

1999–2000 Series: Update Sessions from ACP–ASIM’s 1999 Annual Session

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Update in Gastroenterology

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Among the most important topics attracting investigators’ attention in 1998 were gastroesophageal reflux disease (GERD), the diagnosis and treatment of *Helicobacter pylori* infection, and how best to manage patients with nonulcer dyspepsia. Also worthy of note are reports on the treatment of gastrointestinal bleeding, several aspects of inflammatory bowel disease, chronic pancreatitis, and colonic gas.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease is widely prevalent, affecting roughly 7% of the U.S. population on a daily basis. Many other people are bothered by heartburn every week or month. Perhaps one fourth of all Americans use antacids at least twice a month. Relatively few patients with GERD reach the point of consulting their primary care physician or a gastroenterologist. About 2% of all patients with symptoms of GERD but 10% to 15% of those who do see a specialist have endoscopically documented esophagitis. These represent only the tip of this “iceberg” disease; most symptomatic patients medicate themselves.

Experience with several thousand patients suggests that esophagitis will heal in about one quarter of those given placebo and that symptoms will improve in about the same number. With an H₂-receptor blocker, 60% of patients will feel better and half will be healed; with a prokinetic drug such as cisapride, the percentages are 50% and 40%. When a proton-pump inhibitor such as omeprazole is used, the percentages go up to 80%. Some patients with typical symptoms of reflux do not respond to treatment, even after esophagogastroduodenoscopy, 24-hour pH monitoring, and manometric studies. The problem may be an abnormally sensi-

tive esophageal mucosa, a condition documented in studies in which inflating an esophageal balloon reproduces patients’ symptoms; this effect was not observed in healthy controls. In many cases, this “visceral hyperalgesia” will respond to a drug such as amitriptyline.

“Good” *Helicobacter pylori*: Strains Positive for Cytotoxin-Associated Antigen Carried Lower Risk for Barrett Esophagus and Its Sequelae

Vicari JJ, Peek RM, Falk GW, et al. The seroprevalence of *cagA*-positive *Helicobacter pylori* strains in the spectrum of gastroesophageal reflux disease. *Gastroenterology*. 1998;115:50-7.

In an attempt to clarify the role of *H. pylori* in GERD, 153 consecutive patients who had endoscopically confirmed reflux disease, with or without Barrett esophagus and its complications, were compared with 57 patients undergoing upper gastrointestinal endoscopy for other reasons. *Helicobacter pylori* was identified in about 46% of controls and 36% of patients with GERD. Roughly one third of patients with Barrett esophagus, with or without dysplasia or carcinoma, were infected with *H. pylori*. The striking finding was that 42% of controls harbored strains that were positive for cytotoxin-associated antigen (*cagA*), but the prevalence of these strains declined linearly as the severity of GERD increased. None of seven *H. pylori* strains in patients whose Barrett esophagus was accompanied by dysplasia or adenocarcinoma were positive for *cagA*. In patients with these strains, the gastric cardia contained more mononuclear cells and a more dense population of *H. pylori*.

These findings suggest that the *cagA*-positive strain of *H. pylori* may somehow protect against esophageal adenocarcinoma, as well as the less consequential complications of GERD. At the same time, *H. pylori* infection remains an important pathogenetic factor in duodenal ulcer disease,

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For author affiliation and current address, see end of text.

Table 1. Hospitalization and Mortality Rates Due to Peptic Ulcer, Reflux Disease, and Cancer

Disease	Hospitalization Rates per 10 000 Patients		Mortality Rates per 1 000 000 Patients	
	1970-1974	1990-1995	1968-1972	1988-1993
Gastric ulcer	68	50	22	8
Duodenal ulcer	160	45	25	9
Reflux disease				
White men	52	350		2.4
Nonwhite men	48	160		1.6
Cancer of the gastric corpus				
White men		90	165	
Nonwhite men		130	90	
Cancer of the gastric cardia				
White men			1.5	4.7
Nonwhite men			0.9	1.0

chronic gastritis, stomach cancer, and mucosa-associated lymphoid tissue lymphoma.

Opposed Time Trends: As *Helicobacter pylori* Infection and Ulcer Disease Declined, Gastroesophageal Reflux Disease Was on the Rise

el-Serag HB, Sonnenberg A. Opposing time trends of peptic ulcer and reflux disease. *Gut*. 1998;43:327-33.

This huge survey looked at more than 940 000 patients in Veterans Affairs hospitals to learn whether, from 1970 through 1995, the historical decline in *H. pylori* infection—and the concomitant decrease in peptic ulcer disease—has brought with it an increase in GERD. The answer is yes (Table 1). Both gastric and duodenal ulcers, especially the latter, have become less prevalent, and mortality rates are currently about one third of what they were at the start of the period studied by el-Serag and Sonnenberg. The rate of cancer of the body of the stomach and mortality rates from this disease have decreased at the same time, whereas rates of cancer of the cardioesophageal junction have increased markedly in white men but not in African-American men. Although far from proving a causative link, this study certainly supports the theory that the decline in *H. pylori* infection has contributed to the striking increase in esophageal adenocarcinoma. It is fair to say that GERD has replaced peptic ulcer as the major dyspeptic disorder.

