Although imaging, serum IgG4 levels, and involvement of other organs can distinguish autoimmune pancreatitis from pancreatic cancer, one-third of patients must undergo biopsy, steroid trial, or surgery to make this distinction.

**Background:** Autoimmune pancreatitis (AIP) can appear to be quite similar to pancreatic cancer (PaC).

**Objective:** To develop a strategy to help differentiate AIP from PaC in patients presenting with obstructive jaundice and/or mass or enlargement of the pancreas.

**Design:** A retrospective review of prospectively collected data on patients with AIP and a retrospective record review for PaC patients.

**Participants:** 100 patients with PaC and 48 patients with AIP.

**Methods:** Presenting symptoms were recorded, a radiologist blinded as to the disease re-read the CT films, serologies for IgG4 and Ca 19-9 were noted, extrapancreatic findings were searched for in the record, and histology and response to steroids were noted. Indications were determined for core biopsy of the pancreas and steroid therapy.

**Results:** Patients with AIP were younger (61 years vs 67 years, respectively) and were more likely to be male (85% vs 57%, respectively) than were patients with PaC. Three groups were determined from imaging analysis: group 1 had features highly suggestive of AIP with classic diffuse involvement of the pancreas (n=25, 100% AIP); group 2 had features indeterminate for AIP, with normal pancreatic size or focal pancreatic enlargement, (n=20, 75% AIP); and group 3 had features highly suggestive of PaC, with pancreatic low density mass, pancreatic duct cutoff, or upstream pancreatic atrophy (n=103, 92% PaC). In group 1 patients, only 20 of 25 had elevated IgG4 levels or other organ involvement. Of patients in groups 2 and 3, all those with elevated serum IgG4 levels and other organ involvement had AIP (n=15). In AIP patients without elevated serum IgG4 levels or other organ involvement (n=14), diagnosis required pancreatic biopsy (n=7), steroid trial (n=5), or resection (n=2).

**Conclusions:** The use of pancreatic imaging, serum IgG4 levels, and determination of other organ involvement can accurately differentiate PaC from AIP in two-thirds of cases, with the remaining third requiring biopsy, steroid trial, or surgery to make the diagnosis.

**Reviewer's Comments:** The authors of this paper nicely outline an appropriate strategy to differentiate AIP from PaC. For patients presenting with obstructive jaundice and/or mass or enlargement of the pancreas, guidelines for which patients need potentially morbid biopsy procedures include those with a negative workup for cancer, those lacking serologies suggestive of AIP, or those lacking other organ involvement suggestive of AIP. Steroid trials are indicated when (1) patients with typical imaging have additional findings of AIP or (2) patients without typical imaging have a negative cancer workup and suggestive collateral evidence for AIP. Steroid trials are discouraged in those patients without collateral evidence of AIP. The diagnostic algorithm in the article is a useful guide in the diagnostic strategy for patients whose presenting findings are initially nondiagnostic for AIP versus cancer of the pancreas. (Reviewer-J. Mark Lawson, MD).

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Keywords: Autoimmune Pancreatitis vs Pancreatic Cancer

Print Tag: Refer to original journal article
A unique antibody to peptide AIP\textsubscript{1-7} is found in the serum of 94\% of patients with autoimmune pancreatitis but not in the serum of healthy controls.

**Objective:** To characterize and describe serologic markers that might help distinguish autoimmune pancreatitis (AIP) from pancreatic cancer (PaC).

**Design:** Prospective controlled study.

**Participants:** Initially, serum from 20 patients with AIP, 40 patients with PaC, 21 patients with alcoholic chronic pancreatitis, 18 patients with intraductal papillary mucinous neoplasms (IPMN), 20 patients with rheumatoid arthritis (RA), and 17 patients with systemic sclerosis were studied. Forty age-matched and gender-matched healthy controls were also analyzed. A second set of sera was used to validate the initial findings, which included 15 patients with AIP and 70 patients with PaC. Peptide-specific antibodies to autoantigen targets were produced by screening a random peptide library with pooled IgG obtained from 20 AIP patients.

**Results:** Sera from 18 of 20 AIP patients recognized peptide AIP\textsubscript{1-7}. Of 40 patients with PaC, 4 also reacted to peptide AIP\textsubscript{1-7}, but no reaction was seen in controls or patients with other diseases (RA, scleroderma, chronic pancreatitis, IPMN). This peptide demonstrated homology with the plasminogen-binding protein of *Helicobacter pylori* and ubiquitin-protein ligase E3 component n-recognin 2, which is a protein expressed to a high degree in pancreatic acinar cells. The validation group showed that 14 of 15 AIP patients and 1 of 70 PaC patients had the antibody. Combining both groups demonstrated that 33 of 35 AIP patients (94\%) and 5 of 110 PaC patients (5\%) had the antibody in their sera.

**Conclusions:** Antibody to peptide AIP\textsubscript{1-7} was found to be of higher sensitivity and specificity for the diagnosis of AIP than was IgG4.

**Reviewer's Comments:** The authors are very modest in downplaying the sensitivity and specificity of the antibody regarding its ability to differentiate AIP from PaC. However, the test was positive in 94\% of patients with AIP and was negative in 95\% of patients with PaC. While not 100\% sensitive and specific, these parameters are far superior to the IgG4 antibody test. If the anti-AIP\textsubscript{1-7} antibody becomes available for clinical use, it would be very helpful for diagnosing AIP. This was not a blinded study, however, and it would be useful to repeat the study prospectively where the authors found out the diagnosis after running the test samples for the anti-AIP\textsubscript{1-7}. (Reviewer-Ingram M. Roberts, MD).

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Keywords: Pancreatic Cancer vs Autoimmune Pancreatitis, Diagnosis

Print Tag: Refer to original journal article
In a series of experiments, human fecal microbiota was successfully transplanted into germ-free mice, and the transplanted microbiota can alter the host adipose tissue.

**Background:** Advances in DNA sequencing technology have greatly altered the study of gastrointestinal tract microflora. Reliance on microbial culture is no longer necessary. Genetic, or metagenomic methods, are used to characterize microbial communities — the so-called microbiota, or microbiome. Gnotobiotic mice are mice raised in germ-free environments and then colonized at different life stages with different microbial communities. Prior gut microbiota transplantation has been with mouse microflora only.

**Objective:** To investigate the transplantation of adult human fecal microbiota into germ-free mice.

**Design:** Series of animal experiments.

**Participants:** Germ-free C57BL/6J mice.

**Methods:** Fresh or frozen adult human fecal microbiota were transplanted into recipient germ-free mice. Mice were fed either a standard low-fat & plant polysaccharide-rich (LF/PP) diet or a Westernized high-fat, high-sugar, obesity inducing diet.

