In a series of elegant experiments in mice, transplanting the intestinal microbiota from affected mice to germ-free mice induces the metabolic syndrome.

**Background:** The current obesity epidemic is associated with the metabolic syndrome: hyperglycemia; insulin resistance; hyperlipidemia; hypertension; fatty liver; and elevated levels of proinflammatory cytokines. Toll-like receptors (TLRs) are a class of proteins involved with innate immunity. TLR5 is a transmembrane protein that is highly expressed in intestinal mucosa and that recognizes bacterial flagellin. TLR5 knockout mice (T5KO) are used as colitis models. Four-week-old T5KO survivors were noted to have a 15% increase in body mass.

**Objective:** To investigate the interaction between gut microbiota and the metabolic syndrome in T5KO mice.

**Design:** Series of experiments with T5KO mice.

**Methods:** The authors manipulated the gut microbiota of the T5KO mice to create an experimental group with attenuated colitis and 20% increase in body mass. These mice also developed manifestations of the metabolic syndrome, such as hypertension, hyperlipidemia, and insulin resistance.

**Results:** When fed a high fat diet, their metabolic syndrome worsened. The mice were observed to increase their intake by 10%. Administration of antibiotics for 12 weeks reduced the total gut bacterial load by 90% and corrected the metabolic syndrome. Analysis of the microbiota of the T5KO mice and their wild-type litter mates demonstrated significant differences in their species composition. Finally, the authors transplanted the T5KO gut microbiota into wild-type germ-free mice. The recipient mice developed many of the manifestations of the metabolic syndrome (hyperphagia, obesity, hyperglycemia, insulin resistance, and elevated levels of pro-inflammatory cytokines).

**Conclusions:** The intestinal microbiota appears to contribute to the development of the metabolic syndrome in a T5KO mouse model.

**Reviewer's Comments:** Although there is, as of yet, no clinical practicality to the information gleaned from these experiments, they add to the growing body of evidence that suggests the importance of the relationship between the intestinal microbiota and obesity. We certainly are not ready to treat obesity or metabolic syndrome with antibiotics or probiotics. Nonetheless, this work further suggests that our gut microbiota is intimately involved with our lives and our phenotypes. (Reviewer-Timothy O. Lipman, MD).

© 2010, Oakstone Medical Publishing

Keywords: Intestinal Microbiota, Metabolic Syndrome, Toll-Like Receptor 5

Print Tag: Refer to original journal article
Background: Treatment of irritable bowel syndrome (IBS) is difficult and frustrating. Individual probiotics can modulate gastrointestinal tract inflammation, motility, and visceral sensitivity. Probiotics may be useful therapy for IBS and are widely promoted and used. However, results of randomized controlled trials have been conflicting.

Objective: To evaluate the impact of probiotics on IBS symptom relief.

Design: Systematic review and meta-analysis.

Methods: A comprehensive literature search, with no language restrictions, for randomized controlled trials (RCTs) comparing probiotics with placebo or no treatment for at least 1 week in IBS was undertaken. The primary clinical outcome of interest was change in global IBS symptoms reported as a dichotomous or continuous variable. Abdominal pain data were included if global symptoms were not available. Study quality was judged by the Jadad scale, which includes randomization, double-blinding, allocation generation, and description of dropouts.

Results: 18 papers, involving 1650 participants, met the inclusion criteria. Ten studies (918 participants) reported IBS symptoms as a dichotomous outcome. In these trials, probiotics were significantly better than placebo, with a number needed to treat of 4 (95% CI, 3 to 12.5). Funnel plot analysis of these trials suggested possible publication bias. Higher quality studies did not demonstrate treatment benefit. Fifteen trials reported IBS symptoms as a continuous variable and also demonstrated treatment benefit for probiotics. Funnel plot analysis of these trials did not suggest publication bias, and significant benefit remained with inclusion of only high quality trials.

Conclusions: The authors conclude that overall study quality was good, and that probiotics appear to be efficacious in IBS. The authors note that since so many species, strains, and doses of probiotics are used, it is difficult to reach conclusions about an optimum probiotic strategy.

Reviewer's Comments: I reported an earlier, similar systematic review in the August 2009 Practical Reviews in Gastroenterology. That review concluded that most RCTs of probiotic use for IBS have not used appropriate study design and that there was inadequate data to comment on probiotic efficacy. Why the differences in these 2 systematic reviews, both of which used proper systematic review methodology? I think that the reasons are 2-fold. Each study identified similar numbers of studies, but not all included studies were the same, and only 11 studies overlapped in the 2 systematic reviews. Additionally, the earlier systematic review used a much more rigorous approach to study quality, allowing them to conclude that overall study quality was low. As I have looked at some of these RCTs over the past several years, I agree that study quality is low, risk of bias is high, and purported benefits must be greeted with skepticism. Altering intestinal bacterial milieu for IBS treatment is a compelling hypothesis, and the hype is strong; all we lack is good data. (Reviewer-Timothy O. Lipman, MD).

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Keywords: Irritable Bowel Syndrome, Treatment, Probiotics

Print Tag: Refer to original journal article
Wind Instrumentalists May Be at Increased Risk for Reflux Symptoms

Reflux Symptoms in Wind Instrument Players.
Cammarota G, Masaia G, et al:

Aliment Pharmacol Ther 2010; 31 (March): 593-600

A cohort of Italian orchestral wind instrument musicians was found to have a higher prevalence of reflux as compared with their non-wind instrument orchestral colleagues.

**Background:** Opera choristers, when compared with the general population, have a higher prevalence of reflux symptoms. Wind instrument musicians perform playing tasks that require constant use of the diaphragm, including repeated abrupt and prolonged increases in intra-abdominal pressure, deep inspiration, and straining. Wind instrumentalists have been found to have breathing difficulties and reduced pulmonary function in several studies. The authors postulated that orchestral wind instrument players have an occupational susceptibility to reflux.

**Objective:** To compare self-reported reflux symptoms in wind instrument players as compared with other orchestral players.

**Design:** Cohort analysis.

**Participants:** Wind (single reed [clarinet, saxophone], double reed [oboe, bassoon], lip-driven brass [trumpet, trombone, tuba], and air-jet driven [flute]) instrumentalists and non-wind instrumentalists from 21 different orchestras in 15 Italian cities were included.

