's Comments:** As the authors indicate, the full picture of the importance of non-hospital health care-related transmission of the bloodborne hepatitis viruses is unknown but it is likely to be considerably larger than that reported here. Many infections may not be apparent and unrecognized as health care-related, and mini-outbreaks may be under-reported. Since a substantial proportion of patients with HBV and HCV infections fail to identify a known risk factor, could health care-related transmission be responsible? For gastroenterologists, the message is clear. Scrupulously follow aseptic technique, review infection-control practices frequently, provide continuing education for staff, including anesthesia personnel, and monitor your practices regularly for possible lapses. (Reviewer-Raymond S. Koff, MD).

© 2009, Oakstone Medical Publishing

**Keywords:** Health Care-Related Transmission

**Print Tag:** Refer to original journal article
In a Canadian cohort of liver transplant recipients, the incidence of post-transplant colorectal cancer was 2.5 times that expected when compared to the general Canadian population.

**Background:** Several follow-up studies of patients after liver transplantation have found increased cancer incidence. However, these studies have been hampered by small sample sizes and data from only single centers.

**Objective:** To characterize patterns of cancer incidence among liver transplant recipients as compared with cancer rates in the general population.

**Design:** Retrospective analysis of cohort data.

**Participants:** Canadian liver transplant recipients from 1983 through October 1998 enrolled in the Canadian Organ Replacement Registry.

**Methods:** Incident cancer cases were identified through linkage to the Canadian Cancer Registry. Cancer incidence rates in the cohort were compared with incidence rates in the general Canadian population by calculating the standard incidence ratio (SIR).

**Results:** 2034 transplant recipients were identified, who accrued 10,370.6 person-years of follow-up. In the cohort, there were 113 incident cancers versus an expected 44.8 cases, for a significant SIR of 2.5 (95% CI, 2.1 to 3.0). The highest SIR for non-Hodgkin's lymphoma was 20.8 (95% CI, 14.9 to 28.3). In total, 14.0 colorectal cancers were identified, whereas 5.3 were expected, for a SIR for colorectal cancer of 2.6 (95% CI, 1.4 to 4.4). After 10 years of follow-up, the cumulative incidence for all cancers was estimated to be 8.6%. The majority of these were non-Hodgkin's lymphoma. Risks for development of cancer were more pronounced during the first year of follow-up and in younger (aged <35 years) transplant recipients.

**Conclusions:** In a Canadian cohort of liver transplant patients, there is an increased risk of cancer as compared with the general Canadian population. The most frequent cancer is non-Hodgkin's lymphoma. Colorectal cancer is also increased about 2.5-fold compared with the general population.

**Reviewer's Comments:** If we look at the actual numbers, the colorectal SIR of 2.5 is less than overwhelming. All told, there were 14.0 colorectal cancers in the cohort of 2034 liver transplant recipients compared with an expected 5.3 in the general population. Many colonoscopies would have to be performed to find the 9 additional cancers. In the present study, we have no knowledge of the eventual clinical outcomes or assurance that these patients would have benefited from enhanced surveillance. In a world of unlimited resources, earlier and more frequent surveillance would not present a problem. However, our country is in the worst financial crisis since the great depression, and resources are finite and limited. Validation from other cohorts is needed. A smaller Finnish study in the October 2008 *Liver Transplantation* did not seem to find increased colorectal cancer risk. (Reviewer-Timothy O. Lipman, MD).

© 2009, Oakstone Medical Publishing

Keywords: Colorectal Cancer

Print Tag: Refer to original journal article
PPIs Other Than Pantoprazole Should Be Avoided When Taking Clopidogrel


Juurlink DN, Gomes T, et al:

CMAJ 2009; January 28 (epub ahead of print):

Pantoprazole is one of the few PPIs that do not affect the platelet inhibition of clopidogrel.

**Background:** Recent studies have suggested that some proton pump inhibitors (PPIs) may interfere with the antiplatelet effect of clopidogrel.

**Objective:** To determine the effect of concurrent use of clopidogrel and PPIs in a population who are recovering from myocardial infarction (MI).

**Design/Methods:** A population-based nested case-control study was performed on a group of patients aged ≥66 years who took clopidogrel upon discharge from the hospital following an MI and were readmitted with another MI within 90 days of discharge.

**Results:** 734 of >13,000 patients who were discharged from the hospital following an MI and taking clopidogrel were readmitted within 90 days with another MI. Following extensive multivariable adjustment, current use of PPIs were found to be associated with an increased risk of reinfarction (adjusted odds ratio [OR], 1.27; 95% confidence interval [CI], 1.03 to 1.57). By the use of a stratified analysis, it was found that pantoprazole did not inhibit cytochrome P450 and thus had no association with readmission for a recurrent MI (adjusted OR, 1.02; 95% CI, 0.70 to 1.47).

**Conclusions:** Following an acute MI, patients discharged on clopidogrel were at increased risk for another MI if they were placed on a PPI because these drugs inhibit the antiplatelet effect of clopidogrel. The one exception to the finding in this study was pantoprazole, a PPI that does not appear to inhibit cytochrome P450 and thus does not diminish the efficacy of clopidogrel in inhibiting platelet function.

