Update in Gastroenterology and Hepatology

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This year's Update in Gastroenterology and Hepatology incorporates articles on screening and surveillance for Barrett esophagus, antimicrobial resistance in *Helicobacter pylori*, recurrent ulcer bleeding treatment, celiac disease diagnosis, optimal inflammatory bowel disease treatment, cyclosporine use for ulcerative colitis, the role of nonsteroidal agents in ulcerative ileitis, the effect of probiotics on antibiotic-associated diarrhea, the use of aspirin to prevent colorectal adenomas, chronic liver disease diagnosis, and the causes of acute liver failure.

Esophagus, Stomach, and Small Bowel

Cost-Effective Screening and Surveillance for Barrett Esophagus Are Limited to Patients with Dysplasia

Inadomi JM, Sampliner R, Lagergren J, et al. Screening and surveillance for Barrett esophagus in high-risk groups: a cost–utility analysis. Ann Intern Med. 2003;138:176-86. [PMID: 12558356]

Although one-time screening endoscopy for Barrett esophagus is recommended for patients with gastroesophageal reflux disease (GERD), little evidence exists about the cost-effectiveness of this practice. With as much as 10% of the population estimated to have GERD, many people need screening. Moreover, once a person has Barrett esophagus, the risk for cancer is only about 0.5% per year. Among patients given a diagnosis of Barrett esophagus, current guidelines recommend periodic endoscopic surveillance to detect early cancer and dysplasia.

Inadomi and colleagues wanted to determine the cost-effectiveness of screening 50-year-old white men with GERD—the subgroup at highest risk for developing esophageal adenocarcinoma—and to offer further surveillance if Barrett esophagus is diagnosed. They developed a decision analytic model to examine 3 policies: no screening or surveillance, screening and surveillance only for patients with Barrett esophagus and dysplasia, and extending surveillance to patients with Barrett esophagus and no dysplasia.

The investigators found that screening for Barrett esophagus followed by surveillance limited to patients with Barrett esophagus and dysplasia was cost-effective, requiring $10 440 per quality-adjusted life-year (QALY) saved compared with no screening or surveillance. Screening followed by surveillance for all patients with Barrett esophagus every 5 years, however, cost much more—$596 000 per QALY saved—than surveillance only for patients with Barrett esophagus and dysplasia. For surveillance of patients with Barrett esophagus and no dysplasia to yield an incremental cost-effectiveness ratio less than $50 000 per QALY saved, the annual incidence of adenocarcinoma in Barrett esophagus would have to exceed 1 case per 54 patient-years of follow-up (annual risk, 1.9%), which is substantially higher than the actual risk of 0.5% per year.

In conclusion, screening 50-year-old patients with GERD symptoms to detect Barrett esophagus and dysplasia or adenocarcinoma is probably a cost-effective strategy, but only if subsequent surveillance is limited to patients with Barrett esophagus and dysplasia on the screening endoscopy. Future research should identify the distinguishing characteristics of patients with Barrett esophagus or GERD who are at the highest risk for cancer so that physicians can focus on that subgroup rather than subjecting all patients to upper endoscopy.

Previous Use of Macrolide Antibiotics Was Associated with *Helicobacter pylori* Resistance

McMahon BJ, Hennessy TW, Bensler JM, et al. The relationship among previous antimicrobial use, antimicrobial resistance, and treatment outcomes for *Helicobacter pylori* infections. Ann Intern Med. 2003;139:463-9. [PMID: 13679322]

The investigators wanted to find out whether previous use of antibiotics would affect eradication rates of *Helicobacter pylori* infection. They retrospectively reviewed 125 patient records to identify antimicrobial agents prescribed in the 10 years before an endoscopic diagnosis of *H. pylori* infection. They also obtained the antimicrobial susceptibility of *H. pylori* isolates from endoscopic gastric biopsy specimens.