How often does endoscopy change the way in which symptomatic GERD is treated? A study of 742 patients, many of whom had not responded to treatment, showed hiatal hernia, esophagitis, and gastritis to be the most common diagnoses; 18% of these patients had normal findings (1). For patients already receiving omeprazole, 47% continued taking 20 mg per day, 17% received a higher dose, and 15% also began receiving a prokinetic drug. Among

patients already receiving an H₂-blocker, 68% were switched to omeprazole. Thus, esophagogastroduodenoscopy may not appreciably alter the management of GERD in patients already taking a proton-pump inhibitor.

A recent study exploring the mechanisms underlying transient relaxation of the lower esophageal sphincter used cholestyramine to stimulate the release of endogenous cholecystokinin, which promotes postprandial relaxation of the lower esophageal sphincter when given exogenously (2). Not only did cholecystokinin enhance sphincter relaxation and cause more episodes of reflux, but the cholecystokinin receptor antagonist loxiglumide prevented these effects. Antagonist therapy might prove to be a novel way of avoiding the effects of a fatty meal on function of the lower esophageal sphincter and reflux.

***Helicobacter pylori* Infection: Diagnosis and Management**

Important recent work on *H. pylori* infection has focused on the role of serologic testing to confirm cure, whether proton-pump inhibitor therapy can obscure the diagnosis, and current guidelines for detecting and eliminating the organism.

Seroconversion Helped To Confirm Cures of Treated *Helicobacter pylori* Infection

Feldman M, Cryer B, Lee E, et al. Role of seroconversion in confirming cure of *Helicobacter pylori* infection. *JAMA*. 1998;280:363-5.

The prognostic value of serologic testing for *H. pylori* was examined in 23 generally healthy patients whose active infection was affirmed by gastric biopsy, a positive result on a urease test, and positive findings on serologic testing. Serum IgG titers were monitored for 18 months after a 2-week course of bismuth, metronidazole, and tetracycline therapy. Cure was documented in 15 patients (65% of those followed); these patients had no residual detectable antibody and had negative results on a repeated biopsy. In patients who remained infected, the titer declined—but not to zero. Seroconversion was 100% specific (but only 60% sensitive) for eradication of *H. pylori*. The investigators suggest that for patients who received antimicrobial therapy more than 12 months previously, seroconversion reliably indicates a cure and probably should be the test of first choice.

Proton-Pump Inhibitor Therapy Interfered with the Urea Breath Test for *Helicobacter pylori*

Laine L, Estrada R, Trujillo M, et al. Effect of proton-pump inhibitor therapy on diagnostic test-

ing for *Helicobacter pylori*. *Ann Intern Med.* 1998; 129:547-50.

Evidence that proton-pump inhibitors such as lansoprazole suppress *H. pylori* but rarely eradicate it by themselves prompted Laine and colleagues to determine how often such treatment converts an initially positive ^{13}C urea breath test result to negative. Ninety-three patients with GERD or dyspepsia, all of whom had biopsy or serologic findings consistent with *H. pylori* infection and a positive urea breath test result, received a 4-week course of lansoprazole therapy (30 mg daily). At the end of treatment, one third of patients had a spuriously negative urea breath test result. One week after treatment ended, however, 97% of patients tested positive, and after 2 weeks, all patients again had a positive urea breath test result. The conclusion: The urea breath test for *H. pylori* may be misleading if the patient has received a proton-pump inhibitor in the past 2 weeks. Physicians should check for infection before prescribing one of these drugs.

Guidelines Were Offered for Diagnosing and Treating *Helicobacter pylori* Infection

Howden CW, Hunt RH. Guidelines for the management of *Helicobacter pylori* infection. Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. *Am J Gastroenterol.* 1998;93:2330-5.

The role of *H. pylori* in peptic ulcer disease has changed rather abruptly. Whereas 5 years ago up to 90% of patients with ulcer harbored the organism, today at least one fourth and as many as 40% of patients with a documented duodenal or gastric ulcer test negative for *H. pylori*.

Whom To Test

Testing should be done in patients with active peptic ulcer disease or a documented history of such disease and in patients with mucosa-associated lymphoid tissue lymphoma of the stomach. At present, there is no consensus about testing patients who have GERD and are receiving long-term proton-pump inhibitor therapy.

How To Test

If esophagogastroduodenoscopy is indicated, it is best to obtain a biopsy specimen from the antral region and perform a urease test on the specimen. If esophagogastroduodenoscopy is not done, the best option is a serologic test for anti-*H. pylori* antibody. The best way of detecting active infection is to perform a urea breath test (but not within 2 weeks of starting treatment with a proton-pump inhibitor).