**Methods:** An extensive questionnaire (previously used in the chorister study) that asked about reflux, other abdominal symptoms, demographics, and life-style factors was administered over 1 hour to the orchestral players. Crude and adjusted prevalence rate ratios (PRRs) were calculated.

**Results:** 1083 instrumentalists, including 414 wind players, completed the questionnaire. The wind instrument players reported a significant 23% higher prevalence of heartburn in the year prior to the questionnaire as compared with the non-wind instrument players (adjusted PRR, 1.23; 95% CI, 1.04 to 1.46). There was also a nonstatistically significant increase in regurgitation reported by the players of wind instruments. Belching was also more common, but gastroesophageal disease was not different between the 2 groups. Further analysis of the wind instrumentalists found significantly increased adjusted PRRs for the flutes and double-reed players as compared with the brass and single-reed players.

**Conclusions:** There is a higher prevalence of heartburn among orchestral wind instrument players as compared with other orchestral musicians. Air-driven wind instruments (flutes) appear to be associated with a higher risk of reflux symptoms compared with the other wind instruments.

**Reviewer's Comments:** There may be an overestimation of the effect reported in this paper, because there does not appear to have been any statistical correction for multiple measurements. (Recall that if one measures 20 parameters and sets the significance level at 5%, by chance, 1 of these measurements will be "significantly" different. This study has far more than 20 comparisons.) I found the conclusions in this paper fun and intriguing. Certainly, it suggests that wind instrumentalists are at increased risk for reflux symptoms, and it provides another question that can be asked in taking a history for evaluation of reflux—Do you play a wind instrument? (Reviewer-Timothy O. Lipman, MD).

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Keywords: Wind Instrumentalists, Occupational Hazards, Reflux

Print Tag: Refer to original journal article
For patients with HCV-related bridging fibrosis or cirrhosis, neither AFP, DCP, nor the combination of the 2 are useful in the detection of early HCC.

**Background:** Hepatocellular carcinoma (HCC) surveillance using imaging is imperfect. The American Association for the Study of Liver Diseases (AASLD) guidelines does not recommend the use of α-fetoprotein (AFP). In 1984 des-gamma-carboxy prothrombin (DCP) was found in the sera of 91% of patients with biopsy-confirmed HCC. Although used widely for HCC surveillance in Japan, few studies of DCP are available in the United States.

**Objective:** To determine the utility of AFP and DCP in HCC surveillance.

**Methods:** Data were collected prospectively in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial of 1050 hepatitis C virus (HCV)-positive nonresponders with bridging fibrosis or cirrhosis. All were required to have negative imaging for possible HCC and a serum AFP <200 ng/mL prior to enrolling in the study. AFP and DCP levels were measured at 3-month intervals. Ultrasound examinations were performed 6 months after enrollment and annually thereafter for 3.5 years. The diagnosis of HCC was based on histologic examination or a new hepatic mass with an AFP >1000 ng/mL. Presumed HCC was diagnosed by less stringent criteria. For this analysis, a nested case-control study with 2 matched controls for each HCC patient was used to assess both the sensitivity and specificity of AFP and DCP in the 12 months prior to and at the time of HCC detection.

**Results:** 1031 patients were analyzed. The mean AFP level in the 39 patients who developed HCC (24 designated early HCC) rose from 37 ng/mL 12 months before diagnosis to a mean of 297 at diagnosis. DCP levels rose from 79 mAU/mL to 413 mAU/mL. Levels of both were stable in the 77 controls. Using a cutoff of 40 mAU/mL and 150 mAU/mL for DCP, the sensitivity at diagnosis was 74% and 43%, respectively, and the specificity was 86% and 100%, respectively. Using a cutoff of 20 ng/mL and 200 ng/mL for AFP, sensitivity was 61% at the low cutoff and 22% at the higher cutoff, and specificity was 81% and 100%, respectively. At 12 months before HCC diagnosis, the sensitivity and specificity of the DCP low cutoff was 43% and 94%, respectively, and for AFP, it was 47% and 75%, respectively. The sensitivity of combining AFP and DCP at the low cutoffs was 73% at 12 months before diagnosis and 91% at diagnosis; specificity at 12 months before diagnosis was 71% and 74%, respectively, at diagnosis.

**Conclusions:** Neither DCP nor AFP nor the combination of the 2 are useful in HCC surveillance.

**Reviewer's Comments:** Earlier studies of the utility of AFP, DCP, and lens culinaris agglutinin-reactive AFP (L3-AFP) have shown their limitations in the diagnosis of HCC. Although the present study is limited by the small number of HCC patients analyzed and by verification bias because AFP was used to define cases, it nevertheless suggests that AFP and DCP are similarly ineffective in HCC surveillance. (Reviewer-Raymond S. Koff, MD).

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Keywords: Hepatocellular Carcinoma, Surveillance, Biomarkers

Print Tag: Refer to original journal article
Background: Compared to normal pregnancy, 10- to 100-fold elevations of serum bile acids, particularly taurine and glycine conjugates, are characteristic of symptomatic intrahepatic cholestasis of pregnancy (ICP), a relatively rare disorder associated with pruritus, abnormal liver chemistries, and adverse fetal outcomes. Previous studies using radioimmunoassays reported increases in cholic acid, chenodeoxycholic acid, and deoxycholic acid levels during gestation in both ICP and pruritus gravidarum (PG). However, only very limited information is available about changes in specific conjugated and nonconjugated bile acids over time in ICP, PG, and normal pregnancy.

Objective: To assess changes in levels of individual bile acids over time during pregnancy in normal women and those with ICP and PG and to determine the effect of ursodeoxycholic acid treatment on bile acid levels.

Methods: Pregnant women with pruritus were recruited from 3 London hospitals. Among those 63 women with ICP, 54 were recruited at the visit to confirm the diagnosis and 9 were recruited before diagnosis. Another 43 women with PG and 26 healthy pregnant women were also studied. Serum samples, taken >2 hours postprandial were obtained at 4-week intervals for 16 weeks of gestation and 4 to 6 weeks postpartum. Bile acids were measured by a HPLC-mass spectrometry system with an electrospray interface that permitted determination of 15 bile acids in a single sample.