Resistance to the antibiotics used to eradicate *H. pylori* was common: 30% of the patients ($n = 37$) had *H. pylori* isolates resistant to the macrolide clarithromycin, and 66% ($n = 83$) had *H. pylori* isolates resistant to metronidazole. Resistance to both antibiotics was associated with their use in the previous 10 years. Harboring resistant *H. pylori* had consequences. Patients with resistant *H. pylori* had a much lower chance of successful eradication of *H. pylori.* Of 53 patients treated with clarithromycin-based regimens, treatment failed in 10 of 13 patients carrying clarithromycin-resistant *H. pylori* but in only 5 of 40 patients with clarithromycin-susceptible strains (relative risk, 6.2 [95% CI, 1.9 to 37.1]; $P < 0.001$). The odds of resistance increased in relation to the number of doses of the macrolide used in the past 10 years.

In conclusion, previous use of macrolide antibiotics or metronidazole, which is commonly used in the obstetric–gynecologic setting, is associated with antibiotic-resistant

Ann Intern Med. 2004;141:374-380.
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H. pylori. Searching for patient-specific data on antimicrobial use may help physicians choose a regimen for *H. pylori* eradication. To eradicate *H. pylori* in patients with a history of macrolide or metronidazole use, an alternative antibiotic regimen is preferred. For those patients with a high risk for resistance, physicians might consider confirming successful eradication by performing a urea breath test or stool antigen test.

Celecoxib Is as Effective as Diclofenac plus Omeprazole at Reducing Ulcer Bleeding

Chan FK, Hung LC, Suen BY, et al. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. N Engl J Med. 2002;347:2104-10. [PMID: 12501222]

Current guidelines recommend that patients who are at risk for ulcer disease and require treatment for arthritis should receive either a cyclooxygenase-2 (COX-2) drug or a nonselective nonsteroidal anti-inflammatory drug (NSAID) with a proton-pump inhibitor. However, whether these regimens are effective in patients at high risk for ulcer complications is unknown. The investigators wanted to compare the effect of the COX-2 inhibitor celecoxib on recurrent ulcer bleeding with the effect of an NSAID and proton-pump inhibitor combination of diclofenac plus omeprazole in patients at high risk for bleeding.

The randomized, controlled trial included patients who used NSAIDs for arthritis and who presented with ulcer bleeding. Once the patients' ulcers healed, the investigators assigned the *H. pylori*–negative patients to receive either 200 mg of celecoxib twice daily plus daily placebo ($n = 144$) or 75 mg of diclofenac twice daily plus 20 mg of omeprazole daily ($n = 143$) for 6 months. The primary outcome was recurrence of ulcer bleeding.

Among patients with a history of ulcer bleeding, celecoxib was as effective as diclofenac plus omeprazole with respect to recurrent bleeding. After 6 months, recurrent ulcer bleeding occurred in 7 (4.9%) patients receiving celecoxib and 9 (6.4%) patients receiving diclofenac plus omeprazole. Adverse events included hypertension in 20 (14%) patients in the celecoxib group and 27 (19%) patients in the diclofenac plus omeprazole group; edema in 7 (5%) patients in the celecoxib group and 8 (6%) patients in the diclofenac plus omeprazole group; and creatinine levels greater than 167.8 μmol/L (>2.2 mg/dL) in 8 (6%) patients in the celecoxib group and 9 (6%) patients in the diclofenac plus omeprazole group. In conclusion, among patients with a history of ulcer bleeding, celecoxib was as effective as diclofenac plus omeprazole with respect to recurrent bleeding. Adverse events were, however, common in high-risk patients receiving either regimen. Proton-pump inhibitors may reduce risk, but they clearly do not prevent recurrent bleeding in high-risk patients.

In earlier studies involving patients who are at lower risk for gastrointestinal bleeding and were given COX-2 inhibitors, the incidence of bleeding was 0.5% to 1.5% lower than the greater than 5% incidence in these high-risk patients. Therefore, if low-risk patients take NSAIDs, they do not require a COX-2 inhibitor or a proton-pump inhibitor.

Irritable Bowel Syndrome Was Significantly Associated with Celiac Disease

Sanders DS, Carter MJ, Hurlstone DP, et al. Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care. Lancet. 2001;358:1504-8. [PMID: 11705563]

Irritable bowel syndrome (IBS) is common, affecting 5% to 15% of the population. The frequency of celiac sprue in patients with IBS is not known. The investigators wanted to determine whether celiac sprue causes symptoms that are misdiagnosed as IBS. By using the Rome II criteria for diagnosing IBS, they examined the association between IBS and celiac sprue in patients presenting with IBS. The Rome II criteria define IBS as 12 weeks or more (which need not be consecutive) of abdominal discomfort or pain in the preceding 12 months. The pain or discomfort should have at least 2 of 3 features: relieved with defecation, associated with a change in frequency of stool, or associated with a change in form (consistency) of stool.