**Results:** (1) After transplantation, the recipient mice maintained the human fecal microbiota characteristics over time. (2) After establishment of the adult human fecal microbiota transplant, recipient mice were switched to the Westernized diet. The change in the administered diet resulted in an alteration of the original transplanted fecal microbiome in the recipient mice within a day. (3) The transplanted human fecal microbiome could be transplanted to new generations of germ-free mice, no matter whether the donor mice were eating the LF/PP diet or the Westernized diet: that is, generation-to-generation transplantation of the humanized microbiome is possible. (4) The Westernized diet produced obesity in the transplanted mice whereas the LF/PP diet did not. (5) Microbial transmission of obesity was demonstrated. Two groups of germ-free mice were transplanted with either the microbiome from the Western diet humanized obese mice or with the microbiome from standard LF/PP diet humanized lean mice. Both groups were then fed the LF/PP diet. The Western-diet–fed fecal microbiome produced increased adipose tissue in the recipient mice.

**Conclusions:** Adult human fecal microbiome can be transplanted into germ-free mice. The recipient mouse humanized fecal microbiome is altered in response to dietary changes. The humanized fecal microbiome transplanted from donor mice fed a high-fat, high-sugar, obesity inducing Westernized diet induces increased adipose tissue in the recipient mice.

**Reviewer’s Comments:** These are a series of elegant animal experiments. The authors state, appropriately, I think, that these humanized gnotobiotic mice will be useful for conducting “proof of principle clinical trials” testing the effects of environmental and genetic factors on the gut microbiota and host physiology. More importantly, these experiments add to our knowledge regarding the interplay between the gut microbiota and obesity. (Reviewer-Timothy O. Lipman, MD).

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Keywords: Gastrointestinal Microbiota, Obesity

Print Tag: Refer to original journal article
Nothing to Sneeze At -- Probiotic Reduces Common Cold’s Duration

Probiotic Bacteria Reduced Duration and Severity But Not the Incidence of Common Cold Episodes in a Double Blind, Randomized, Controlled Trial.

de Vrese M, Winkler P, et al:

Vaccine 2006; 24 (November 10): 6670-6674

In a high risk-of-bias randomized controlled double-blind clinical trial, a combination of 3 probiotics with a multivitamin/multimineral preparation appears to reduce the duration and severity of the common cold.

Background: Probiotics are microorganisms that, when ingested, provide purported health benefits to the host. Animal and a few human studies have suggested that some probiotic species can reduce the duration and severity of upper respiratory illness.

Objective: To determine if a specific combination of probiotic species ingested during the winter season affects viral respiratory tract infections.

Design: Double-blind, randomized, controlled clinical trial.

Participants: Healthy adults not vaccinated against influenza virus within the past 12 months.

Methods: Subjects were randomly assigned to receive the active probiotics (1 Lactobacillus species and 2 Bifidobacterium species [Tribion harmonis™]) plus multivitamins and minerals or multivitamins and minerals alone (controls) throughout the respiratory illness season. The study preparations consisted of a single tablet taken once daily. Subjects kept daily, validated symptom diaries.

Results: 454 of 479 subjects completed the trial. During the trial, 311 upper respiratory infections occurred, including 158 in the probiotic group and 153 in the control group (no difference between groups). However, in the probiotic group, the duration of illness was significantly shorter by almost 2 days and the total symptom score was significantly, albeit modestly, reduced. All of the respiratory illnesses were due to cold viruses as opposed to the influenza virus. Flow cytometry found significant increases in cytotoxic T cells as well as CD8+ T suppressor cells in the probiotic group.

Conclusions: A specific commercially available combination of 3 probiotics taken in daily combination with multivitamins and minerals appears to reduce the duration and severity of the common cold.

Reviewer’s Comments: Several months ago, a health column in the New York Times discussing probiotics claimed that probiotics can shorten the duration of colds. Because some consider all probiotic action within the realm of gastroenterology, I present this paper on probiotics and colds. In this study, the authors suggest that the probiotic effects found are of the same magnitude as those found with neuraminidase inhibitors in influenza symptom reduction. The study has several strengths: large sample size, assessment of viral and immune status, and measurement of fecal Lactobacillus and Bifidobacterium excretion, confirming viability of the active ingredients. However, a number of methodological flaws render this a high risk-of-bias study: no description of randomization method; no assurance of allocation concealment; no accounting for dropouts (per-protocol rather than intention-to-treat analysis); no power calculation or sample size determination; and failure to account for multiple end points in the statistical analysis. High risk-of-bias studies tend to find more favorable outcome benefits. This trial would not pass muster for the United States Food and Drug Administration’s requirements for a new drug. It is intriguing that probiotics might alter the gastrointestinal immune system to affect infections elsewhere in the body. As with virtually all probiotic studies, the results are tantalizing but leave us wishing for more rigorous trials. (Reviewer-Timothy O. Lipman, MD).

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Keywords: Probiotics, Effect of Influenza & Colds

Print Tag: Refer to original journal article
The results of several clinical trials suggest that various combinations of probiotics and prebiotics may reduce the incidence and severity of respiratory illnesses.

**Background:** Probiotics are microorganisms that, when ingested, have purported health benefits on the host. Prebiotics are the nutrient substrates for probiotics. Synbiotics are combinations of probiotics and prebiotics. Probiotics have been studied in intestinal function, but their ability to affect distant immune function is less clear.

**Objective:** To investigate the ability of several different synbiotic combinations to improve intestinal health and alter respiratory infections.

**Design:** Review of 3 placebo-controlled, double-blind, randomized clinical trials carried out during 3 separate winter seasons of respiratory illness.

**Participants:** Healthy adult Italian volunteers. **Study 1 (Year 1):** Synbiotic A consisted of 3 probiotics enhanced with fructooligosaccharides (FOS). The effect of symbiotic A on respiratory infections was compared to that of a placebo. **Study 2 (Year 2):** The effect of symbiotic A on respiratory infections was compared to that of (1) symbiotic A plus lactoferrin and (2) placebo. **Study 3 (Year 3):** Synbiotic B consisted of 5 probiotics enhanced with FOS. The effect of symbiotic B on respiratory infections was compared to that of (1) placebo and (2) symbiotic C (same 5 probiotics enhanced with galactooligosaccharides).

**Methods:** The number of subjects in each study ranged from 234 to 250. Each subject took a study preparation dissolved in water once daily for 90 days. Outcomes were by self-reported questionnaires and periodic telephone contact.