Results: Serum bile acid concentrations from 28 weeks of gestation onward were significantly higher in ICP patients than in PG or normal pregnancy patients. Bile acid levels in ICP patients rose by 325% from week 20 to week 40 compared to controls. Serum cholic acid levels were higher in patients with ICP but similar in PG patients and healthy controls. Taurocholic and glycocholic acids and taurochenodeoxycholic and glycochenodeoxycholic acid levels were also higher in ICP women. Taurolithocholic acid levels did not change during pregnancy but were higher in ICP and PG patients compared to controls, and an association of increasing levels of this bile acid and severity of pruritus was observed in women with ICP. Among women with ICP treated with ursodeoxycholic acid for >21 days, significant reductions in cholic acid, taurocholate, taurochenodeoxycholic and taurodeoxycholic acid, but little change in glycine-conjugated bile acids, were found. No effect was seen after 7 days of ursodeoxycholic acid treatment.

Conclusions: The authors suggest a role for taurine-conjugated bile acids in ICP patients (but not in PG patients) that appears to be a distinct disorder.

Reviewer's Comments: These observations suggest that measurement of taurocholic acid and taurochenodeoxycholic acid at week 28 or even earlier may aid in diagnosis of ICP. Furthermore, low levels at late pregnancy in a woman with pruritus suggest that ICP is unlikely to emerge on follow-up. As indicated in an accompanying laudatory editorial, this new methodology for measuring bile acids may contribute importantly to the understanding of ICP. (Reviewer-Raymond S. Koff, MD).

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Keywords: Serum Bile Acids, Intrahepatic Cholestasis, Pregnancy, Pruritus Gravidarum

Print Tag: Refer to original journal article
Colectomy is indicated for IBD patients with confirmed flat HGD or non–adenoma-like DALMs. Immediate colectomy is controversial for confirmed flat LGD.

**Objective:** To present highlights of the American Gastroenterological Association (AGA) Medical Position Statement and Technical Review providing support data. The data were divided into 2 separate articles because of length. **CRC Risk Factors in Inflammatory Bowel Disease (IBD):** Patients with IBD are at increased risk for colorectal cancer (CRC). Meta- analyses show risk of CRC to be 2% after 10 years, 8% after 20 years, and 18% after 30 years. Older studies from tertiary care centers found a higher risk of CRC compared to more recent population-based studies that included patients with less severe and/or limited (left sided) disease and who are now are almost all treated with aminosalicylates. Disease extent correlates with CRC risk, with the highest risk in pancolitis, intermediate risk in left-sided colitis up to the splenic flexure, and little or no increased risk in patients with proctitis or proctosigmoiditis. The risk of CRC in ulcerative colitis (UC) patients with primary sclerosing cholangitis (PSC) is increased 4-fold compared to the risk of CRC in UC patients without PSC. Other risk factors include colonic strictures (especially in UC patients), multiple postinflammatory pseudopolyps, and chronic inflammation. The risks of CRC in extensive Crohn's disease of the colon and extensive UC appear to be equivalent (RR, 2.64 and 2.75, respectively). **Dysplasia:** Dysplasia can be flat and endoscopically invisible or raised (dysplasia-associated lesion or mass [DALM]). Immediate colectomy is recommended in patients with confirmed flat high-grade dysplasia (HGD) since synchronous CRC may be found in >40% of colectomy specimens. Management of confirmed flat low-grade dysplasia (LGD) is considered controversial even though a 19% to 27% prevalence of synchronous CRC at the time of colectomy has been reported, and rates of progression from flat LGD to HGD or CRC over 5 years are as high as 33% (Mayo Clinic) and 53% (Mount Sinai). Raised dysplastic lesions or DALMs may be adenoma-like or non–adenoma-like. Adenoma-like DALMs may be sessile or pedunculated, are smooth and well circumscribed, and are endoscopically and histologically similar to sporadic adenomas. If they can be completely excised and there is no evidence of flat dysplasia in adjacent mucosa, they can be managed by continued surveillance. Non–adenoma-like DALMs may have velvety patches, plaques and nodules, and often appear as an irregular broad-based slightly raised mass. There is a high association of such lesions with CRC and colectomy is indicated.

**Reviewer's Comments:** The statement that current evidence is insufficient to recommend colectomy for flat LGD appears to be a non sequitur with respect to data from the Mayo Clinic and Mt Sinai in which a significant number of patients developed CRC during surveillance after identification of flat LGD. How many, if any, patients subsequently died from CRC diagnosed during surveillance for previously diagnosed LGD is not addressed. Is our goal to save lives or colons? (Reviewer-Allen L. Ginsberg, MD).
In experienced hands, chromoendoscopy can more than triple the detection of dysplasia; however, when this leads to colectomy, an increase in the number of cancers has not yet been shown.

Objective: To review the American Gastroenterological Association Medical and Technical Position Statement. Positions taken in Part 1 and 2 are graded based on certainty of evidence and net benefits: Grade A, high certainty of evidence and net benefits high; Grade B, moderate certainty of evidence and net benefits moderate; Grade C, net benefits small; Grade D, net benefits 0 or negative; and Grade I, evidence insufficient to assess benefits and harms. Surveillance Colonoscopy in Inflammatory Bowel Disease (IBD): (Grade B) Given that there is increased risk of colorectal cancer (CRC) in patients with IBD and there is (Grade A) a high degree of certainty that colectomy should be performed in IBD patients with non–adenoma-like dysplasia-associated lesion or mass and for flat high-grade dysplasia, it is surprising that the effectiveness of surveillance could be questioned. There is an absence of randomized controlled trials because of ethical issues related to withholding surveillance from a control group and the long duration of follow-up required to show survival benefit. Pooled data suggest that with surveillance, cancers are detected at an earlier stage, which should lead to a better prognosis. Recommendations: Screening colonoscopy begins 8 years after onset of symptoms. Patients with only proctitis or proctosigmoiditis are not at increased risk. Patients with extensive or left-sided colitis should have a colonoscopy every 1 to 3 years. Patients with primary sclerosing cholangitis (PSC) should begin yearly examinations at the time of diagnosis, and surveillance should be performed when the disease is in remission. A minimum of 33 biopsies in cases of pancolitis have been recommended. Chromoendoscopy utilizing 0.1% methylene blue is more sensitive and specific for identifying neoplasia allowing targeted biopsies that have been reported to triple the yield of dysplastic lesions. However, despite increased detection of dysplasia, when colectomy based on chromoendoscopy has been performed, unexpected cancers have not been found. Should Chemopreventive Agents Be Used to Lower Risk of Dysplasia or CRC? Ursodeoxycholic acid (UDCA) has been shown in multiple studies to reduce the occurrence of dysplasia and CRC in ulcerative colitis (UC) patients with PSC (RR, 0.26; Grade A: high certainty). Data are insufficient to know if UDCA is of any value in IBD patients without PSC. Evidence also supports a chemoprotective effect of aminosalicylates against CRC (Grade B: moderate certainty). Corticosteroids do not protect against CRC (Grade D), and data are insufficient with respect to thiopurines, folic acid, and statins.