The investigators designed a case–control study at a university hospital involving 300 consecutive patients who met the Rome II criteria and 300 age- and sex-matched healthy controls. They investigated all patients for celiac sprue, as analyzed by serum IgA antigliadin, IgG antigliadin, and endomysial antibodies. They offered duodenal biopsy to confirm the possibility of celiac disease to patients and controls with positive antibody results.

Sixty-six patients with IBS had positive antibody results. Of these, 43 patients had normal duodenal mucosa and 14 (4.7%) had celiac sprue (11 of these 14 patients had positive results for endomysial antibodies and 3 had negative results for endomysial antibodies) confirmed by duodenal biopsy. Two patients in the control group had positive results for endomysial antibodies and had celiac sprue. Nine patients with IBS and positive antibody results were lost to follow-up or declined biopsy, but the remaining 16 patients with celiac sprue (14 patients with IBS and 2 controls) responded to treatment with a gluten-free diet and improvement in their IBS-like symptoms. The study showed that compared with matched controls, IBS was significantly associated with celiac sprue (odds ratio, 7.0 [CI, 1.7 to 28.0]; $P = 0.004$). In summary, physicians should consider investigating for celiac sprue in patients with IBS who are referred to a secondary care center. The physician should not rely on a positive endomysial antibody test result to diagnose celiac disease, since the test may have missed 3 of 14 celiac sprue cases. Therefore, performing

upper endoscopy is important if an endomysial antibody test result is negative and suspicion of celiac disease is high.

Inflammatory Bowel Disease

Review Provided Advice on Overcoming Errors in Inflammatory Bowel Disease

Sachar DB. Ten common errors in the management of inflammatory bowel disease. Inflamm Bowel Dis. 2003;9:205-9. [PMID: 12792229]

This review listed the 10 common errors that doctors make when managing patients with inflammatory bowel disease.

1. Overtreating the irritable bowel component: Many people have gas, bloating, and cramps, especially after eating certain foods. In patients with ulcerative colitis and Crohn disease who get these symptoms, physicians should not respond by automatically increasing their doses of anti-inflammatory drug.

2. Undertreating with aminosalicylic acid preparations: The dosage of the mesalamine Asacol (Procter & Gamble, Cincinnati, Ohio) for severe cases is 4.8 g/d, and the dosage of the mesalamine Pentasa (Shire, Inc., Florence, Kentucky) is 4 g/d.

3. Overtreating with steroids: Patients with inflammatory bowel disease should usually be treated with steroids for no longer than 3 to 6 months.

4. Undertreating with antimetabolites: The maintenance drug of choice for patients with Crohn disease is now 6-mercaptopurine. Careful dosing is required to achieve the optimal therapeutic level. Physicians can check for therapeutic blood levels by ordering special tests, such as 6-thioguanine.

5. Misusing infliximab: Avoid giving infliximab to patients who do not need or cannot benefit from it. Formulate an exit strategy for patients treated with infliximab.

6. Misusing cyclosporine: Physicians need to ask the following questions: Is there a luxury of time? Is the colon really worth saving? If patients do not respond to cyclosporine within 4 to 7 days, colectomy should be recommended. What is an appropriate exit strategy for patients receiving cyclosporine? Cyclosporine is commonly used for very sick patients as bridge therapy to treatment with 6-mercaptopurine rather than as maintenance therapy.

7. Misunderstanding obstruction in Crohn disease: Surgery is required in a patient with Crohn disease who has high-grade, localized obstruction with clinically significant ileal narrowing and has had an episode of intestinal obstruction. Giving this patient steroids or infliximab may just delay the inevitable.