**Results:** Overall, intestinal function improved significantly in the various synbiotic groups, although no intestinal problems were described at baseline. The intake of various synbiotic preparations was associated with significant reductions in the incidence, severity, and duration of various respiratory illnesses. Lactoferrin did not appear to provide any added benefit.

**Conclusions:** Various synbiotic combinations may reduce the incidence, severity, and duration of respiratory illness.

**Reviewer's Comments:** Because some consider all probiotic action to be within the realm of gastroenterology, I present this report of a United Nations Food and Agricultural Organization Technical Meeting on prebiotics. These data were reported in a symposium on prebiotics and, as such, probably have not undergone peer review. The results represent high risk-of-bias data, consequent to multiple methodologic flaws, including (1) no evidence for concealment of allocation; (2) no evidence that power calculations were performed, especially important since 2 of the 3 studies had 3 arms, comparing active interventions; (3) no accounting for dropouts, thus making the analysis “per-protocol” rather than “intention to treat;” and (4) multiple measures were presented without evidence of statistical correction for these measurements, raising the possibility that many of the “significant” findings were due to chance. The concept that probiotics or synbiotics can alter the gut bacterial flora, or gut-associated immune system, in such a way that respiratory infections are ameliorated is a fascinating concept, but it remains unproven by properly performed clinical trials. (Reviewer-Timothy O. Lipman, MD).

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Keywords: Probiotics, Effect on Respiratory Infections

Print Tag: Refer to original journal article
Mutations for IL-10 Receptor Linked to Severe Colitis

Inflammatory Bowel Disease and Mutations Affecting the Interleukin-10 Receptor.

Glocker EO, Kotlarz D, et al:


Stem cell transplantation may play a therapeutic role in highly selected patients with Crohn disease.

Background: It is widely believed that the interaction of proinflammatory and antiinflammatory cytokines plays an important role in the pathogenesis of inflammatory bowel disease (IBD). Interleukin-10 (IL-10) is secreted by a wide variety of cells and limits the secretion of proinflammatory cytokines such as tumor necrosis factor α (TNF-α) and IL-12. Mice deficient in either IL-10 or its receptor develop a severe enterocolitis.

Objectives: To describe, in humans, the identification of a homozygous recessive loss-of-function mutation in the IL-10 receptor genes IL10RA and IL10RB, which are associated with severe Crohn enterocolitis.

Participants: Children from 2 unrelated consanguineous families who had a severe, progressive, poorly treatable form of Crohn disease (CD) characterized by onset in the first year after birth. Six other children with severe CD developing in the first year of after birth were also studied.

Methods: Genetic-linkage analysis and candidate-gene sequencing was performed on patient samples. Functional assays in patients’ peripheral-blood mononuclear cells were performed, including the transduction of cell lines and mutant cells with retroviral vectors encoding IL10RA and IL10RB complementary DNA. This demonstrated that the defect in IL-10 signaling was corrected by replacing the mutant IL-10 receptor with a normal receptor. An allogenic hematopoietic stem cell transplantation was performed in 1 patient.

Results: Three distinct homozygous mutations in genes IL10RA and IL10RB encoding IL10R1 and IL10R2 proteins which form the IL-10 receptor were identified in 4 children with severe enterocolitis. These mutations were not found in any of more than 100 unaffected subjects or 45 patients with adult-onset CD or 45 patients with UC. The mutations blocked IL-10–induced signaling, leading to increased secretion of TNF-α and other proinflammatory cytokines from peripheral blood mononuclear cells. Allogenic hematopoietic stem cell transplantation utilizing stem cells from an unaffected HLA-matched sibling donor was performed in 1 patient with severe ileocolitis. Following stem cell transplantation, all fistulas healed, and the patient has remained in continuous remission for >1 year.

Conclusions: Homozygous mutations in genes encoding the IL-10 receptor subunit proteins were found in patients with early onset severe enterocolitis. The IL-10 receptor mutations were associated with an unchecked release of proinflammatory cytokines. Allogenic stem cell transplantation resulted in disease remission in 1 patient.

Reviewer’s Comments: This report provides the first significant evidence for a functional role of IL-10 and its receptor proteins in the pathogenesis of IBD. It is impressive that the mouse model of enterocolitis seen in mice deficient in IL-10 or its receptor is replicated in humans and can be corrected with stem cell transplantation. (Reviewer-Allen L. Ginsberg, MD).

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Keywords: Inflammatory Bowel Disease, Cytokines, Interleukin-10

Print Tag: Refer to original journal article
Appendectomy Used As Therapy for Ulcerative Proctitis

Appendectomy as a Therapy for Ulcerative Proctitis.
Bolin TD, Won S, et al:

Am J Gastroenterol 2009; 104 (October): 2476-2482

Background: Numerous case-control studies have found that previous appendectomy decreases the risk of subsequent development of ulcerative colitis (UC). Recent data found that appendicitis at age <20 years, rather than appendectomy, reduced the risk of UC. Appendectomy for a normal appendix did not affect the incidence of UC.

Objective: To determine whether appendectomy can affect the clinical course in patients with refractory ulcerative proctitis.

Design: Prospective case series.

Patients: 30 consenting patients with active ulcerative proctitis who agreed to appendectomy in the absence of symptoms of appendicitis. All patients had continued symptoms despite medical therapy with oral and topical 5-aminosalicylic acid (5-ASA) and corticosteroids, with some also treated with immunomodulators and anti–tumor necrosis factor biologics. A clear cutoff of granular, friable rectal mucosa from normal appearing sigmoid mucosa was apparent in all cases. Patient ages ranged from 17 to 70 years, with only 1 patient younger than age <20 years. All were nonsmokers.

Methods: Clinical activity was measured with the Simple Clinical Colitis Activity Index (SCCADI). Post-appendectomy scores were assessed monthly by phone or in person for a median of 14 months.

Results: 29 of the 30 removed appendices appeared macroscopically normal, and 1 had a mucous cyst adenoma. After appendectomy, improvement in SCCADI scores occurred in 27 of 30 patients (90%), decreasing from a median score of 9 to 2 ($P<0.0005$). Of the 30 patients, 12 (40%) had complete clinical resolution (SCCADI score of 0) and withdrawal of all medical therapies. Time required for complete resolution ranged from 1 to 12 months (median, 3 months). To date, all of these 12 patients have remained in remission, off all therapy, for a median of 9 months (range 6 to 25 months).

Conclusions: The data suggest a possible role for appendectomy in the treatment of refractory ulcerative proctitis.