Reviewer's Comments: In my 37 years of treating IBD patients, I have been impressed that in many patients, especially those with UC, sulfasalazine or mesalamine can eliminate inflammation and induce and maintain complete clinical, endoscopic, and histologic remission. Chronic inflammation in many parts of the body can lead to cancer, and hence it has been logical to assume that suppression of inflammation and maintenance of remission in UC with sulfasalazine or 5-ASA would reduce the risk of CRC. Mounting evidence supports this concept. (Reviewer-Allen L. Ginsberg, MD).
Mucosal Healing Predicts Sustained Clinical Remission in Early CD

Mucosal Healing Predicts Sustained Clinical Remission in Patients With Early-Stage Crohn's Disease.

Baert F, Moortgat L, et al:

Gastroenterology 2010; 138 (February): 463-468

Mucosal healing is predictive of, but not essential for, achieving a sustained steroid-free clinical remission in early CD.

Background: Therapy of Crohn’s disease (CD) with biologic and immunosuppressive agents has been reported to produce mucosal healing, which is widely believed to predict a better long-term outcome. Endoscopic scores, however, correlate poorly with clinical scores, and prospective data demonstrating the clinical benefit of mucosal healing are needed.

Objectives: To determine whether complete endoscopic mucosal healing in early CD is predictive of a better outcome.

Design: Prospective cohort study. Patients: 49 of 133 recent onset CD patients who had completed a 2-year randomized trial comparing combined immunosuppressive therapy (CIS) with conventional management (CM). The 49 participants had a complete ileocolonoscopy at the end of the initial study and agreed to participate in a study extension for an additional 2 years through year 4.

Methods: In the initial trial, patients were randomized to CIS or CM. CIS therapy consisted of azathioprine (AZA) 2.5 mg/kg and 3 infusions of infliximab (IFX). Relapse was treated with IFX infusions as needed. CM therapy consisted of corticosteroid (CS) taper with the addition of AZA after 2 flares with taper or withdrawal of CS. IFX was given after failure of 3 months of AZA. At the end of 2 years, although CIS resulted in a higher rate of mucosal healing, clinical steroid-free remission rates were similar. This study reports on an additional 2-year follow-up through year 4. Patients continued with the same treatment and were evaluated at 3-month intervals. Patients in need of repeated on-demand IFX were switched to infusions every 8 weeks. The main end point was stable remission (Crohn’s Disease Activity Index <150 or Harvey Bradshaw Index <3) without CS during the entire follow-up period.

Results: At the 4-year end point, data were available on 46 of the 49-patient cohort (25 CIS and 21 CM patients). Twenty-four of the 46 patients had complete mucosal healing at 2 years, and 22 had endoscopic lesions. Of the 24 who had complete mucosal healing, 17 (70.8%) maintained steroid-free clinical remission during observation through years 3 and 4, with 15 not requiring IFX infusions. This contrasted with only 6 of the 22 (27.3%) who had endoscopic lesions at year 2, maintaining steroid-free remission through year 4 \( (P =0.036) \), with only 4 patients not requiring IFX during years 3 or 4.

Conclusions: Complete endoscopic mucosal healing in early CD is associated with an increased likelihood of steroid-free and IFX-free clinical remission 4 years after commencing therapy.

Reviewer’s Comments: Although complete endoscopic mucosal healing resulted in a higher rate of steroid-free remission at 4 years, several of these patients still required IFX infusions. Furthermore, 27% of those with endoscopic lesions at year 2 also maintained a steroid-free clinical remission at year 4. (Reviewer-Allen L. Ginsberg, MD).

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Keywords: Early-Stage Crohn’s Dz, Mucosal Healing, Clinical Outcome

Print Tag: Refer to original journal article
Use EUS in the evaluation of acute pancreatitis when no etiology is found by traditional studies.

**Background:** In 10% to 30% of acute pancreatitis cases, no etiology is found for the disease. Endoscopic retrograde cholangiopancreatography (ERCP) helps in defining the etiology of these idiopathic cases, but this test is not without morbidity. Endoscopic ultrasonography (EUS) has been proposed as an alternative to ERCP in trying to find the etiology of these idiopathic cases.

**Objective:** To evaluate the diagnostic yield of EUS in idiopathic acute pancreatitis (IAP), to find factors that are predictive of a positive EUS, and to determine if the findings obtained in this manner are maintained during follow-up.

**Participants/Methods:** Between July 2004 and August 2007, 44 patients with IAP were evaluated by means of EUS.

**Results:** Of the 44 patients studied, 7 had normal EUS examinations (16%) leaving 37 patients with positive findings. Three patients were found to have cholelithiasis and 20 had microlithiasis, 14 patients had chronic pancreatitis, 3 had pancreatic divisum, 1 had a pancreatic mass, and apudoma was found in 1 patient. Cystic tumors of the pancreas were found in 2 patients and 2 others had choledocholithiasis. The sex of the patient, the severity of the pancreatitis, nor the history of recurrence had any influence on the likelihood of having positive EUS findings. Patients who were <65 years of age and those who had gallbladders were most likely to have positive findings on EUS. During a mean follow-up period of 28.95 ± 10.86 months, there were only 2 patients whose etiologic diagnosis changed decreasing the diagnostic yield to 79%.

**Conclusions:** In 79% of cases of IAP evaluated with EUS, an etiology was found for the acute pancreatitis. Patients who were <65 years of age and those who had a gallbladder in situ were more likely to have positive EUS findings. The majority of the diagnoses made by means of EUS was maintained during several years of follow-up and appear to be reliable.

**Reviewer's Comments:** This study should provide an impetus to perform EUS when available in patients who are found to have IAP. The performance of EUS in experienced hands is associated with minimal risk and provides valuable and reliable information that should be helpful in the treatment and follow-up of patients with IAP. (Reviewer-Michael M. Phillips, MD).