8. Not appreciating the urgency of "toxic" colitis.

9. Misunderstanding cancer risk: In patients who have had ulcerative colitis (that is, universal colitis or pan-colitis) for more than 10 years, the cancer risk is 0.5% a year. Thus, the cumulative risks are 5% at 10 years and 10% at 20 years. A patient whose surveillance biopsy specimens show evidence of dysplasia should have colectomy, even when the patient is asymptomatic and has an endoscopic examination that is normal or shows inactive disease. Despite showing inactive colitis, the patient with dysplasia is at greatly increased cancer risk. The standard of practice in monitoring patients with ulcerative colitis and pan-colitis is to start endoscopic surveillance at 7 years after diagnosis and perform biopsies throughout the colon even if the mucosae appear normal. For patients with colitis limited to the descending colon, the standard of practice is similar except that surveillance starts 10 years after diagnosis.

10. Setting the wrong goals of therapy: Surgery only as a treatment of last resort is not a good strategy.

Table 1. **Current Status of Drug Therapy for Irritable Bowel Disease***

Drug	Ulcerative Colitis		Crohn Disease	
	Short-Term	Maintenance	Short-Term	Maintenance
5-acetylsalicylic acid	+	+	±	± (colon)
Steroids	+	−	+	−
6-mercapturine or azathiopine	−	+	−	+
Methotrexate	−	?	±	+
Cyclosporine	+	− (bridge)	−	−
Anti–tumor necrosis factor	?	?	±	+
Probiotics	No data	±	No data	±

* Plus sign = effective; minus sign = not recommended; plus/minus sign = equivocal data; question mark = only small trials reported.

Table 1 summarizes the current status of drug therapy in inflammatory bowel disease. The drug 5-aminosalicylic acid is effective in short-term treatment of ulcerative colitis, as well as maintenance therapy. In Crohn disease, 5-acetylsalicylic acid is most effective in patients who have colon-only Crohn disease of recent onset and no previous therapy. Steroids are recommended for acute flares of the disease, although the physician must taper steroids to the lowest possible maintenance dose because of the substantial propensity for steroid side effects. The drugs of choice for maintenance therapy in Crohn disease are 6-mercaptopurine and azathioprine. For patients who cannot tolerate 6-mercaptopurine, methotrexate is a reasonable alternative for maintenance therapy.

Cyclosporine is a salvage treatment for patients with acute ulcerative colitis or severe refractory colitis whose other forms of therapy have failed. Anti–tumor necrosis factor antibodies, such as infliximab, have been shown to be an effective maintenance therapy for people with Crohn disease, particularly if they have fistulous disease or if all other treatments have failed. The use of anti–tumor necrosis factor antibodies for treating acute ulcerative colitis or maintenance therapy has not been tested in large con-

trolled trials. In small trials, probiotics are effective adjunctive maintenance drugs, but data on their use as drugs for short-term therapy are not available.

The safety of 6-mercaptopurine in pregnant patients is unknown. Investigators at Mt. Sinai Hospital in New York studied 155 patients who had conceived at least 1 pregnancy after developing inflammatory bowel disease (1). They analyzed the pregnancies of patients who had taken 6-mercaptopurine before or at the time of conception and compared the findings with patients with inflammatory bowel disease who became pregnant before taking 6-mercaptopurine. Used before conception, at conception, or during conception, 6-mercaptopurine was not associated with increased prematurity, spontaneous abortion, congenital abnormalities, or neonatal and childhood infections. The results add to the body of evidence about the safety of patients with inflammatory bowel disease taking 6-mercaptopurine before and during pregnancy, but they do not yet prove that the drug is safe. The safety of giving 6-mercaptopurine to patients with Crohn disease who present to physicians during their pregnancy and have never taken the drug before is not known.

High-Dose Cyclosporine Had No Additional Clinical Benefit over Low-Dose Cyclosporine for Severe Ulcerative Colitis

Van Assche G, D'Haens G, Noman M, et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. Gastroenterology. 2003;125:1025-31. [PMID: 14517785]

Cyclosporine is known to be highly effective for patients with severe ulcerative colitis, inducing remission in 50% of patients treated acutely. However, sustained remission occurs in only about one third of patients at 1 year. Cyclosporine also has serious, mainly dose-dependent, side effects. In this randomized, controlled trial, Van Assche and colleagues compared the clinical benefit of intravenous cyclosporine, 4 mg/kg of body weight, the dose typically used, with intravenous cyclosporine, 2 mg/kg, for the short-term treatment of severe ulcerative colitis.