Reviewer's Comments: Idiopathic ulcerative colitis/proctitis is characterized by remissions and exacerbations, the causes of which are often unknown. In this report, following appendectomy, SCCADI improvement occurred in 90% of patients. However, there was no control group; time to resolution of symptoms after appendectomy in 2 patients took 12 months; exacerbations after remission were not mentioned; and there was no endoscopic or histologic confirmation of improvement or resolution. Despite these negatives, it is impressive that 12 of 30 patients (40%) achieved complete remission off all therapy. Two of these 12 patients before appendectomy had suffered from unremitting proctitis for 2 and 10 years, respectively. A third patient who had a clinical score of 11 pre-appendectomy (despite topical and oral 5-ASA and steroids and immunomodulator and biologic therapy) also achieved complete remission off all medical therapy at 12 months after appendectomy. Where there is smoke there may be fire. Further investigation is indicated. (Reviewer-Allen L. Ginsberg, MD).

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Keywords: Ulcerative Proctitis, Treatment, Appendectomy

Print Tag: Refer to original journal article
Concomitant aminosalicylate therapy is associated with an increased likelihood of sustained remission in patients with ulcerative colitis who are receiving azathioprine.

Background: Azathioprine (AZA) induces remission in two-thirds of patients with ulcerative colitis (UC). Maintenance AZA is generally effective in sustaining remission. However, concern about long-term adverse effects may result in discontinuation of AZA.

Objectives: To determine the frequency and predictors of clinical relapse in UC patients in steroid-free remission withdrawn from maintenance AZA.

Design: Retrospective multicenter observational study. Patients: 127 UC patients in steroid-free remission for at least 3 months at the time of withdrawal from maintenance AZA. Of these patients, 54% had extensive disease, 30% had left-sided disease, and 16% had proctosigmoiditis. Overall, 91 (72%) were taking concomitant oral and/or topical aminosalicylates (ASA).

Methods: Frequency of clinical relapse or colectomy was analyzed. Relapse was defined as occurrence of symptoms or signs of UC requiring reintroduction of rescue therapy.

Results: The median duration of AZA therapy was 47 months (range 3-105 months). Of 127 patients, 94 (74%) maintained a sustained remission without relapse the entire time they were treated with AZA. Only concomitant ASA therapy was predictive of sustained remission while on maintenance AZA. AZA was stopped electively in 73% of patients and was discontinued because of adverse effects in 27%. The adverse effects included leukopenia (n=17), infection (n=6), hepatotoxicity (n=12), pancreatitis (n=1), and alopecia (n=1). Median follow-up after AZA withdrawal was 55 months (range, 1-182 months). The cumulative relapse rate after AZA withdrawal was 35% at 1 year, 49% at 2 years, and 65% at 5 years. Predictors of relapse included lack of sustained remission while on AZA maintenance (HR 2.35, P=0.001) and extensive colitis versus left-sided colitis (HR 1.79, P=0.028). Patients treated for a short duration (<6 months) were also more likely to relapse than were patients treated >48 months (HR 2.78, P=0.008).

Conclusions: Concomitant ASA therapy decreases the relapse rate of UC in patients on maintenance AZA. Withdrawal of maintenance AZA is associated with a high relapse rate.

Reviewer's Comments: AZA therapy is usually initiated in UC patients who have not been controlled on 5-ASA alone and when those treated with concomitant steroids repeatedly experience disease exacerbations after the steroids are tapered or discontinued. AZA therapy results in steroid-free remission in two-thirds of these patients. It has been unclear whether continued 5-ASA therapy is of added benefit. In this study, an aside observation revealed that continuation of 5-ASA contributed to the sustained steroid-free remission induced by AZA maintenance. In fact, despite taking maintenance AZA, relapses were 4 times as likely in patients not taking 5-ASA (HR 4.12, P=0.009). Message 1: DO NOT stop concomitant therapy with 5-ASA. Message 2: When AZA is discontinued, the cumulative relapse rate is high (one-third at 1 year, one-half at 2 years, and two-thirds at 5 years). DO NOT stop concomitant therapy with 5-ASA. (Reviewer-Allen L. Ginsberg, MD).

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Keywords: Treatment, Azathioprine, Aminosalicylates

Print Tag: Refer to original journal article
Cyclosporin A Effective for Fulminant UC

Treatment of Fulminant Ulcerative Colitis With Cyclosporine A.

Holme O, Thiis-Evensen E, Vatn MH:

Scand J Gastroenterol 2009; 44 (October): 1310-1314

Cyclosporin A prevents colectomy in almost 50% of patients treated for fulminant ulcerative colitis.

**Background:** In cases of fulminant ulcerative colitis (UC) which have failed to respond to high-dose corticosteroids, cyclosporin A (CyA) given IV brings about an excellent short-term response. Because of fear of drug toxicity and the belief that such treatment leads to high short-term and long-term colectomy rates, the use of CyA has not gained widespread acceptance.

**Objective:** To report on experience gained in Oslo, Norway, regarding the use of CyA in the treatment of fulminant UC.

**Design:** During a 13-year study interval beginning in 1993, 18 patients with fulminant UC who failed treatment with high-dose corticosteroids were treated with IV CyA (5 mg/kg). All patients who responded were then given oral CyA for 6 months, as well as azathioprine (AZA). These patients were prospectively followed up at 2, 6, 12, and 24 months after discharge.

**Results:** Of the 18 patients treated with CyA, 15 (83%) responded to this treatment. During the follow-up, no colectomy had been performed in 72% of patients at 2 months, in 67% at 6 months, in 61% at 12 months, and in 56% at 24 months. Eight patients (44%) had not had a colectomy during a median follow-up of 60.3 months (range, 1.7 to 146 months). At least one relapse occurred in all of the patients during the follow-up. Of interest is the fact that only 1 patient had to discontinue CyA because of adverse effects.

**Conclusions:** This study demonstrated that, at this institution, CyA treatment for fulminant UC was both safe and effective.

**Reviewer’s Comments:** This report should encourage clinicians use CyA to treat patients with fulminant UC as when given in the way used in this study – it seems to be both safe and effective. (Reviewer-Michael M. Phillips, MD).

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Keywords: Fulminant Ulcerative Colitis, Treatment

Print Tag: Refer to original journal article
Selective serotonin reuptake inhibitors, especially when taken with NSAIDs, increase the risk for upper gastrointestinal bleeding.

**Background:** During the past decade, there has been evidence that selective serotonin reuptake inhibitors (SSRIs) are associated with upper gastrointestinal bleeding (UGIB). The magnitude and level of this risk has not been determined, nor has the possible enhanced risk of bleeding when these drugs are taken with NSAIDs.