**Reviewer's Comments:** This study has demonstrated that pantoprazole may be the only PPI that is safe to give patients who are taking clopidogrel following an MI or placement of a drug-eluting stent. Other PPIs appear to inhibit the antiplatelet effect of clopidogrel and therefore pose a risk to those patients. Another study has been published which found that esomeprazole may not inhibit clopidogrel. The present study did not appear to include esomeprazole as a drug associated with an increased risk or recurring infarction, so from what has been published it seems likely that esomeprazole may be included in the safe drugs to give with clopidogrel. (Reviewer-Michael M. Phillips, MD).

© 2009, Oakstone Medical Publishing

Keywords: Drug Interaction

Print Tag: Refer to original journal article
An inverse association between the performance of colonoscopy and colon cancer mortality exists, but it is only present with left-sided cancer.

**Background:** Case-control studies have found an association between sigmoidoscopy and not dying of distal (but not proximal) colon cancer. The explanation in the past has been that the instrument does not visualize the right side of the colon, but it is possible that there are biologic differences between cancers on each side.

**Objective:** To undertake a case-control study to seek an association between colonoscopy and colorectal cancer (CRC) mortality.

**Design:** Case-control study.

**Participants:** Patients enrolled in the Ontario health care system.

**Methods:** Records were searched to identify patients who were diagnosed with CRC between January 1, 1996, and December 31, 2001, and who died of CRC before December 31, 2003. For each subject, 5 controls were age/sex/economically/regionally matched and could not have had CRC diagnosed prior to December 31, 2003. Records were searched for the performance of any colonoscopy done between January 1, 1992, and the index date (6 months before the date of diagnosis) and how many were complete (reached the cecum). The cancer was also classified as being left- or right-sided.

**Results:** 10,292 cases of fatal colon cancer and 51,460 controls were identified. In total, 719 (7.0%) and 5031 (9.8%) of each group underwent a colonoscopy during the time preceding the index date (odds ratio [OR], 0.69; 95% confidence interval [CI], 0.57 to 0.54). Overall, 523 of 3999 of them were complete studies (OR, 0.63; 95% CI, 0.57 to 0.69). Polyps were removed from 1.8% and 2.0% of study and control groups, respectively. When the cancers were separated into those on the left or right side, the significant inverse association remained for the left-sided ones (OR, 0.39/0.33 for all/complete colonoscopies). However, there was no difference with regard to all (OR, 1.07; 95% CI, 0.94 to 1.21) or complete (OR, 0.99; 95% CI, 0.86 to 1.14) colonoscopies.

**Conclusions:** While the performance of colonoscopy is associated with a reduction in CRC deaths, this relationship was only found for left-sided lesions. It is unlikely that inadequate examination of the right colon alone was responsible for the lack of efficacy, and it may be that differences in the biology of cancer on the right side compared to the left side limit the utility of colonoscopic screening.

**Reviewer's Comments:** Case-control studies cannot establish causation. Another explanation for the sigmoidoscopy outcomes in case-control studies would be that right-sided cancers behave differently, perhaps in not being as amenable to polypectomy. It is too naïve a perspective to assume that all cancer arises from adenomas protruding into the lumen of the colon. We know that at least some cancers do arise from flat mucosa and/or grow so aggressively that screening will not detect them. (Reviewer-Ronald L. Koretz, MD).
Colon cancer screening should be done on average-risk subjects between the ages of 50 and 75 years employing fecal occult blood testing, sigmoidoscopy, or colonoscopy.

**Background:** In 2002, the United States Preventive Services Task Force (USPSTF) issued a recommendation for colorectal cancer (CRC) screening of average-risk subjects. At that time, the type of test to be used, as well as the age limits for screening, was not established.

**Objective:** To expand the recommendation by focusing on the age limits and assessing the benefits and harms of the various potentially available tests, namely various tests for fecal hemoglobin (ranging from the standard guaiac-based assay for pseudoperoxidase activity of hemoglobin, more sensitive assays for this enzyme [Hemoccult SENSA], immunochemical tests [ICT] for human hemoglobin, and DNA from neoplasms), flexible sigmoidoscopy (FS), colonoscopy, and CT colonography.

**Methods:** Guidelines based on prior systematic reviews of the literature, a recent upgraded targeted systematic review (Whitlock EP et al, *Ann Intern Med* 2008; 149:638-658), and a recent decision analysis (Zauber AG, *Ann Intern Med* 2008; 149:659-669) were reviewed. Recommendations were made allegedly based on the available evidence. Interventions included CRC screening by the techniques noted above as well as a combination of FS every 5 years with interval-sensitive assays for fecal hemoglobin (either Hemoccult SENSA or ICT).

**Results:** Colonoscopy was the most sensitive test for finding cancer and adenomas. However, since it was the most invasive test, the non-colonoscopic tests were considered as a mechanism to reduce the absolute number that would be done. The newer fecal blood tests were more sensitive, but often less specific, than standard hemoccult. While the fecal DNA test may have been more sensitive, the data are very limited. FS every 5 years and interval fecal tests were comparable to colonoscopy or annual newer fecal blood tests. CT colonography was comparable to colonoscopy for detecting cancer and polyps >1 cm, but not for smaller lesions. This technique has other problems, including potential cancer risk and lack of insight into the utility of finding extracolonic processes. Colonoscopy produced serious complications in 1 in 400 subjects; the rate for FS was almost 10-fold lower. While screening individuals aged 75 to 85 years yielded extra life-years, the additional resource utilization was large.