The trial involved 73 patients after exclusion of any patients with serum creatinine levels greater than 152.5 μmol/L (>2.0 mg/dL) or serum total cholesterol levels less than 3.9 mmol/L (<150 mg/dL) (because these patients are at risk for central nervous system side effects). The primary end point was clinical response, and the secondary end points were time to response, colectomy rate, and adverse effects.

On day 8 of treatment, 32 of the 38 (84.2%) patients in the 4-mg/kg group and 32 of the 35 (85.7%) patients in the 2-mg/kg group responded to treatment. The median time to response was 4 days in both groups. The short-term colectomy rates (at $\leq$14 days) were 13.1% in the 4-mg/kg group and 8.6% in the 2-mg/kg group. The median change in clinical activity index was -7 in the 4-mg/kg group and -6 in the 2-mg/kg group. Mean cyclosporine blood levels ($\pm$SD) were 276.2 $\pm$ 35.8 nmol/L in the 4-mg/kg group and 197.2 $\pm$ 27.5 nmol/L in the 2-mg/kg group. Hypertension occurred in 9 (23.7%) patients in the 4-mg/kg group and only 3 (8.6%) patients in the 2-mg/kg group. The median endoscopy score was 2 for both groups on days 0 and 8.

In this study, high-dose intravenous cyclosporine had no additional clinical benefit over low-dose intravenous cyclosporine in treating patients with severe ulcerative colitis. While the response rate with cyclosporine is 50%, it decreases to about one third of the responders in each group after 1 year.

Nonsteroidal Agents Probably Contributed to Ulcerative Lesions in Patients with Ulcerative Ileitis

Lengeling RW, Mitros FA, Brennan JA, Schulze KS. Ulcerative ileitis encountered at ileo-colonoscopy: likely role of nonsteroidal agents. Clin Gastroenterol Hepatol. 2003;1:160-9. [PMID: 15017486]

We know that NSAIDs have deleterious effects in the lower small bowel and colon. Lengeling and colleagues wanted to evaluate the effects of long-term use of NSAIDs in patients with ulcerative ileitis. The terminal ileum is a site for many infections or inflammatory processes, including cytomegalovirus infection, *Yersinia* infection, tuberculosis, actinomycosis, *Salmonella* infection, and Crohn disease. Furthermore, chemical injury from NSAIDs also typically occurs around the ileocecal valve. The authors identified 40 patients with ulcerative ileitis from 1900 consecutive ileoscopies. Thirty-three of the 40 patients were taking long-term NSAID therapy, including enteric-coated aspirin, 325 mg/d or less (n = 19); selective COX-2 inhibitors (n = 5); and nonacetylated salicylates (n = 3). The investigators then analyzed the clinical, endoscopic, and histologic findings of these patients and related the findings to NSAID use.

The ileitis contributed to blood loss in 14 patients. Endoscopy revealed some clinically significant lesions; several discrete, fibrin-covered ulcerations in the prevalvular area; erythematous stippling; and occasional mucosal scars and webs. The histologic findings included focal superficial neutrophilic infiltrates, edema, mucosal hemorrhages, and lymphatic dilation. The investigators did not see granulomas or fissured ulcers, which are characteristic of Crohn disease, after a median follow-up of 3.2 years. After the NSAID therapy was discontinued, the lesions disappeared; in some patients who resumed NSAID therapy, the lesions reappeared.

In summary, ulcerative lesions are not rare on terminal ileoscopy, and these lesions probably contribute to gastrointestinal blood loss and other clinical manifestations. The probable cause of the lesions is NSAID therapy, including treatment with low-dose NSAIDs and COX-2 inhibitors. Features of NSAID-associated ileitis overlap

with Crohn ileitis. This study demonstrates that ulcerative lesions of the ileum do not necessarily establish the diagnosis of Crohn disease.

Probiotics Helped Prevent Antibiotic-Associated Diarrhea

D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. BMJ. 2002; 324:1361. [PMID: 12052801]

Health food stores are stocked with heavily advertised probiotics, which are mixtures of microorganisms. Since antibiotic-associated diarrhea is a common problem due to overgrowth with *Clostridium difficile*, it seemed appropriate to evaluate the effect of probiotics on antibiotic-associated diarrhea. The risk factors for antibiotic-associated diarrhea are age older than 65 years, immunosuppression, prolonged hospitalization, and care in an intensive care unit. About 20% of people who have *C. difficile* will relapse at least once, and 5% will relapse several times.