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Keywords: Diagnostic Imaging, Pancreatitis, Endosonography, Reliability

Print Tag: Refer to original journal article
Use Thermal Coagulation, Endoclips to Control Bleeding in High-Risk Lesions

International Consensus Recommendations on the Management of Patients With Nonvariceal Upper Gastrointestinal Bleeding.

Barkun AN, Bardou M, et al:

Ann Intern Med 2010; 152 (January 19): 101-113

No benefit is found in urgent (<12 hours after admission) endoscopy versus early (>12 hours after admission) endoscopy.

Objective: To convene a multidisciplinary panel to review the current state-of-the-art literature on the management of nonvariceal upper gastrointestinal bleeding (UGIB).

Design: An international expert group of investigators was assembled and charged with reviewing the evidence-based approach to nonvariceal UGIB.

Participants: 34 researchers from 15 countries participated in the conference held in Vienna in 2008.

Methods: The authors reviewed MEDLINE, the Cochrane Central Register of Controlled Trials, and the ISI Web of Knowledge for randomized clinical trials on nonvariceal UGIB. Seven new meta-analyses were performed before the meeting. Recommendations were made by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) procedure in order to prepare the strength of each recommendation clinically. Each recommendation statement was voted on by the consensus panel for agreement or disagreement.

Results: A summary table of recommendations in 5 general areas was prepared: resuscitation; endoscopy; pharmacology; nonpharmacologic/nonendoscopic management; and postdischarge management. Some highlights include endoscopy within 24 hours, endoscopic hemostasis for high-risk lesions with thermal coagulation and/or clipping, and the use of proton pump inhibitors; routine "second look" endoscopy is not necessary, and patients who require cardiovascular or cerebrovascular prophylaxis with aspirin should be restarted after patient stabilization.

Conclusions: The conference guidelines for management were produced using the evidence-based medicine data reviewed by the authors. The investigators anticipate that these guidelines will be updated as new evidence becomes available.

Reviewer's Comments: These suggestions of the authors are supported by real evidence culled from the medical literature. However, the American Gastroenterological Association, the American College of Gastroenterology, and the American Society for Gastrointestinal Endoscopy have not yet endorsed these recommendations. (Reviewer-Ingram M. Roberts, MD).

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Keywords: Nonvariceal UGIB, Management, Recommendations

Print Tag: Refer to original journal article
Two Drug Regimens Successfully Treat Whipple’s Disease

Efficacy of Ceftriaxone or Meropenem as Initial Therapies in Whipple’s Disease.

Feurle GE, Junga NS, Marth T:

Gastroenterology 2010; 138 (February): 478-486

Either ceftriaxone or meropenem IV therapy for 14 days followed by oral trimethoprim-sulfamethoxazole for 12 months provides a curative regimen for Whipple’s disease.

Objective: To investigate the efficacy of 2 different antibiotics that cross the blood-brain barrier for the treatment of Whipple’s disease, a chronic infection caused by Tropheryma whippelii.

Design: Open-label, prospective, randomized, controlled intention-to-treat trial.

Participants: 40 patients from central Europe with Whipple’s disease were enrolled at the trial center in Neuwied, Germany, starting in 1999. The tissue diagnosis of Whipple’s disease was confirmed by 2 histopathologists from the same institution.

Methods: Blood and spinal fluid for T. whippelii for polymerase chain reaction (PCR) assay was obtained at study entry. Patients were initially randomized to receive a 14-day infusion of either 2 g of ceftriaxone IV once daily or 1 g meropenem IV 3 times daily, followed by administration of oral trimethoprim-sulfamethoxazole 160/800 mg twice daily for 12 months. PCR was repeated at 6 and 36 months after enrollment. Small bowel biopsies were obtained at 6, 12, 24, and 36 months after enrollment, and adherence to medications was ascertained at 3, 6, and 12 months into the study. Loss of subtype 1 macrophages in the intestinal mucosa was considered indicative of bacterial eradication.

Results: During a median observation period of 89 months, all patients underwent clinical remission on these treatment regimens. Two patients died from causes unrelated to their Whipple’s disease over the course of the study. Only 1 patient had asymptomatic infection in the cerebrospinal fluid requiring additional therapy with a response to minocycline and chloroquine.

Conclusions: Treatment with either IV meropenem or ceftriaxone over a 2-week period followed by oral trimethoprim-sulfamethoxazole for 12 months is curative for Whipple’s disease.

Reviewer’s Comments: This was a well-designed landmark study comparing 2 drug regimens for the treatment of Whipple’s disease. Whipple’s disease remains a fascinating example of abnormal host response to a usually nonpathologic bacterium as several studies have documented the presence of T. whippelii-positive PCR in healthy asymptomatic individuals. Why only about 500 cases in the literature have been reported is still a mystery. (Reviewer-Ingram M. Roberts, MD).

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Keywords: Whipple's Dz, Ceftriaxone, Meropenem

Print Tag: Refer to original journal article
HCV-Related Cirrhosis Projected to Increase in Next 10 Years

Aging of Hepatitis C Virus (HCV)-Infected Persons in the United States: A Multiple Cohort Model of HCV Prevalence and Disease Progression.

Davis GL, Alter MJ, et al:

Gastroenterology 2010; 138 (February): 513-521

If all identified and currently unrecognized CH-C patients were treated with antiviral therapy that was 80% effective in 2010, the risk of cirrhosis would decline by approximately 30%.

Background: In the U.S., the prevalence of chronic hepatitis C (CH-C) has been estimated since the 1980s from analyses of the National Health and Nutrition Examination Surveys, which have important limitations, since many high-risk subpopulations are not measured. A decade ago, early modeling studies painted a bleak picture of increasing morbidity and mortality with dramatic increases in end-stage liver disease, premature death, hepatocellular carcinoma (HCC), and an extraordinary increase in the demand for liver transplantation. Because each of these outcome projections had serious limitations, future morbidity and mortality remained speculative.

Objective: To develop a more sophisticated computer model for assessing future disease outcomes.

Methods: A model that permitted the construction of multiple Markov models with variable progression rates based on age, gender, and other factors was developed. A second model to assess the effects of antiviral treatment was also designed. Transitional probabilities were estimated from the literature, including meta-analyses and reported observational studies. All-cause mortality was derived from U.S. mortality tables, and sensitivity analyses were performed.