**Conclusions:** CRC screening should be done in average-risk subjects between the ages of 50 and 75 years using yearly sensitive tests for fecal hemoglobin, FS every 5 years, plus interval fecal hemoglobin testing, or 10-yearly colonoscopy.

**Reviewer’s Comments:** Both the 2002 and the current recommendations do not consider data from randomized trials that argue against CRC screening. The only available trial of FS found that the screened group had a higher total mortality and the 4 large trials of hemoccult have not been able to show that any life-years have been saved. (Reviewer-Ronald L. Koretz, MD).

© 2009, Oakstone Medical Publishing

Keywords: Colon Cancer Screening

Print Tag: Refer to original journal article
Fiber, Antispasmodics, Peppermint Oil Inexpensive, Safe Tx for IBS

Effect of Fibre, Antispasmodics, and Peppermint Oil in the Treatment of Irritable Bowel Syndrome: Systematic Review and Meta-Analysis.

Ford AC, Talley NJ, et al:

BMJ 2008; 337 (November 13): a2313

Fiber (especially ispaghula husk), antispasmodics, and peppermint oil are all relatively inexpensive and safe agents that are effective in the treatment of irritable bowel syndrome.

Background: While recent emphasis on the treatment of irritable bowel syndrome (IBS) has centered on expensive pharmaceuticals that act on various gastrointestinal tract receptors, a number of other more inexpensive and safe agents have been tested in the past.

Objective: To assess the utility of fiber, antispasmodics, and peppermint oil in treating IBS.

Design: Systematic review and meta-analysis.

Participants: Adults with IBS.

Methods: The authors searched Medline, Embase, and the Cochrane Library for randomized controlled trials in adults with IBS. The trials had to compare 1 of the 3 modalities to placebo or no treatment, to have followed the patients for at least a week, and to have provided outcomes as either a global assessment of cure or improvement of symptoms. No language restrictions were applied. Two reviewers abstracted the data independently as dichotomous outcomes, namely improved or not improved. The risk of bias of each trial was assessed with the Jadad scale, which considers the generation of the randomization scheme, blinding, and accounting for dropouts. The data were then pooled for each treatment modality using meta-analysis.

Results: 12 trials assessed fiber. Overall, the relative risk (RR) of not improving was 0.87 (95% confidence interval [CI], 0.76 to 1.00; \( P =0.05 \)). The effect was limited to ispaghula husk. However, when only trials with low risk of bias were considered, the significant differences disappeared. Antispasmodics (22 trials) were also found to be beneficial and the effect persisted in the trials with low risk of bias. Peppermint oil (4 trials) was the most effective (RR, 0.43; 95% CI, 0.32 to 0.59) and the effect was still present when only the trials with low risk of bias were considered.

Conclusions: Fiber (especially ispaghula husk), antispasmodics, and peppermint oil were all effective and safe.

Reviewer's Comments: With so much publicity being focused on more expensive, and perhaps more toxic, agents, it is comforting to know that older, simpler, and safer agents still have a place in the management of IBS. This is particularly the case for peppermint, which was used in doses of about 200 mg 2 to 4 times daily. Peppermint has long been recognized as a smooth muscle relaxant; in fact, one of the potential side effects of its use is an increase in gastroesophageal reflux symptoms. (Reviewer-Ronald L. Koretz, MD).

© 2009, Oakstone Medical Publishing

Keywords: Irritable Bowel Syndrome

Print Tag: Refer to original journal article
Gum chewing after colectomy decreases the time for gastrointestinal function to return and may even translate into a reduced duration of hospitalization.

**Background:** Small trials have produced different conclusions regarding the effect of postoperative gum chewing on gastrointestinal function and length of stay.

**Objective:** To undertake a systematic review of all identifiable randomized trials that have compared gum chewing to no gum chewing after colectomy.

**Design:** Systematic review and meta-analysis.

**Participants:** Patients undergoing colectomies.

**Methods:** Medline, Ovid, and the Cochrane Library were electronically searched for trials in which patients were randomized to gum chewing or no gum chewing after abdominal surgery. The trials had to report at least 1 of 2 outcomes: return of gastrointestinal function (time to first passage of flatus or time to first bowel movement) or length of postoperative hospitalization. The trials were assessed for risk of bias with the Jadad score. A variety of subgroup analyses were planned. A power calculation suggested that 80 patients would be needed in each arm to see a difference in length of stay of -1.25 days.

**Results:** 5 randomized trials, enrolling 158 patients (78 study/80 controls), were identified. Four of the trials were performed in patients undergoing open colectomies. Three of the studies were graded as being at low risk of bias. In only 2 of the trials were the patients allowed to begin oral fluids before the passage of flatus. When the trials were combined, there were significant reductions in both the time until flatus was passed (-0.66 days) and the time until the first bowel movement (-1.10 days). Four of the trials reported data regarding duration of postoperative stay. This number was also shorter in the gum chewers (-1.25 days; 95% confidence interval [CI], -3.27 to 0.77), a non-significant difference. Similar estimates were made when only the trials at low risk of bias or those employing open colectomies were considered. Two of the trials included patients in whom stomas were created; when these trials were omitted, the reduction in hospital stay (-2.46 days; 95% CI, -3.14 to -1.79) was significant.