**Objective:** To systematically evaluate the risk of UGIB when SSRIs are used and to determine their potential interaction with NSAIDs.

**Design:** A search was made of PubMed, Science Citation Index, and trial registries for information on SSRIs, NSAIDs, and UGIB. Unpublished reports of adverse events submitted to pharmaceutical companies were also reviewed. For the meta-analysis, 1 cohort study and 3 case-control studies that evaluated 153,000 patients were used.

**Results:** The results of the meta-analysis demonstrated that the odds ratio for a UGIB was 2.36 with the use of an SSRI alone (95% CI: 1.44-3.85; \( P=0.0006 \)) and was 6.33 for an SSRI plus an NSAID (95% CI: 3.40-11.8; \( P<0.00001 \)). It was found that, in patients aged >50 years with no risk factors for UGIB, the number-needed-to-harm per year is 411 for SSRIs alone and 106 with the concomitant use of NSAIDs. In analyzing 101 spontaneous reports, it was found that UGIB occurred after a median of 25 weeks with SSRIs. Approximately two-thirds of these patients were also taking NSAIDs.

**Conclusions:** The use of SSRIs alone or in combination with NSAIDs significantly increases the risk of UGIB. Physicians caring for patients taking SSRIs, especially in those who are also taking NSAIDs, should be vigilant for evidence of UGIB.

**Reviewer's Comments:** I suspect that many clinicians are not aware of the findings of this study. The importance of these findings is great, especially in patients aged >50 years and those who have risk factors for UGIB who are taking SSRIs and NSAIDs. In view of these findings, one might consider the use of an H2 blocker or proton pump inhibitor in those patients in these groups. (Reviewer-Michael M. Phillips, MD.)

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Keywords: Upper GI Bleeding, SSRIs vs Bleeding Risk

Print Tag: Refer to original journal article
Large balloon sphincteroplasty without papillotomy is safe and effective for the removal of large bile duct stones.

**Background:** The use of large-diameter balloons to dilate the bile duct for removal of large bile duct stones has become popular. Frequently, a sphincterotomy is performed prior to the dilation to reduce the risk of pancreatitis, although this practice is not accepted in all circles.

**Objective:** To evaluate the safety and efficacy of large balloon sphincteroplasty (LBS) without preceding sphincterotomy (EST) for the removal of large common bile duct stones (>15 mm).

**Design:** Single-institution study for cases seen from 2005 to 2009.

**Participants:** 38 patients with large common bile duct stones.

**Methods:** Patients with sphincterotomy or prior papillary dilation were excluded. After wire-guided bile duct cannulation, the stone size was measured, and a 15-mm dilation balloon was inflated across the sphincter with a small amount of contrast instilled in the balloon. Stones were then extracted with a retrieval balloon or via a crushing basket.

**Results:** The overall success rate for stone removal was 97.4%, with only 1 patient developing mild post-procedure pancreatitis. No mechanical lithotripsy was required for stone removal in 76% of cases, and complete stone removal was achieved in 1 session of LBS in 65% of cases. Using this technique, the authors failed to remove the stone adequately in only 1 patient. Success with stone removal was predicted by a ratio of stone size to balloon diameter.

**Conclusions:** The results of this study suggest that, for the removal of bile duct stones >15 mm, LBS without sphincterotomy is safe and effective.

**Reviewer’s Comments:** The use of large dilation balloons for the removal of large bile duct stones has revolutionized the technique and has enhanced the success rates for removal of large bile duct stones. The authors of this paper postulate that the use of large-diameter balloons may actually lessen the risk of pancreatitis, which had been described with the use of smaller balloons to dilate the sphincter. Perhaps the larger balloons are less frequently associated with obstructing edema that has been thought to cause post-ERCP pancreatitis in some papers. This is an intriguing thought that will require further studies to prove that sphincterotomy in not necessary when balloons 15 mm or larger are used to dilate the biliary sphincter for stone removal. Meanwhile, I favor a small sphincterotomy with large balloon dilation and keeping the lithotripter on the back shelf. (Reviewer-J. Mark Lawson, MD).

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**Keywords:** Large Bile Duct Stones, Sphincteroplasty

**Print Tag:** Refer to original journal article
In dysenteric illnesses characterized by bloody diarrhea, Shiga toxin-producing *E coli* and O157:H7 should be checked on stool samples.

**Objective:** To summarize the current clinical management algorithms for the diagnosis and management of acute bacterial diarrheas

**Methods:** This article was basically a literature review from an internationally known infectious disease physician whose area of expertise is bacterial diarrhea. The author referenced approximately 50 recent publications (many of which he authored) and produced a concise informative review.

**Results:** Workup of bacterial diarrheas should always include a stool culture for shigella, salmonella, and campylobacter. Bloody diarrhea should be evaluated by checking the stool for presence of Shiga-like toxin, which is seen with hemorrhagic *Escherichia coli*. When diarrhea is dehydrating or following seafood consumption, vibrios should be excluded as the cause. The major cause of bacterial diarrhea in the United States is still *Campylobacter jejuni*, while toxigenic *E coli* remains as a cause for >50% of the cases of “traveler’s diarrhea.” Treatment for bacterial diarrhea includes hydration and electrolyte replacement, but antimitoty agents should not routinely be used in patients with fever and dysenteric symptoms. Nontyphoid salmonellosis requires antibiotic therapy in certain patient subgroups that have a high risk of developing complications, and antibiotics are not suggested to treat patients with Shiga-like toxin-producing *E coli*, including O157:H7. Traveler’s diarrhea may be empirically treated with antibiotics without stool cultures and, prophylactic antibiotics may be effective to administer to patients traveling to South America, Africa, and Asia.

**Conclusions:** Stool cultures should be obtained when diarrhea is severe, prolonged, or complicated by fever and dysenteric symptoms (blood in the stool, etc.) or when an outbreak is noted in a cohort of patients.

**Reviewer’s Comments:** This is a brief, yet comprehensive, review by an expert on the diagnosis, therapy, and management of the various commonly seen causes of bacterial diarrhea. All gastroenterologists will find this an excellent reference and will enjoy reading this article. (Reviewer-Ingram M. Roberts, MD).

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Keywords: Bacterial Diarrhea

Print Tag: Refer to original journal article
Serum CK-18 fragments predict histologic nonalcoholic steatohepatitis and may be useful as noninvasive biomarkers in clinical practice.

**Background:** Nonalcoholic fatty liver (NAFL) is a spectrum of liver disease including simple steatosis to nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and liver failure. Currently, liver biopsy is the only way to differentiate NAFL from NASH. There is an urgent need to develop simple noninvasive tests that can accurately make this distinction. Previous studies have shown that cytokeratin-18 (CK-18) fragments correlate with the magnitude of hepatocyte apoptosis and predict NASH.