Results: Based on the model, the peak prevalence of CH-C occurred in 2001 and has declined since then and will continue to do so through 2030. Cirrhosis prevalence increased sharply after 1990, with a projected prevalence in 2010 of 25%, rising to 37% in 2020, and 45% in 2030. The majority of current patients with cirrhosis are men infected before age 50 years. The model estimated that 12% of current patients with cirrhosis have hepatic decompensation, and the frequency will increase until 2022. Similarly, HCC incidence in CH-C is projected to rise to a peak in 2019, and liver-related deaths due to hepatitis C virus (HCV) will rise to a peak in 2022. The effects of future antiviral treatment, based on a possible sustained virological response of 80% overall and treatment of all patients might reduce the risk of development of cirrhosis by upwards of 30% in the 10 years following 2010. Conclusions: HCV-related cirrhosis and its complications are projected to increase in the next 10 years, and men >60 years old will be the most affected. More effective and more widely applied antiviral treatment should reduce disease progression.

Reviewer’s Comments: While the model developed here supports previous models projecting increases in future HCV disease burden, it is somewhat surprising that the future need for liver transplantation was not assessed. Had it been done, it would have been possible to determine whether the model accurately projected the number of patients on the United Network for Organ Sharing (UNOS) waiting list in 2010 and the trends in the proportion of patients transplanted for HCV-related end-stage liver disease and HCC over the past decade. Such data are available from UNOS. (Reviewer-Raymond S. Koff, MD).

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Keywords: Chronic HCV, Complications, Cirrhosis, Aging

Print Tag: Refer to original journal article
Endoscopy in heartburn patients who fail to respond to PPI therapy rarely demonstrates findings.

**Background:** Endoscopy is commonly used in the evaluation of patients who have failed proton pump inhibitor (PPI) therapy for reflux.

**Objective:** To compare endoscopic and histologic findings in patients with heartburn treated with once daily PPI versus those not receiving antireflux treatment.

**Design:** Cross-sectional study.

**Participants:** Adult patients with at least 3 heartburn episodes per week for the last 3 months who were not treated for at least 3 months. The PPI failure group failed to obtain complete relief of symptoms as perceived by the patient.

**Methods:** Patients were prospectively recruited from a gastrointestinal outpatient clinic. Patients filled out a number of baseline questionnaires including a GERD Symptoms Checklist, a quality-of-life assessment (Short Form 36 Questionnaire), and demographics. Upper endoscopy with esophageal biopsy was performed in a standard fashion.

**Results:** 105 subjects with a mean age of 54.7 years were enrolled; 71 men and 34 women were in the PPI failure group 68 men and 23 women were in the untreated group (mean age, 53.4 years; \( P = \text{ns} \)). Significant findings were statistically more common in the untreated group versus the treated group. Erosive esophagitis was found in 30.8% versus 6.7%, respectively. Eosinophilic esophagitis (EE) was only found in 0.9% of the PPI failure group.

**Conclusions:** Heartburn patients who fail once-daily PPI therapy demonstrated few findings on upper endoscopy and rarely had EE on biopsy.

**Reviewer's Comments:** This interesting paper addresses a question we have all been wondering about, what is the utility of endoscopy when patients fail PPI therapy for reflux symptoms. Although this paper clearly suffers from small cohort size and the use of a single center, its results do call into question the benefit of endoscopy in this group of patients and the etiology of their breakthrough symptoms. Clearly a larger multicenter study of this hypothesis will be needed to definitively answer this question. Of note is that the incidence of Barrett's esophagus was a low 3% in both groups. I suspect that current guidelines regarding the use of endoscopy in reflux patients will be amended in the future when additional studies on this subject are available. (Reviewer-J. Mark Lawson, MD).

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**Keywords:** Reflux Endoscopy, PPI Failure, Heartburn

**Print Tag:** Refer to original journal article
In NAFLD, hepatocellular iron deposition is associated with advanced hepatic fibrosis, independent of HFE status.

**Background**: Elevated ferritin levels and increased hepatic iron deposition are frequent in nonalcoholic fatty liver disease (NAFLD) and have been linked to higher stages of hepatic fibrosis in NAFLD. In some studies, an association with HFE mutations, excluding C282Y homozygosity, has also been linked to advanced fibrosis.

**Objective**: To identify the relationships of hepatic iron accumulation with HFE mutations and hepatic fibrosis in NAFLD.

**Design/Participants**: In this retrospective, multicenter investigation, Italian patients with biopsy-proven NAFLD and DNA samples for HFE mutation analysis comprised the study cohort. HFE mutations also were assessed in healthy blood donors. Only patients homozygous for the C282Y mutation were excluded.

**Methods**: Fibrosis was staged, and iron accumulation was denoted as hepatocellular or nonparenchymal/mixed based on prevalence of distribution.

**Results**: HFE mutation frequency was similar in the 587 NAFLD patients and in the 184 controls. Transferrin saturation was higher in NAFLD patients with HFE mutations, and ferritin levels were increased in all mutations except the H63D heterozygote. Ferritin levels were significantly higher in patients with a nonparenchymal pattern of iron deposition. Hepatocellular iron deposition was more prevalent in patients with HFE mutations (27% to 41%) than in those without mutations (18%). Nonparenchymal siderosis was also generally more common in those with mutations at 19% to 57% versus 25% for those without mutations. However, nonparenchymal siderosis was not associated with increased hepatic fibrosis. In contrast, hepatocellular iron deposition was linked with a 1.7-fold increased risk of fibrosis stage greater than F1 compared to the absence of detectable siderosis, and the risk of fibrosis stage greater than F1 was independent of HFE mutations. Patients with hepatocellular iron were more likely to have lower platelet counts, higher bilirubin levels, and less steatosis than those with nonparenchymal siderosis.

**Conclusions**: Hepatocyte iron deposition is linked to advanced hepatic fibrosis in NAFLD but HFE mutations, with the exception of C282Y homozygotes, could not be associated with increased fibrosis.

**Reviewer’s Comments**: Only 26% of the NAFLD cohort had fibrosis stage F2 or higher suggesting that approximately 25% of patients in this study already had progressed to NASH at recruitment. However, the proportion with biopsy-confirmed NASH was not stated. No information is provided on the interval between first recognition of NAFLD and biopsy in this study although it is stated that most of the patients were biopsied because of persistently abnormal enzymes or ferritin levels, a long-standing history of steatosis, or during bariatric surgery. No mention is made of whether any had been phlebotomized or received any treatment. Nonetheless, testing for HFE mutations in the absence of extensive hepatocellular iron deposition appears to have no utility in NAFLD, regardless of ferritin levels or transferrin saturation. (Reviewer-Raymond S. Koff, MD).