**Conclusions:** Chewing gum enhances bowel recovery and may shorten length of stay.

**Reviewer’s Comments:** The reduction in length of stay was only seen in one of several analyses, and no correction was made for multiple such calculations. However, the intervention appears to be safe and inexpensive. There is evidence from at least 15 randomized trials of early feeding (patients being given fluids, or even food, before the appearance of bowel sounds or stool) that such an intervention will also reduce the length of stay. One might wonder if gum chewing is a form of sham feeding. (Reviewer-Ronald L. Koretz, MD).

© 2009, Oakstone Medical Publishing

Keywords: Chewing Gum

Print Tag: Refer to original journal article
A 3-gram dose once daily of mesalazine is as effective as 1 gram 3 times a day for the treatment of mild and moderately active ulcerative colitis.

**Objective:** To compare the efficacy of once daily mesalazine granules versus 3 times daily dosing for the treatment of ulcerative colitis (UC).

**Design:** Randomized double blind double-dummy parallel phase III study to test non-inferiority of the single daily dosing schedule.

**Participants:** 380 patients from 54 institutions in 13 countries with >15 cm from the anus involvement with UC participated in the study. Patients were enrolled from July 2005 through April 2006. All other medications were discontinued and patients were randomized to receive either 3 grams of mesalazine granules orally once a day or 1 gram of mesalazine granules 3 times a day. Analysis was by intention to treat. The study period lasted for 8 weeks with follow-ups at 2, 4, and 6 weeks. The study end point was achieving clinical remission (clinical activity index <4).

**Results:** 79.1% of patients in the once-daily treatment group had clinical remission, while 75.7% in the 3 dose per day group also went into remission ($P < 0.0001$ for non-inferiority). In total, 80% of patients preferred the once-daily dosing regimen. Both regimens were safe and generally well tolerated with adverse events occurring in only 28.8% of the daily dose group versus 32.3% in the 3 doses per day schedule.

**Conclusions:** As there was no clinical difference between the once-daily versus 3 times daily dose regimen of mesalazine for treatment of UC, the single-dose 3 gram daily treatment schedule is preferable.

**Reviewer's Comments:** The "non-inferiority" hypothesis is an interesting one in the fact that most studies compare treatments to see which of the 2 regimens is better. It is not surprising that most patients preferred the single-dose regimen (this is always expected to be the case). Finally, although we always "treat the patient, not the endoscopic appearance," 70% of patients in either group had endoscopic remission. (Reviewer-Ingram M. Roberts, MD).

© 2009, Oakstone Medical Publishing

Keywords: Mesalazine

Print Tag: Refer to original journal article
Collagenous Colitis Responsive to CIR Budesonide

Oral Budesonide for Maintenance Treatment of Collagenous Colitis: A Randomized, Double-Blind, Placebo-Controlled Trial.

Miehlke S, Madisch A, et al:

Gastroenterology 2008; 135 (November): 1510-1516

Controlled ileal release budesonide is highly effective in induction and maintenance of remission in collagenous colitis patients.

Background: Collagenous colitis (CC) is characterized by the presence of a subepithelial collagen band and microscopic colitis in the absence of macroscopic colonoscopic findings. Patients usually experience chronic diarrhea. The annual incidence in the U.S. is estimated to be 5 of every 100,000 cases. 

Objective: To evaluate the safety and efficacy of oral, controlled ileal release budesonide (Entocort CIR) for induction and maintenance of remission in patients with CC.

Design: Randomized double-blind placebo-controlled trial.

Participants: 48 patients with symptomatic, histologically proven CC from 38 centers. Patients had >3 watery bowel movements/day during >4 of the previous 7 days, and were not taking salicylates or aminosalicylates.

Methods: All patients received open-label budesonide 9 mg/day for 6 weeks. Patients then in remission (<3 stools/day) were randomized to receive 6 mg budesonide or placebo for 6 months. Primary efficacy end point was the cumulative relapse rate (>3 stools/day) at the end of the 6-month maintenance phase.

Results: Remission was achieved in 46 of 48 patients (96%) within 2 to 30 days (mean, 6.4 days). There were 21 relapses in the maintenance phase, almost all of which occurred in the first 2 months. A significantly higher proportion of the budesonide-treated patients maintained remission at 2, 4, and 6 months. The cumulative relapse rate at 6 months was 6 of 23 (26%) in the budesonide-treated patients and 15 of 23 (65%) in the placebo group (P=0.022). No serious adverse events were observed in either study phase.

Conclusions: Oral budesonide is safe and effective in inducing and maintaining remission in patients with CC.

Reviewer's Comments: Although no significant adverse effects were seen in this study, the risk of steroid-related adverse events remains a concern in patients requiring long-term maintenance therapy. The results of further follow-up off medication will be interesting and should allow us to determine what percentage of patients can maintain steroid-free long-term remission following 6 months of budesonide therapy. (Reviewer-Allen L. Ginsberg, MD).

© 2009, Oakstone Medical Publishing

Keywords: Budesonide Therapy

Print Tag: Refer to original journal article
In this meta-analysis of randomized placebo-controlled trials, there was significant heterogeneity in placebo relapse in CD patients.