**Objective:** To validate the use of CK-18 to differentiate NAFL from NASH.

**Design:** Retrospective case-control study.

**Participants:** 139 well-characterized subjects with NASH from 8 centers in the NASH Clinical Research Network (CRN) and 150 age-matched healthy controls.

**Methods:** Demographic and clinical data were obtained from the NASH CRN database. Histology was examined for the presence of steatosis, inflammation, and fibrosis according to the NASH activity score (Kleiner, 2005) and categorized as no NASH, borderline NASH, and NASH. CK-18 fragments were measured from stored blood within 3 months of biopsy by ELISA and compared among those with simple steatosis, borderline NASH, NASH, and controls.

**Results:** The demographics of the cohort did not differ between among the NAFL groups (median age, 48 years; 63% female; 79% white; and BMI 34). Approximately one-third of patients had 5% to 33% steatosis, one-third had 34% to 66% steatosis, and one-third had >66% steatosis. Hepatocyte ballooning was seen in 60% (few, 35%; many, 25%) while stage 1, 2, and 3 fibrosis was seen in 28%, 21%, and 11%, respectively. CK-18 fragments ranged from 68 to 3000 U/L and were much higher in those with NASH (median, 335 U/L) compared to those with borderline NASH (194 U/L), simple steatosis (200 U/L), or controls (145 U/L; \( P<0.001 \)). CK-18 correlated with NASH activity score (\( r=0.51 \)), and CK-18 levels remained an independent predictor of NASH after adjusting for age, biopsy length, liver enzymes, and fibrosis. The area of the ROC curve for CK-18 was 0.83, with levels of 216 U/L giving the highest sensitivity (77%) and 287 U/L giving the highest specificity (92%).

**Conclusions:** Serum CK-18 fragments predict histologic NASH and may be useful in clinical practice.

**Reviewer's Comments:** The accuracy of CK-18 in predicting NASH is similar to other noninvasive markers. Because 15% to 30% may be misclassified, liver biopsy will remain important. Whether CK-18 fragments can add to existing models is unknown. (Reviewer: Richard Keith Sterling, MD).

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Keywords: Nonalcoholic Steatohepatitis, Serum Markers

Print Tag: Refer to original journal article
NBI Differentiates Adenomas From Hyperplastic Polyps

Hyperplastic Polyposis Syndrome: A Pilot Study for the Differentiation of Polyps Using High-Resolution Endoscopy, Autofluorescence Imaging, and Narrow-Band Imaging.

Boparai K, van den Broek FJ, et al:

Gastrointest Endosc 2009; 70 (November): 947-955

Narrow-band imaging, but not autofluorescence imaging, can differentiate hyperplastic polyps from adenomas with a diagnostic accuracy of up to a 94%.

Background: Hyperplastic polyposis syndrome (HPS) is a relatively recently recognized but not widely appreciated condition that may be associated with the presence of serrated adenomas. HPS carries an elevated risk of colorectal cancer. The use of autofluorescence imaging (AFI), and narrow-band imaging (NBI), and high-resolution endoscopy (HRE) for the differentiation of polyps has been widely reported with varying detection rates.

Objective: To determine the value of trimodal imaging in the differentiation of polyps in patients with the HPS.

Design: Prospective polyp series.

Participants: Consecutive patients with HPS.

Methods: Procedures were performed with a trimodal imaging system with HRE, AFI, and NBI. Polyps were assessed for size, location, AFI color, and Kudo pit pattern on NBI. All lesions were evaluated by a blinded pathologist.

Results: Seven patients were enrolled and found to have 19 hyperplastic polyps (HPs), 32 sessile serrated adenomas (SAAs), and 15 adenomas. The diagnostic accuracy in differentiating HPs from SAAs was 55% for AFI, 55% for Kudo pit pattern, and 52% for vascular pattern intensity. The accuracy of differentiating adenomas from HPs was 65%, 94%, and 90%, respectively. Size >3 cm and a proximal location had a diagnostic accuracy of 76% in differentiating SSAs from HPs.

Conclusions: The differentiation of HPs from SAAs using trimodal endoscopic imaging techniques was unsatisfactory. The differentiation of adenomas from HPs was possible with NBI.

Reviewer's Comments: Many of the newer endoscopy scopes contain NBI, and the question has always been exactly what are we supposed to be doing with it. This technology and other technologies for imaging polyps in the hopes of differentiating neoplastic from non-neoplastic lesions are clearly not ready for prime time and represent the release of a technology before any proven utility has been demonstrated. I think it will be years before guidelines and techniques are defined for using imaging in differentiating premalignant polyps from non-neoplastic lesions. Meanwhile, our time is better spent on careful split-dose bowel preparations and careful withdrawal techniques with the destruction of all lesions detected rather than keeping our finger over the NBI button. (Reviewer-J. Mark Lawson, MD).

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Keywords: Hyperplastic Polyposis Syndrome, Imaging

Print Tag: Refer to original journal article
Cyanoacrylate Therapy Treats Varices, Reduces Morbidity


Procaccini NJ, Al-Osaimi AM, et al:

Gastrointest Endosc 2009; 70 (November): 881-887

Cyanoacrylate injection therapy of bleeding gastric varices is as safe and as effective as transjugular intrahepatic portosystemic shunt.

**Background:** The treatment of gastric variceal bleeding remains difficult. In the past, endoscopic therapy has proven to be ineffective for acute control and prophylaxis of gastric varices. Cyanoacrylate has been shown in some studies to be effective in controlling variceal bleeding.

**Objective:** To compare the incidence of rebleeding, survival, and complications between initial treatments with cyanoacrylate injection versus transjugular intrahepatic portosystemic shunt (TIPSS).

**Design:** Retrospective cohort analysis.

**Participants:** Cirrhotic patients with gastric variceal hemorrhage determined by active bleeding or high-risk stigmata treated with cyanoacrylate therapy or TIPSS.

**Methods:** Patients who were treated with cyanoacrylate injection had their eyes covered, and refrigerated enbucrilate was mixed with ethiodol in a 1:1 ratio and gently stirred and drawn into a 23-gauge cannula. The working channel of the scope was flushed with a mixture of olive oil and simethicone to prevent adherence to the scope during suctioning. The sclerotherapy catheter was preloaded with the 1:1 mixture after flushing with ethiodol. A small drop of polymer was ejected to insure liquidity, and then the needle was inserted into the varix, 2 mL of the mixture was injected into each varix, and the needle was withdrawn while still injecting to prevent entrapment. A new needle was used for each varix. TIPSS was performed with standard techniques. Within 1 to 4 weeks, repeat endoscopy was performed and then repeated every 3 to 6 months or if rebleeding occurred.