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**Keywords**: Hepatocyte Iron Deposition, HFE Mutations, Hepatic Fibrosis, NAFLD

**Print Tag**: Refer to original journal article
Patients with inflammatory bowel disease who are taking thiopurines have an increased risk of developing lymphomas compared to patients not taking thiopurines.

**Background:** Patients taking thiopurines for immunosuppression after organ transplantation have an increased risk of developing lymphomas. Thiopurines are used in patients with inflammatory bowel disease (IBD), and there may be a similar risk in these patients.

**Objective:** To assess a large number of patients with IBD to look for an association between the use of thiopurines and development of lymphoma.

**Design/Participants:** A prospective observational study of a cohort of patients with IBD was conducted. The patients were being seen by gastroenterologists in France who agreed to provide data.

**Methods:** All 4171 gastroenterologists and pediatricians in France who were on a mailing list for the yearly French national gastroenterology meeting were asked to participate in the study in early 2004; 817 of them agreed. Each participant submitted electronic case reports on each consecutive patient with IBD that they saw. The enrollment period was from May 2004 to June 2005, follow-up ended on December 31, 2007. The submitted data included demographic characteristics, type of IBD, date of diagnosis, cumulative disease location, and exposure to, or changes in, immunosuppressive therapy during the follow-up. Any patient who had a history of, or developed a lymphoproliferative disorder during the follow-up, was separately assessed with a different case report form. Patients were separated into 3 groups consisting of current usage, discontinued usage, and no usage of thiopurines. The incidence of lymphoproliferative disorders during the follow-up period was assessed. A standardized incidence ratio was calculated using data from the general French population.

**Results:** 20,775 patients were initially enrolled, but 1289 were excluded because of incomplete data. A total of 5867 patients were current users of thiopurines, 2809 had discontinued use at some time, and 10,830 never used thiopurines. During the >49,000 patient-years of follow-up, 23 patients developed lymphomas. The incidence rates in the 3 groups were 0.90 (users), 0.20 (discontinued users), and 0.24 (never users) per 1000 patient-years. Compared to the nonusers, the unadjusted hazard ratios for users and discontinued users were 3.45 and 0.74, respectively. The adjusted hazard ratio for current users was 5.28. The hazard ratio increased at a rate of 1.06 per year of age. Nonusers did not have any increased risk compared to the general population.

**Conclusions:** Patients with IBD who are using thiopurines have an increased risk of developing lymphomas.

**Reviewer’s Comments:** This study cannot prove that the thiopurines caused the lymphomas. Since the amount of thiopurines that were consumed prior to the study was not assessed, no dose-response data were available. This same group reported a protective effect of thiopurines with regard to the development of colonic neoplasia. (This study was presented at the 2009 DDW AGA Plenary Session and was reviewed by me in a previous issue of *Practical Reviews in Gastroenterology.* ) (Reviewer-Ronald L. Koretz, MD).

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Keywords: Inflammatory Bowel Disease, Thiopurines, Lymphoproliferative Disorders

Print Tag: Refer to original journal article
Citalopram Does Not Benefit Nondepressed IBS Patients

Citalopram Provides Little or No Benefit in Nondepressed Patients With Irritable Bowel Syndrome.
Ladabaum U, Sharabidze A, et al:
Clin Gastroenterol Hepatol 2010; 8 (January): 42-48

It is not likely that SSRIs in general will be of great benefit to nondepressed patients with IBS.

Background: Antidepressants are often used to treat irritable bowel syndrome (IBS), even in patients who are not depressed. The data are especially established for tricyclic agents; the role of selective serotonin reuptake inhibitors (SSRIs) is less clear although a recent meta-analysis did suggest some effect.

Objective: To assess the efficacy of 1 SSRI, citalopram, in treating nondepressed patients with IBS. A secondary objective was to assess the correlation between toleration to rectal distension and IBS symptoms.

Design: Randomized, double-blind controlled trial.

Participants: Patients with IBS satisfying Rome II criteria, who had no history of depression and scored <16 on the Beck's Depression Inventory (meaning normal or only mild mood disturbance) were included.

Methods: Potential patients completed a 1-week run-in phase during which time they completed symptom diaries. Those with a pain/discomfort score >3 (out of 10) were randomized into 1 of 2 groups, citalopram (20 mg/day for 4 weeks, then 40 mg/day for 4 weeks) or matching placebos. Symptom diaries were kept for the entire period. Barostat studies (assessing the patient's sensation and tolerance to balloon distension in the rectum) were done at baseline and at 8 weeks.

Results: 27 patients were randomized into each arm. Twelve of the 15 citalopram recipients/controls responded to treatment. No significant differences were seen between the 2 groups during any week of the trial. Quality-of-life scores improved comparably in both groups. There was no correlation between the Barostat scores and the clinical scores.

Conclusions: Citalopram was no better than placebo with regard to improving symptomatology in nondepressed patients with IBS. In the Discussion section of the article, the investigators did cite 5 other trials of SSRIs in patients with IBS, noting that the results were mixed, with 3 of them showing an effect. However, 2 of these 3 trials did not exclude all depressed patients. The investigators opined that SSRIs are probably not going to have any dramatic impact on the symptoms of IBS. They also did not believe that tests of rectal sensitivity would be of much use as markers for treatment trials in IBS.

Reviewer's Comments: Although the trial was small, it was well designed, executed, and reported. Attention was paid to the various details, so the measurements of the effects being assessed were at low risk of bias. (Reviewer-Ronald L. Koretz, MD).

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Keywords: Citalopram, Irritable Bowel Syndrome, Nondepressed Patients

Print Tag: Refer to original journal article
Diarrhea-related deaths in Mexican children fell after introduction of a monovalent rotavirus immunization program.

**Objective:** To determine the effects of previous rotavirus vaccine administration on infant deaths from diarrhea.

**Design:** Retrospective review of data on infant deaths before and after the introduction of a national vaccination program for rotavirus infection.