**Background:** It is essential to determine both the natural history of Crohn's disease (CD) patients after surgical resection, an accurate calculation of rate of clinical relapse, and rate of endoscopic recurrence when treated postoperatively with placebo. This information is also necessary for evaluating maintenance medication efficacy.

**Objective:** To evaluate the placebo rates of clinical relapse and rates of severe endoscopic recurrence in CD patients following surgical resection, and to identify what factors may influence these rates.

**Design:** Meta-analysis.

**Participants:** 799 placebo recipients from 16 randomized placebo-controlled trials of postoperative CD patients.

**Methods:** This meta-analysis of randomized placebo-controlled trials evaluated postoperative maintenance therapies including 5-ASA, azathioprine, 6-MP, metronidazole, ornidazole, fish oil, probiotics, IL-10, and budesonide. Studies were identified on MEDLINE from 1990 to 2006. Primary outcomes were clinical relapse (Crohn's disease Activity Index [CDAI] >150 or an increase >60 points above baseline), or severe endoscopic recurrence (Rutgeerts score ≥2).

**Results:** The pooled estimate of placebo relapse rate was 23.7% (range, 0 to 78%), and the pooled estimate of severe endoscopic recurrence was 50.2% (range, 30% to 79%). Only duration of follow-up was associated with placebo clinical relapse rate, with studies with a longer duration of follow-up having a higher placebo relapse rate. Clinical relapse was heterogeneous and unrelated to other variables such as disease duration, percent first resection, CDAI >200, colonic versus ileocolonic disease location, or indication for surgery (fistula vs stenosis). Severe endoscopic recurrence in placebo-treated patients did not correlate with any variable evaluated, including study follow-up duration.

**Conclusions:** There was significant heterogeneity in placebo relapse, and endoscopic recurrence rates that did not correlate with evaluated variables.

**Reviewer's Comments:** Because of the variability of study follow-up duration, it is difficult to derive useful rates of relapse or endoscopic recurrence. As expected, clinical relapse rate increased with study duration, while unexpectedly, severe endoscopic recurrence did not correlate with duration of follow-up. This somehow doesn't make sense. Endoscopic recurrence doesn't correlate well, with clinical relapse rate being twice as common (50.0% vs 23.7%). It is reasonable to speculate that endoscopic recurrence is a precursor to clinical relapse. On the other hand, patients with severe endoscopic recurrence may go for years without symptoms and without therapy. (Reviewer-Allen L. Ginsberg, MD).

© 2009, Oakstone Medical Publishing

**Keywords:** Postop Clinical Relapse

**Print Tag:** Refer to original journal article
Background: The United States Preventive Services Task Force, which previously advocated colorectal cancer (CRC) screening, commissioned a systematic review to assess the various tests that could be used.

Objective: To undertake a systematic review to assess the test characteristics and potential harms from fecal occult blood tests (FOBTs)—particularly the more sensitive guaiac-based and immunochemical assays and tests—for malignancy-associated DNA, flexible sigmoidoscopy (FS), colonoscopy, and CT colonography.

Design: Targeted systematic review.

Methods: A systematic review was undertaken to identify data regarding the sensitivity and specificity of the indicated tests as well as any harms that are associated with them. No new information was sought regarding the efficacy of screening itself.

Results: 2 to 3 days of FOBT was better than a single test. The newer FOBTs were more sensitive for diagnosing cancer, and perhaps also benign neoplasia, than was standard hemoccult. However, the tests were often less specific. The DNA FOBTs did appear to be more sensitive, but the data were too limited to allow any hard conclusions. CT colonography was comparable to colonoscopy for identifying both cancer and large (at least 10 mm) polyps, but less sensitive for smaller polyps. Potential harms from CT colonography included cancer risk (estimated at 1 in 333 to 1 in 3000) and an unknown consequence of identifying extracolonic abnormalities. The perforation rate was very low. Colonoscopy misses 10% of adenomas, even those >10 mm. There are 2.8 serious complications for every 1000 colonoscopies undertaken; the rate is increased if polypectomy is also performed (and lower if it is not). The sensitivities of FS for cancer and adenomas are 58% to 75% and 72% to 86%, respectively. Presumably, these figures include the use of colonoscopy in selected cases. There are 3.4 serious complications for every 10,000 procedures.

Conclusions: More sensitive FOBTs are reasonable substitutes for standard hemoccult testing. CT colonography cannot be recommended at this time because of uncertainties about potential harm.

Reviewer's Comments: The authors claimed not to have found any new reports about the impact of screening on mortality, disregarding the 2006 systematic review suggesting that hemoccult screening does not improve overall mortality because the reduction in CRC deaths is compensated for by an increase in non-CRC deaths (Moayyedi P and Achkar E, Am J Gastroenterol 2006; 101:380-384). The Task Force has already noted, but then disregarded, a randomized trial assessing FS that indicated that total mortality was increased in the screened group (Thiis-Evensen E, et al, Scand J Gastroenterol 1999; 34:414-420). The assumption that CRC screening is effective and cost-effective is still open to challenge. (Reviewer-Ronald L. Koretz, MD).

© 2009, Oakstone Medical Publishing

Keywords: Fecal Occult Blood Tests

Print Tag: Refer to original journal article
The best strategies for colon cancer screening are colonoscopy every 10 years, annual sensitive fecal hemoglobin test, or flexible sigmoidoscopy every 5 years with an interval-sensitive fecal hemoglobin test.