**Results:** 105 patients were enrolled with similar demographics and disease severity. The rate of acute complications, survival, and rebleeding were similar between the 2 treatment arms. The long-term morbidity requiring hospitalizations was significantly higher in the TIPSS group ($P<0.001$).

**Conclusions:** In patients with gastric variceal bleeding, cyanoacrylate injections were as effective as TIPSS in controlling and preventing variceal bleeding with equal long-term survival. Less long-term morbidity related to therapy was seen in the cyanoacrylate group.

**Reviewer's Comments:** Although the risk of bleeding from gastric varices is 50% of that seen with esophageal varices, the mortality rate is much higher. Management has been difficult in the past with TIPSS being used as rescue therapy. This interesting paper highlights the effectiveness and safety of cyanoacrylate therapy for the prevention and control of gastric variceal hemorrhage. The devil, as always, is in the details: if this agent is not mixed correctly or administered correctly, it may be ineffective and permanently damage the endoscope. Attention to detail is paramount when using this agent. Hopefully, more easy-to-administer agents such as thrombin will fare as well in head-to-head trials so that we need not worry about damaging expensive equipment or the occasional risk of serious embolization. (Reviewer-J. Mark Lawson, MD).

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Keywords: Gastric Variceal Bleeding, Treatment

Print Tag: Refer to original journal article
In a study assessing the relationship between folate intake and colorectal cancer in hospitalized Korean adults, folate intake was inversely related to colorectal cancer risk in women, but not men.

**Background:** Folate intake has been associated with both protective and stimulatory effects in colorectal cancer (CRC). The incidence of colorectal cancer in Korea has increased 6-fold to 7-fold over the past 3 decades.

**Objective:** To examine the relationship between folate intake and colorectal cancer in a Korean population.

**Design:** Hospital-based, case-control study.

**Participants:** 596 consecutive subjects with colorectal cancer and 509 controls (age range for both groups: 30-79 years) admitted to 2 Seoul, Korea, university hospitals. It is not clear how the controls were matched to the cases.

**Methods:** A trained nurse conducted structured interviews assessing smoking, alcohol, lifestyle factors, and a food-frequency questionnaire, from which nutrient intakes were calculated. Analysis used logistic regression models to calculate odds ratios (OR).

**Results:** Cases more frequently had a history of CRC among first-degree relatives, consumed more alcohol, and were more sedentary than controls. With respect to folate, overall combined data demonstrated a reduced risk for CRC in the highest versus lowest quartile of dietary folate intake (OR=0.47; 95% CI, 0.32-0.69). When analyzed by gender, women had a significant inverse association (reduced risk) for combined CRC, colon cancer, and rectal cancer, but the association was not significant in men. When total folate intake (dietary plus supplements) was assessed, the relationship was less strong, finding only a significant inverse association in women for rectal cancer, but no other significant associations were identified.

**Conclusions:** Reduced risk for colorectal cancer is associated with higher intakes of dietary folate in Korean women, but not men.

**Reviewer’s Comments:** As a case-control study, these findings can only be taken as associations, not causal. I find the results somewhat confusing. Why should the protective effect of folate be found only in women, but not in men? Also, why should the addition of folate supplements actually attenuate any benefits, except for a reduction in rectal cancer only in women? It is possible that the positive findings are due to chance only. After many observational studies — case-control and cohort — we are left with a confusing picture as to the putative relationship between folate intake and colorectal cancer. Is there a protective effect, an adverse effect, or no effect? The answer is by no means clear. (Reviewer-Timothy O. Lipman, MD).
In a 6-month multicenter randomized controlled intervention trial comparing oil-rich fish intake, lean fish intake, and dietary advice alone, no differences were found in colonic mucosa apoptotic and mitotic rates.

**Background:** Fish has been associated in observational studies with decreased colorectal cancer (CRC) risk. If fish is protective, it is not known whether the protective effect is due to content of omega-3 (n-3) fatty acids or other nutrients. Since a randomized controlled trial of fish consumption with colorectal cancer incidence as an end point is virtually impossible, intermediate or surrogate end points might be used to assess CRC risk. Colonic mucosal cell proliferation (mitosis) and apoptosis are 2 such end points. Increased mitosis and decreased apoptosis are associated with increased CRC risk.

**Objective:** To assess the effects of oil-rich or lean fish on colonic mucosa mitosis and apoptosis.

**Design:** Multicenter randomized controlled trial.

**Participants:** 242 Dutch and British subjects with colorectal polyps, inactive ulcerative colitis, or no colonic pathology.

**Methods:** Participants were randomly assigned to receive 6 months of dietary advice plus 2 weekly servings of oil-rich fish (salmon; n=82), lean fish (cod; n=78), or dietary advice alone (n=82). Mitosis and apoptosis were measured in colonic biopsy samples before and after the intervention.

**Results:** 216 subjects completed the 6-month intervention, and biopsy results were available for analysis in 213. The total number of apoptotic cells per crypt in either the salmon or the cod group did not differ from the dietary advice-alone group. Similarly, the total number of mitotic cells per crypt did not differ significantly among the 3 groups.

**Conclusions:** Six months of fatty or lean fish consumption did not change intermediate markers of CRC risk. These results fail to confirm observational studies suggesting that fish intake is associated with decreased CRC risk.

**Reviewer's Comments:** This was a well-designed and well-conceived randomized controlled trial. The authors should be commended for using a food intervention rather than an individual nutrient. Several difficulties in the trial may have contributed to the “null” outcome: (1) The study did not achieve the 100 subjects per arm determined to be necessary in the original power calculation. Therefore, the study may have been functionally underpowered to demonstrate a difference in outcomes. (2) At study conclusion, it became obvious that a sample population of fish eaters had been selected; the baseline consumption of fish was already 1.5 portions per week and only increased by <1.5 portions per week. Therefore, the goal to increase in fish consumption was not achieved. (3) Finally, mitosis and apoptosis may be the wrong markers of CRC risk. Nonetheless, the results from this randomized controlled trial do not support the hypothesis that fish consumption reduces CRC risk. (Reviewer-Timothy O. Lipman, MD).

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Keywords: Fish Consumption, Colorectal Cancer Risk

Print Tag: Refer to original journal article
Objective: To determine to what extent obesity is associated with hepatic steatosis in patients with chronic hepatitis C.