**Participants:** Data on death from diarrhea in Mexican children between the years 2003 and 2009 were obtained from the National Institute of Statistics, Geography, and Informatics and the Ministry of Health's General Directorate of Health Information. The National Center for Child and Adolescent Health (CENSIA) purchases rotavirus vaccine for roughly 50% of Mexican children.

**Interventions:** CENSIA maintains an electronic registration of vaccine doses given for the various states in Mexico; vaccination coverage data were assessed between the years 2006 (when the vaccine became available) and 2009.

**Results:** 74% of children age <11 months received a dose of rotavirus vaccine by December 2007. In 2008, deaths from diarrhea dropped from 1793 to 1118 in children aged <5 years, and diarrhea-related mortality decreased from 18.1 deaths per 100,000 children to 11.8 per 100,000 children, a 35% rate reduction ($P <0.001$). In infants <11 months, the reduction in diarrhea-related mortality (61.5 deaths per 100,000 children vs 36 deaths per 100,000 children) was even greater (41%; $P <0.001$). The reduction in deaths related to diarrhea persisted through 2008 and 2009. Unvaccinated children did not experience a reduction in mortality.

**Conclusions:** An oral rotavirus vaccine significantly reduced diarrhea-related death in Mexican children demonstrating efficacy of the vaccine.

**Reviewer’s Comments:** This study demonstrates that, once again, good vaccines can give the greatest “bang for the buck” when it comes to cost-effective health care. The benefits of vaccines far outweigh the risks of vaccination, and patients should be encouraged to get them both in this country and abroad. (Reviewer-Ingram M. Roberts, MD).

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Keywords: Mexico, Childhood Diarrhea, Fatality, Rotavirus Vaccine, Effects

Print Tag: Refer to original journal article
Live Oral Rotavirus Vaccine Prevents Severe Gastroenteritis in African Infants

Effect of Human Rotavirus Vaccine on Severe Diarrhea in African Infants.

Madhi SA, Cunliffe NA, et al:


This study shows that a live oral rotavirus vaccine prevented severe gastroenteritis in Malawi and South-African infants.

**Objective:** To determine the efficacy of a live oral rotavirus vaccine in African children.

**Design:** Double-blind, randomized, placebo-controlled multicenter study.

**Participants:** 3166 healthy infants from South Africa and 1773 healthy infants from Malawi participated in the study. Patients were enrolled from October 2005 through January 2006 and from November 2006 through February 2007 to encompass the rotavirus seasons of 2006 and 2007.

**Methods:** The children were randomly assigned in a 1:1:1 fashion; one group received 2 doses of rotavirus vaccine at 10 and 14 weeks of age (plus 1 dose of placebo), one group received 3 doses of vaccine at 6, 10, and 14 weeks of age; and the final group received 3 doses of placebo. Stool samples were tested for rotavirus with an enzyme-linked immunosorbent assay (ELISA), and stools with positive ELISAs were further tested for rotavirus using polymerase chain reaction (PCR). Blood samples were tested for IgA antibody to rotavirus 1 month after the last dose of vaccine or placebo was given.

**Results:** Severe rotavirus gastroenteritis was found in 4.9% of the placebo group but in only 1.9% in the pooled groups given the vaccine doses (vaccine efficacy, 61.2%). Efficacy of the vaccine was lower in Malawi versus South Africa (49.4% vs 76.9%, respectively), but severe rotavirus infection was prevented at a higher rate in Malawi versus South Africa (6.7 vs 4.2 cases per 100 infants, respectively). There was no difference in adverse effects in the vaccine groups (9.7%) versus the placebo group (11.5%). Seroconversion occurred in 57.1% (2 doses) and 66.7% (3 doses) in South Africa and 47.2% (2 doses) and 57.1% (3 doses) in Malawi; placebo seroconversion was only 16.7% in South Africa and 40.4% in Malawi.

**Conclusions:** A live oral rotavirus vaccine significantly diminished attacks of severe rotavirus gastroenteritis in African infants.

**Reviewer's Comments:** Again, a well performed study that demonstrates the efficacy and safety of a live oral vaccine for rotavirus infection in a population highly susceptible to gastrointestinal infections. (Reviewer-Ingram M. Roberts, MD).

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Keywords: African Infants, Human Rotavirus Vaccine, Effects

Print Tag: Refer to original journal article
An acute hepatitis presentation of AIH with elevated alanine aminotransferase levels and preserved synthetic function is good prognostically.

**Background/Objective:** Autoimmune hepatitis (AIH) is a liver disease that if untreated will lead to cirrhosis and hepatic failure. Little is known about what factors predict the long-term outcome of this disease. The present study was performed to attempt to determine the symptoms at presentation, prognostic features, management, and treatment in relation to the long-term outcome of AIH.

**Design/Participants:** A multi-center, retrospective analysis of 473 Swedish patients who had AIH.

**Methods:** The patients were studied to determine what symptoms and signs at initial presentation helped to predict the long-term outlook of the disease with regard to death and the need for liver transplantation. Survival and causes of death were obtained from Swedish national registers.

**Results:** 69% of patients’ predominant symptom at the time of diagnosis was fatigue, and 47% were jaundiced. Thirty percent had cirrhosis at the time of diagnosis, and another 10% developed cirrhosis during their period of follow-up. Interestingly, markedly elevated alanine aminotransferase levels at the time of presentation correlated with a more favorable outcome. An elevated international normalized ratio (INR) was the only risk factor at presentation that predicted a need for future liver transplantation. Factors that correlated with a bad outcome were histologic cirrhosis at presentation, decompensation, and nonresponse to initial therapy. Although overall life expectancy was favorable, most deaths were liver related, with liver failure, shock, and gastrointestinal bleeding being the most common.

**Conclusions:** An elevated INR, cirrhosis at presentation, and failure to respond to initial immunosuppressive therapy were associated with a poor outcome and a need for a later liver transplantation. By contrast, presentation with an acute hepatitis onset with elevated transaminases with intact synthetic capacity suggested a good response to therapy and a favorable long-term outlook. The authors believed that lifetime maintenance therapy in most patients was required.

**Reviewer’s Comments:** This interesting study was done on a fairly homogeneous population in Sweden. Although I suspect the findings would apply to a more varied population as would be found in most American studies, I do wonder if the final conclusion on the need for lifetime maintenance therapy would apply to a more diverse population. (Reviewer-Michael M. Phillips, MD).

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Keywords: Characteristics, Initial Tx Response, Long-Term Outcome

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