**Background:** The United States Preventive Services Task Force commissioned a decision analysis to identify preferred colorectal cancer (CRC) screening tests and age groups.

**Objective:** To project the expected outcomes from standard and more sensitive fecal occult blood tests (FOBTs), flexible sigmoidoscopy (FS), and colonoscopy, as well as a combination FS/FOBT.

**Design:** Decision analysis.

**Methods:** 2 complicated models were employed: 1 was based on individuals and the other was based on an entire population. Both models assumed that all cancer arose from adenomatous polyps and that the natural history of colon cancer that was found by screening was the same as that of cancer diagnosed as a result of symptoms. Both incorporated potential harms from the tests, but it was not clear if they included harm from the therapy that arose from a positive test (such as a premature death from surgery undertaken to remove an asymptomatic polyp or cancer). Investigators assessed 6 different interventions (standard hemoccult, more sensitive FOBTs, FS with or without a sensitive FOBT, and colonoscopy) and no intervention. They varied the intervals of the testing (FOBT at 1, 2, and 3 years, endoscopy at 5, 10, and 20 years) and the starting (40, 50, and 60 years) and stopping (75 and 85 years) ages. The principal outcome was total life-years saved. However, since the most effective tests were going to involve colonoscopy (the most invasive test), they undertook a quasi-economic analysis, calculating the number of colonoscopies necessary to save 1 life-year.

**Results:** In both models, the maximum life-year gain was from colonoscopy every 5 years beginning at age 40 years and extending to age 85 years. Increasing the interval to 10 years and using 75 years as the stopping age modestly reduced the total life-year gain, but dramatically reduced the number of colonoscopies. Annual sensitive FOBT and FS every 5 years with an interval-sensitive FOBT produced nearly comparable outcomes.

**Conclusions:** The 3 options proposed were colonoscopy every 10 years, FS every 5 years with an interval-sensitive FOBT, and annual sensitive FOBT.

**Reviewer's Comments:** While standard hemoccult did not appear to be as effective, it was calculated that it would save 200 life-years for every 1000 subjects tested. However, the 4 large randomized trials of hemoccult have not demonstrated that any life-years are gained. There is at least a trend for more non-CRC deaths that offset the reduced CRC mortality; the only available randomized trial of FS demonstrated a higher total mortality rate in the screened group. Cancers identified from screening are slower growing (length-time bias), so fewer overall life-years will be saved. There is also some potential harm from premature deaths arising from the surgery that is performed to remove cancer or large polyps in asymptomatic individuals. (Reviewer-Ronald L. Koretz, MD).

© 2009, Oakstone Medical Publishing

Keywords: Test Strategies

Print Tag: Refer to original journal article
In patients with NASH, significant improvements in hepatic histopathology, but not fibrosis, are seen in patients who lose 9≥% of their body weight.

**Background:** Despite studies of insulin sensitizers, vitamin E, betaine, probucol, losartan, ursodiol, and pentoxifylline, no clearly effective drug therapy for nonalcoholic steatohepatitis (NASH) has been identified. Weight loss is generally recommended and has been associated with improvements in liver enzymes and histology, but is often difficult to achieve. Orlistat, an oral inhibitor of intestinal fat absorption used in the treatment of obesity, has been reported to be beneficial in NASH in 1 controlled trial and 1 case series of NASH patients.

**Objective:** To define the benefits of orlistat combined with caloric restriction and vitamin E in overweight NASH patients.

**Design/Methods:** In this open-label, 2-center trial, 50 overweight patients with biopsy-proved but compensated NASH were randomized into 2 groups. In 1 group, patients received 9 months of treatment with orlistat, 120 mg thrice daily with meals, a 1400-calorie diet, vitamin E (800 IU), and a multivitamin. The other group received the same regimen without orlistat. The primary end point was improvement in hepatic steatosis, NAFLD activity score, and fibrosis score at the end of treatment. Biopsies were evaluated by a single pathologist blinded to the therapy given. Improvements in laboratory data, including liver enzymes, lipid levels, insulin resistance, and cytokine levels were secondary end points.

**Results:** Among the 50 participating patients, 41 completed the trial and had follow-up liver biopsies. The 2 groups were well-matched at baseline, with BMIs of 35 to 37. Only 4 patients were diabetic. Body weight loss in the orlistat-treated group was 8.3% versus 6.0% in the control group, a statistically nonsignificant difference. Aminotransferase levels fell in both groups, but insulin resistance was unchanged. Serum cholesterol and LDL cholesterol declined significantly only in the orlistat-treated patients. Vitamin E levels increased in both groups. Liver biopsy improvements also were similar in both groups at the end of treatment. Regardless of treatment group, patients who lost body weight of ≥9% showed improvement in histology and insulin sensitivity when compared to those with lesser losses. Similarly, those who lost ≥5% had improved insulin sensitivity and steatosis when compared to other with lesser weight losses.

**Conclusions:** Orlistat was not beneficial in improving the histology of NASH, enhancing weight loss, reducing aminotransferase levels, or improving insulin resistance. On the other hand, histologic features, except fibrosis, were improved in those with weight loss of ≥9%.