Design: A cross-section of a population was studied to explore risk factors for hepatic steatosis.

Participants: Patients with chronic hepatitis C from 3 separate locations in the United States (Oregon, Connecticut, and California) who were followed up by gastrointestinal practitioners between 1999 and 2001.

Methods: Trained interviewers collected patient data via a questionnaire, which included demographics, medical history, risk factors for viral hepatitis, medication usage, and alcohol consumption. Liver biopsies were reviewed in a blinded fashion and graded with regard to steatosis, fibrosis, and inflammation. Body mass index (BMI) was determined from data self-reported by the patients. Lifetime alcohol consumption was determined by summing daily average alcohol intake and dividing by the time during which the drinking occurred.

Results: 450 patients had liver biopsies available for review. While 15.8% of patients had steatosis greater than or equal to Ludwig stage 2, 35.9% of patients who were obese had steatosis. Using multivariate analysis, fibrosis >2 (OR, 3.43), obesity (OR, 3.32), hepatitis C genotype 3 (OR, 2.5), and multiple metabolic morbidities (OR, 1.91) were all independently associated with steatosis.

Conclusions: Obesity is independently associated with steatosis in patients with hepatitis C. This finding suggests that weight loss in such patients may be an adjunct to therapy for hepatitis C in this population.

Reviewer's Comments: Some limitations to the study include that BMI was self-reported, the patients were exclusively from GI practices (which may have produced a selection bias), and cause and effect may not necessarily be valid in a cross-sectional study. (Reviewer-Ingram M. Roberts, MD).

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Keywords: Hepatic Steatosis, Effect of Obesity

Print Tag: Refer to original journal article
Drinking, Smoking Predict Chronic Pancreatitis

Alcohol Consumption, Cigarette Smoking, and the Risk of Recurrent Acute and Chronic Pancreatitis.

Yadav D, Hawes RH, et al:
Arch Intern Med 2009; 169 (June 8): 1035-1045

Very heavy alcohol consumption and cigarette smoking are both risk factors for the development of chronic pancreatitis and are independent of each other.

**Objective:** To determine if alcohol consumption and cigarette smoking are independent risks for acute recurring acute pancreatitis and chronic pancreatitis.

**Design:** A multicenter prospective study.

**Participants:** 540 patients with chronic pancreatitis, 460 patients with recurrent acute pancreatitis, and 695 controls from 20 institutions in the United States were enrolled in the study from 2000 to 2006.

**Methods:** With assistance from a study coordinator, patients self-reported their drinking and smoking behaviors with a questionnaire. Heavy drinking was defined as >1 but <5 drinks per day for women and >2 drinks but <5 drinks per day for men. Very heavy drinking was defined as ≥5 drinks per day for both men and women.

**Results:** In the population studied, the mean patient age was 49.7 years, 87.5% were white, and 56.5% were female. Approximately 25% of the patients and controls were lifetime nondrinkers. The group classified as heavy drinkers was comprised of 38.4% of men and 11% of women with chronic pancreatitis and 16.9% of men and 5.5% of women with recurrent acute pancreatitis. Heavy drinkers showed a high association with chronic pancreatitis overall (OR, 3.10) after adjustment for age, gender, smoking, and body mass index. Cigarette smoking was a dose-dependent independent risk factor for both chronic and recurrent acute pancreatitis.

**Conclusions:** Very heavy alcohol drinking and cigarette smoking were independent risk factors for the development of chronic pancreatitis.

**Reviewer's Comments:** This is the first study to prospectively examine the risk of both alcohol and smoking in the development of recurrent acute pancreatitis and chronic pancreatitis. (Reviewer-Ingram M. Roberts, MD).

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Keywords: Pancreatitis, Risk Factors

Print Tag: Refer to original journal article
Liraglutide Induces Weight Loss in the Obese

**Effects of Liraglutide in the Treatment of Obesity: A Randomised, Double-Blind, Placebo-Controlled Study.**
Astrup A, Rossner S, et al:

Lancet 2009; 374 (November 7): 1606-1616

An industry sponsored partially blinded randomized controlled trial demonstrates effective weight loss compared to placebo and orlistat by liraglutide, a glucagon-like peptide-1 analogue.

**Background:** There are few effective pharmacological treatments for obesity. Liraglutide is a glucagon-like peptide-1(GLP-1) analogue, with a 97% structural homology to human GLP-1 but with a far longer half-life when administered by subcutaneous injection. Originally developed as a treatment for type 2 diabetes mellitus, it has caused a dose-dependent weight loss in other trials.

**Objective:** To assess the effect of liraglutide on body weight in varying doses when combined with an energy deficient diet, physical activity, and counseling in obese individuals.

**Design:** Randomized, partially double-blind, placebo, randomized controlled trial with an open-label active drug comparator.

**Participants:** Otherwise healthy men and women (age range, 18 to 65 years) with a body mass index (BMI) between 30 and 40 and without type 1 or 2 diabetes.

**Methods:** Subjects were randomly assigned to 1 of 6 groups: 4 groups of increasing doses of daily subcutaneous injection of liraglutide; subcutaneously injected placebo in volume to match the volume of 1 of the 4 active liraglutide groups (blinding was for liraglutide or placebo, but not dose), or open-label orlistat taken orally three times per day. All participants were instructed in a 500 kcal/day energy deficient diet as well as increased exercise. Based on a sample size calculation, there were 90 to 95 subjects in each group. The primary end points were change in body weight during 20 weeks of active drug and the percentage of individuals losing >5% or 10% of baseline weight, by intention-to-treat analysis. Multiple secondary end points were also assessed.

**Results:** The mean weight loss in all liraglutide groups was significantly greater than placebo, in a dose-dependent fashion, ranging from 4.8 to 7.2 kg. The mean weight loss in the 2 higher dose levels of liraglutide was significantly higher than in the orlistat group. Significantly more subjects lost either 5% or 10% of baseline body weight in the liraglutide groups than in both placebo and orlistat groups. There were more adverse events, mostly nausea and vomiting, in the liraglutide groups.

**Conclusions:** Liraglutide appears to be an effective inducer of weight loss in the obese during a 20-week period when combined with an energy restricted diet and increased exercise.

**Reviewer's Comments:** Although this is a well-designed clinical trial, 2 potential sources of bias are the lack of blinding in the various liraglutide/placebo doses and the fact that this was an industry sponsored study. The long-term efficacy and safety as well as the tolerance to daily subcutaneous injections needed for medication administration need to be assessed. (Reviewer-Timothy O. Lipman, MD).

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**Keywords:** Obesity, Pharmacological Treatment

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