The investigators wanted to evaluate the efficacy of probiotics in preventing and treating antibiotic-associated diarrhea. Probiotics that have been tested for preventing and treating antibiotic-associated diarrhea are *Lactobacillus acidophilus*, *L. casei*, *L. bulgaricus*, *Bifidobacterium*, *Enterococcus faecium,* and *Saccharomyces boulardii*. The investigators identified 9 randomized, double-blind, placebo-controlled trials of probiotics by searching MEDLINE and the Cochrane Library. Two of the trials were in children. Four studies used the yeast *S. boulardii*, 4 used lactobacilli, and 1 used a strain of *Enterococcus*. In all 9 trials, the active treatment group received probiotics in combination with antibiotics, whereas the control group received antibiotics plus placebo. The outcome measure in the trials was the occurrence of diarrhea, defined by a change in normal bowel habits to 2 or more loose stools per day or watery loose stool for more than 2 days.

The results were expressed as the percentage of patients without diarrhea. The 9 trials involved 1214 patients. The pooled odds ratio showed that probiotic treatment was more effective than placebo in preventing diarrhea (relative risk for diarrhea with probiotics, 0.37 [CI, 0.26 to 0.53]). In the probiotic group, 90% of patients did not have diarrhea compared with 78% of patients in the placebo group. The number needed to treat for benefit was 9. Six of the 9 trials showed a statistically significant benefit of probiotics. One study showed the benefit for only a small subgroup of patients.

In conclusion, this meta-analysis suggested that probiotics are effective in preventing antibiotic-associated diarrhea. The limitations of this meta-analysis were the clinical heterogeneity of the trials, the need to define appropriate use of these agents, and the cost. Physicians who are going to prescribe antibiotics should ask their patients whether they have ever taken antibiotics for this condition and then developed diarrhea. If the answer is yes, and particularly if antibiotic-associated diarrhea has recurred more than once, then the physician should suggest that they use a probiotic. If they decide to use a probiotic, they should purchase a refrigerated preparation, such as VSL3 (VSL Pharmaceuticals, Inc., Fort Lauderdale, Florida) or Culturelle with *Lactobacillus* GG (ConAgra Functional Foods, Inc., Omaha, Nebraska). Over-the-counter probiotics may contain inactive bacteria.

Daily Aspirin Use Was Associated with a Reduced Incidence of Colorectal Adenomas

Sandler RS, Halabi S, Baron JA, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med. 2003;348:883-90. [PMID: 12621132]

The use of aspirin to prevent colorectal cancer is controversial and important. Several observational studies have shown that regular use of aspirin is associated with a lower incidence of colorectal cancer in men and women. The investigators organized a double-blind, randomized, controlled trial to determine the effect of aspirin on the incidence of colorectal adenomas in patients who had previous colorectal cancer. They randomly assigned 317 patients to receive aspirin, 325 mg/d, and 318 patients to receive placebo. A total of 517 patients had at least 1 follow-up colonoscopy at a mean of 12.8 months after randomization.

An independent data and safety monitoring board terminated the study early when a planned interim analysis of the data showed a statistically significant advantage to taking aspirin. Daily use of aspirin caused a statistically significant reduction in the incidence of colorectal adenomas in patients with previous colorectal cancer (**Table 2**). The time to detection of a first adenoma was significantly longer in the aspirin group than the placebo group (hazard ratio for detecting a new polyp, 0.64 [CI, 0.43 to 0.94]; $P = 0.022$). The authors adjusted the relative risks for colorectal adenoma for age, sex, cancer stage, the number of colonoscopic examinations, and the time to first colonoscopy.