**Reviewer’s Comments:** This is another piece of evidence supporting the value of weight reduction in the management of NASH. Whether the lack of an effect on fibrosis is simply due to the short treatment period deserves further study. (Reviewer-Raymond S. Koff, MD).
Telithromycin-Associated Hepatotoxicity Rare, Associated With High Risk of Fatality

"Telithromycin-Associated Hepatotoxicity: Clinical Spectrum and Causality Assessment of 42 Cases."
Brinker AD, Wassel RT, et al:

Hepatology 2009; 49 (January): 250-257

Telithromycin-induced liver injury has a short latent period and a high mortality rate.

**Background:** Telithromycin is a ketolide antibiotic currently approved solely for the treatment of community-acquired pneumonia in the U.S. After its introduction, spontaneous reports to the FDA implicated it as a cause of severe drug-induced liver injury and a number of cases were reported in the literature. However, the spectrum of clinically apparent liver disease linked to telithromycin has been uncertain, and no formal causality assessment had been undertaken.

**Objective:** To formally judge the causal association of telithromycin with clinically important liver disease and to describe the pattern of liver injury induced by this drug.

**Methods:** A single, senior, experienced hepatologist reviewed 109 spontaneous reports to the FDA (the MedWatch program) relating liver injury to telithromycin, and selected 42 case reports for review by an ad hoc group of 5 reviewers. This group categorized cases as highly likely, probable, or possible. Causality assessments were originally done independently by each of the 5 investigators, but could be changed after review of the assessments of the other participants and group discussion.

**Results:** Among the 42 cases, the median age was 50 years and two thirds were women. Onset of symptoms or biochemical abnormalities occurred between 2 and 43 days after beginning telithromycin, with a median interval of 10 days and mean interval of 13 days. Individuals who had or had not been previously exposed to telithromycin had similar latent periods. Presenting symptoms included jaundice or bilirubin levels of ≥2.5 mg/dL in 60%, abdominal pain in 45%, fever in 29%, eosinophilia in 19%, and ascites or the development of ascites in 17%. Rash was not mentioned. Four of 42 cases died of liver failure and 1 received a liver transplant. On initial causality assessment, complete agreement by the 5 reviewers was reached in 7%. After improved definitions of causality and group discussion, complete agreement was reached in 64% of cases.

**Conclusions:** Telithromycin hepatotoxicity is rare, is associated with a high risk of fatality, and may have a distinctive clinical pattern.

**Reviewer’s Comments:** This publication reflects the sorry state by which causality in drug-induced liver injury is assessed. The validity of group-think remains questionable, although it may be the best that can be done at this time. The limited utility of the MedWatch program also is demonstrated, since only 38% of reports were deemed “acceptable” (before causality assessment was considered by the group of judges) and apparently no information was available about a previous history of liver injury associated with the use of any macrolide antibiotic. (Reviewer-Raymond S. Koff, MD).

© 2009, Oakstone Medical Publishing

Keywords: Telithromycin-Associated Hepatotoxicity

Print Tag: Refer to original journal article
**Saccharomyces boulardii May Improve Trehalose Malabsorption**

Characterization of α,α-Trehalase Released in the Intestinal Lumen by the Probiotic Saccharomyces boulardii.

Buts JP, Stilmant C, et al:

Scand J Gastroenterol 2008; 43 (12): 1489-1496

---

Both in vitro and in vivo studies potentially suggest that *Saccharomyces boulardii* may improve gastrointestinal symptoms due to α,α-trehalose intolerance.

**Background:** Trehalose is a disaccharide, derived from mushrooms and used as an additive in dried foods. Prior work suggests that trehalase deficiency and trehalose intolerance may be more common than previously thought.

**Objective:** To measure human intestinal α,α-trehalase content and to characterize α,α-trehalase released by *Saccharomyces boulardii*.

**Design:** Human cohort study and animal and in vitro experiments.

**Participants:** 200 adults and children who underwent upper endoscopy for digestive symptoms.

**Methods:** α,α-trehalase activity was assayed in homogenates of human duodenojejunal biopsy specimens. α,α-trehalase activity was measured in lyophilized preparations of *S boulardii*. Growing rats were treated with oral administration of lyophilized *S boulardii*, and endoluminal activity of α,α-trehalase was assayed.

**Results:** Among the 200 patients, 18 (9.0%) had total α,α-trehalase deficiency and 39 (19.5%) had partial deficiency. Four (2%) patients had selective α,α-trehalase deficiency with otherwise normal disaccharidases. α,α-trehalase activity from the lyophilized *S boulardii* was 175 times more active than the human intestinal activity. Treatment of rats with *S boulardii* resulted in significant 25% to 45% increases in endoluminal fluid and intestinal mucosa α,α-trehalase activity compared with controls.

**Conclusions:** Human intestinal α,α-trehalase deficiency may be more common than has been previously thought. Administration of the probiotic *S boulardii* may be a potential treatment option in affected patients with gastrointestinal symptoms.

**Reviewer’s Comments:** This is an interesting paper which documents a potential cause and possible treatment for some patients with non-specific gastrointestinal complaints. Obviously, human clinical trials of *S boulardii* administration in subjects with documented α,α-trehalase deficiency need to be performed.

(Reviewer-Timothy O. Lipman, MD).