Other investigators did a companion study to look at patients who previously had colorectal adenomas but not cancer to see whether aspirin prevented recurrent colorectal adenomas (2). They randomly assigned 1121 patients with

Table 2. **Comparison of Aspirin, 325 mg/d, versus Placebo in Preventing Colorectal Adenomas***

Variable	Aspirin ($n = 259$)	Placebo ($n = 258$)
Patients with adenomas, %	17	27
Adenomas, *n (%)*		
0	216 (83)	188 (75)
1	26 (10)	37 (14)
2	9 (3)	19 (7)
≥3	8 (3)	14 (5)
Mean adenomas, *n*	0.30	0.49
Relative risk	0.65	1.0

* Data obtained from Sandler et al. N Engl J Med. 2003;348:883-90.

Table 3. **Comparison of Aspirin, 81 mg/d and 325 mg/d, versus Placebo in Preventing Colorectal Adenomas***

Variable	Regimen		
	Placebo ($n = 363$)	Aspirin, 81 mg ($n = 366$)	Aspirin, 325 mg ($n = 355$)
Any adenoma, *n (%)*	171 (47)	140 (38)	160 (45)
Advanced lesion, *n (%)*	47 (13)	28 (7.7)	38 (10.7)
Tubular adenoma, *n (%)*	143 (39)	121 (33)	141 (39)
Relative risk	1.0	0.81	0.96

* Data obtained from Sandler et al. N Engl J Med. 2003;348:883-90.

a recent history of histologically documented adenomas to receive 1 of 3 treatment regimens: 81 mg of aspirin per day ($n = 377$), 325 mg of aspirin per day ($n = 355$), or placebo ($n = 372$). The investigators performed colonoscopy 3 years after the qualifying colonoscopy in 1084 patients and removed all polypoid lesions. They compared the incidence of adenomas in these 3 groups. Compared with the placebo group, the unadjusted relative risks for any adenoma were 0.81 (CI, 0.69 to 0.96) in the 81-mg group and 0.96 (CI, 0.81 to 1.13) in the 325-mg group (**Table 3**). Although 81 mg of aspirin per day reduced the risk for recurrent adenomas, the effect was moderate (relative risk reduction, 19%). It was unclear why 325 mg of aspirin per day did not seem to have a protective effect, a finding that was contrary to several observational studies that demonstrated that the more frequent the aspirin use and the higher the dose, the greater the protection against colorectal adenomas.

An accompanying editorial emphasized that aspirin use in either group did not obviate the need for surveillance colonoscopy in these individuals because they are at increased risk for getting recurrent lesions (3). The editorialist concluded that although aspirin reduces the risk for colorectal cancer, it cannot yet be recommended for this indication and is not a substitute for screening and surveillance. Because colorectal lesions grow very slowly (at a rate of 0.2 mm to 2 mm a month) and thus can be present for as long as 5 to 8 years before diagnosis, the 3-year follow-up used in these studies may been too short to determine the natural course of recurrent polypoid lesions. Because several other studies have shown that aspirin reduces the incidence of colorectal cancer, patients who have undergone removal of polyps with advanced features (>1 cm and villous or tuberovillous, with other risk factors for colorectal cancer) should take prophylactic doses of aspirin.

Nonalcoholic Fatty Liver Disease Is Linked to the Metabolic Syndrome

Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol. 2003;98:960-7. [PMID: 12809815]

In the United States, the prevalence and cause of elevated aminotransferase levels, often used to detect liver disease, are unknown. United States. This study analyzed data on 15 676 individuals 17 years of age and older from the Third National Health and Nutrition Examination Survey (1988–1994). The investigators defined an aminotransferase elevation as an aspartate aminotransferase level greater than 37 U/L and an alanine aminotransferase level greater than 42 U/L. (Normal levels are 15 U/L and 20 U/L, respectively, for women and 20 U/L and 25 to 30 U/L, respectively, for men.) They classified an elevation as "explained" if there was laboratory evidence of hepatitis B or C virus infection, iron overload (>50%), or a history of alcohol consumption (>2 drinks per day for men, and >1 drink per day for women). If an individual had none of these 4 factors, the authors classified the aminotransferase elevation as unexplained.

The investigators found that 8% of the sample had an aminotransferase elevation. Aminotransferase elevations were more common in men (9.3%) than women (6.6%) and more common in Mexican Americans (14.9%) and non-Hispanic black people (8.1%) than non-Hispanic white people (7.1%; $P < 0.001$). The apparent causes in 31% of the patients included high alcohol consumption (43%), hepatitis C virus (22%), hepatitis B virus (3%), hemochromatosis (11%), and any combination of these causes (19%). The striking finding of this study is that 69% of individuals had unexplained aminotransferase elevations. The elevated levels in this group were associated with adiposity and other features of the metabolic syndrome: higher body mass index (29.5 kg/m^2), large waist circumference (100.8 cm), elevated fasting insulin level (94 pmol/L), elevated triglyceride level (2.26 mmol/L [200 mg/dL]), type 2 diabetes (especially in women), and hypertension (especially in women).

These findings suggest that nonalcoholic fatty liver disease is clearly linked to the metabolic syndrome. After the known causes of elevated aminotransferase levels were factored out, most of the remaining two thirds of the patients had features of the metabolic syndrome. Nonalcoholic fatty liver disease is common in the metabolic syndrome, and the incidence of nonalcoholic fatty liver disease in the metabolic syndrome is directly proportional to body mass index. The disease is now the most common liver disease in the United States and will become even more prevalent because 65% of the U.S. population has a body mass index greater than the average of 25 kg/m^2. The data presented in this study allow a direct estimate in the prevalence of an elevated aminotransferase level in the general U.S. population. About 10% to 17% of patients with unexplained aminotransferase elevation have unsuspected cirrhosis, and an even higher proportion have clinically significant fibrosis. The incidence of fibrosis and cirrhosis is also directly related to the degree of obesity and increases dramatically from a body mass index of 30 kg/m^2 to 40 kg/m^2.

Acetominophen Overdose Was Determined as the Most Frequent Cause of Acute Liver Failure

Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137:947-54. [PMID: 12484709]

This paper highlights a shift in the cause and prognosis in people with acute liver failure. Few large studies of this condition exist because acute liver failure is rare. The authors of this cohort study aimed to describe the clinical features, presumed causes, and short-term outcomes of acute liver failure.

The prospective cohort study involved 308 consecutive patients with acute liver failure hospitalized over a 41-month period at 17 tertiary care centers. The investigators defined acute liver failure by an international normalized ratio greater than 1.5 and portal systemic encephalopathy within 26 weeks of the first symptoms and no previous liver disease. In the cohort, 73% of the patients were women, the median age was 38 years, and the overall survival rate at 3 weeks was 67%. Twenty-nine percent of the patients had orthotopic liver transplantation, and 43% survived without liver transplantation.

The study's most important finding is that acetaminophen overdose and idiosyncratic drug reactions have replaced viral hepatitis, which accounted for only 12% of cases, as the most frequent cause of acute liver failure (**Table 4**). The median dose of acetaminophen was 13 g, and the daily dose ranged from 2.6 g, which is therapeutic, to 75 g. More than 80% of the patients who overdosed on acetaminophen took more than 4 g, which is the prescribed upper limit of the daily dose. Years ago, research suggested that most patients with acute liver failure who overdosed with acetaminophen were either alcoholic persons taking acetaminophen or people with suicidal intent. This study showed that 68 patients had accidental exposure to too much acetaminophen. An accidental overdose most commonly occurs when an individual has a bad case of the flu, fails to eat or maintain adequate fluid intake, takes acetaminophen around the clock, and then takes additional combination medications for sleep that contain acetaminophen. The typical patient with the flu who has not eaten normally for a few days often will have depleted glutathione stores, which predisposes to acetaminophen-associated liver injury. Thus, at the end of about 3 days of these conditions, the patient is very susceptible to acetaminophen-induced liver injury. Physicians should tell patients that if they're going to use acetaminophen for flu-like symptoms, they must ingest a reasonable amount of calories during that time. Otherwise, they should not use the medication. The survival rate is so high for acute liver failure due to acetaminophen overdose because most emergency departments now know how to treat this kind of overdose by initiating prompt treatment with L-cysteine, which reverses the effects of the disease even if it's started after 72 hours from the time of ingestion.

Table 4. **Causes of Acute Liver Failure**

Cause	Patients, *n (%)*	Transplantation-Free Survival, %
Acetaminophen	120 (39)	68
Other drugs	40 (13)	25
Indeterminate	53 (17)	17
All others	95 (31)	33

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Potential Financial Conflicts of Interest: *Honoraria:* N.J. Greenberger (Janssen, Astra Merck).

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