© 2009, Oakstone Medical Publishing

Keywords: α,α-Trehalase

Print Tag: Refer to original journal article
This study found that metronidazole failure rates were similar in patients with CDI who were treated earlier (1998) compared to recently treated patients (2004 to 2006). Factors that increased failure included recent cephalosporin use, CDI on admission, and a transfer from another hospital.

**Objective:** To determine whether there has been a change in *Clostridium difficile* resistance to metronidazole treatment over time.

**Methods:** 2 cohorts that were patients at different time periods with diarrhea positive for *C difficile* toxin which defined *C difficile* infection (CDI) were studied. Similar data were obtained between these 2 cohorts of patients except that in the later cohort, North American pulsed-field gel electrophoresis type-1 (NAP-1 typing) was obtained to identify a new virulent strain of CDI. Failure of metronidazole therapy was considered to be persistent diarrhea for 10 days following the initiation of therapy or a clinical decision to start vancomycin because of failure of metronidazole treatment.

**Results:** When comparing the 2 cohorts, metronidazole failure rates were similar in both cohorts studied (about 35%). (There was no difference in time to resolution of diarrhea or in the number of patients who had diarrhea for >10 days. Metronidazole failure was associated with cephalosporin use (OR, 32), CDI on admission (OR, 23), and transfer from another hospital (OR, 11). There was no association between NAP-1 infection and the failure of metronidazole therapy with similar infection rates in both cohorts. An overall increase in antibiotic (P <0.04) and proton pump inhibitor use (P <0.04) was noted, especially the use of fluoroquinolones (25% vs 53%; P <0.0007), and a decrease in use of cephalosporins (67% vs 39%; P <0.0009), aminoglycosides (33% vs 4%; P <0.0001), and clindamycin (21% vs 10%; P <0.07). The medical management has changed significantly between the 2 cohorts from supportive care and metronidazole monotherapy to combination therapy (met + vanc) given sequentially or concurrently (P <0.0001). There was no difference in length of stay, although inpatient mortality was noted, and more patients in the later cohort were ICU admissions (P <0.01).

**Conclusions:** There was no difference in metronidazole failures between the 2 cohorts studied. Also, factors which were associated with metronidazole failure included recent cephalosporin use, CDI on admission, and a transfer from another hospital. Patients with NAP-1 strains were not associated with metronidazole failure.

**Reviewer’s Comments:** These data seem contradictory to present clinical experience in that there are more CDIs and a greater number of patients with CDI-resistant disease to metronidazole. A reason for the lack of relationship between poor response to metronidazole therapy and NAP-1 positivity may relate to the fact that there were a limited number of stool samples available for strain typing, possibly reducing the power to detect differences. (Reviewer-Roy K.H. Wong, MD).

© 2009, Oakstone Medical Publishing

Keywords: Metronidazole Failure

Print Tag: Refer to original journal article
Trials of Gluten-Free Diets Not Helpful in Diagnosis of Celiac Disease

Clinical Response to Gluten Withdrawal Is Not an Indicator of Coeliac Disease.
Campanella J, Biagi F, et al:

Scandinavian J Gastroenterol 2008; 43 (November): 1311-1314

Do not use trials of gluten-free diet in patients suspected of having celiac disease.

Background: The diagnosis of celiac disease is made by specific histologic and serologic findings. Many patients who have non-specific gastrointestinal symptoms will put themselves on a gluten-free diet and when their symptoms improve, they become convinced that they have celiac disease.

Objective: To evaluate whether the clinical response of gastrointestinal symptoms to gluten withdrawal and subsequent dietary reintroduction could be an indicator of the presence of celiac disease.

Methods: During the course of >8 years, 180 patients on a gluten-free diet due to a diagnosis of celiac disease not based on appropriate criteria were evaluated. Overall, 112 of these subjects had gluten reintroduced into their diet and subsequently had duodenal biopsies and anti-endomysial antibodies performed. A diagnosis of celiac disease was made in 51 of 112. An analysis was made of the relationship between improvement/worsening of symptoms and withdrawal/reintroduction of gluten.

Results: Of the 51 patients confirmed to have celiac disease, 64.7% had an improvement of gastrointestinal symptoms with gluten withdrawal, but 75.0% of those who were not confirmed to have celiac disease had a similar improvement. In celiac patients gluten reintroduction led to exacerbation of symptoms in 71.4%, and in the non-celiac patients only 54.2% had exacerbation of symptoms when gluten was reintroduced into their diet. The positive predictive value for clinical improvement after gluten withdrawal was 36%; while the positive predictive value for clinical exacerbation after reintroduction of gluten into the diet was 28%.

Conclusions: The clinical response of patients to gluten withdrawal has no role in the diagnosis of celiac disease and the same can be said about the reintroduction of gluten in the diet of those who appear to have an improvement in symptoms on gluten withdrawal.

Reviewer’s Comments: This interesting paper has demonstrated that trials of gluten-free diets are useless in suggesting the diagnosis of celiac disease. If one suspects this diagnosis, obtaining a serum anti-endomysial antibody goes a long way in ruling out or in the diagnosis of celiac disease. (Reviewer-Michael M. Phillips, MD).

© 2009, Oakstone Medical Publishing

Keywords: GlutenWithdrawal

Print Tag: Refer to original journal article