How To Treat *Helicobacter pylori* Infection

Although a 10- to 14-day regimen of a proton-pump inhibitor, clarithromycin, and either amoxicillin or metronidazole is effective, about one in five strains of *H. pylori* is resistant to metronidazole. Tolerance of a proton-pump inhibitor, bismuth, metronidazole, and tetracycline for 2 weeks is lower, but this regimen eradicates the organism about 95% to 98% of the time. Limiting treatment to 1 week eradicates fewer than 90% of isolates. Comparable results are achieved by giving ranitidine, bismuth citrate, clarithromycin, and another antibiotic (amoxicillin, metronidazole, or tetracycline) for 2 weeks.

Controversy continues over the advisability of first eradicating *H. pylori* in patients who are to receive long-term proton-pump inhibitor therapy for GERD. A trial comparing proton-pump inhibitor treatment with fundoplication showed that after 5 years, atrophic gastritis and micronodular hyperplasia had developed in one third of the patients given proton-pump inhibitors who were positive for *H. pylori*, whereas these diseases developed in far fewer of the patients who had surgery (3). This finding prompted a policy of checking patients who are expected to receive long-term proton-pump inhibitor treatment and eradicating *H. pylori* when the organism is present. Some subsequent studies supported this approach, but others did not. At present, eliminating the organism before starting proton-pump inhibitor therapy seems reasonable.

Nonulcer Dyspepsia and *Helicobacter pylori*

In patients with episodic or persistent upper abdominal pain or those with discomfort but normal or nondiagnostic findings on esophagogastroduodenoscopy, the diagnosis is nonulcer dyspepsia. About one third of dyspeptic patients who are put through a comprehensive work-up will be found to have nonulcer dyspepsia. Possible mechanisms for this entity include failure of the gastric fundus or antrum to relax or distend, a hypermotile antrum, and insufficient clearance of acid from the duodenum. In such patients, the duodenum may also be hypersensitive to acid, or acid-induced bowel contractions may be inadequately propagated.

Eradicating *Helicobacter pylori* Did Not Relieve Symptoms of Nonulcer Dyspepsia

Blum AL, Talley NJ, O'Moráin, et al. Lack of effect of treating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. Omeprazole plus Clarithromycin and Amoxicillin Effect One Year after Treatment (OCAY) Study Group. *N Engl J Med.* 1998;339:1875-9.

This double-blind multicenter trial studied 328 patients who had had at least moderate dyspeptic symptoms for 6 months or longer and had documented *H. pylori* infection. The patients were randomly assigned to receive 20 mg of omeprazole twice a day for 1 week or a combination of omeprazole, amoxicillin, and clarithromycin. None of these patients had a history of ulcer disease, and all had normal endoscopic findings. Omeprazole by itself eliminated *H. pylori* in only 2% of patients, whereas the combined regimen was effective in 79%. However, alleviation of symptoms was similar in both groups: 21% of the single therapy group and 27% of the combination therapy group. Whether symptoms resolved had little to do with whether *H. pylori* was eliminated. Diarrhea was a far greater problem in patients given antibiotics along with omeprazole.

Adding Antibiotics to Proton-Pump Inhibitor Therapy Helped Relieve Symptoms of Nonulcer Dyspepsia

McColl K, Murray L, El-Omar E, et al. Symptomatic benefit from eradicating *Helicobacter pylori* in patients with nonulcer dyspepsia. *N Engl J Med*. 1998;339:1869-74.

The 318 patients in this placebo-controlled study had had dyspeptic symptoms for at least 4 months and had no endoscopic signs of current or past ulcer disease. The patients were randomly assigned to receive omeprazole (20 mg twice daily) alone or combined with metronidazole and amoxicillin (or tetracycline in allergic patients) for 2 weeks. *Helicobacter pylori* was eradicated 1 month after treatment ended in 88% of patients given antibiotics but in only 5% of those given only omeprazole. One year later, Glasgow dyspepsia severity scores showed that dyspepsia had resolved in 21% and 7% of these groups, respectively ($P = 0.001$). Patients who had had symptoms for less than 5 years had the best response to combined treatment.

An editorial by Friedman (4) attempted to make sense of these seemingly conflicting findings and to propose a strategy for dealing with patients who present with nonulcer dyspepsia. The fact that symptoms resolved in less than one fourth of patients, even in the study showing some efficacy, suggests that eliminating *H. pylori* is not often the answer. Gastritis caused by *H. pylori* infection is not much more prevalent than gastritis in the general population. Relatively few patients whose nonulcer dyspepsia is accompanied by symptoms of disordered motility (such as early satiety and postprandial bloating) may respond to a promotility drug. In time, a peptic ulcer will probably develop in 5% to 15% of *H. pylori*-positive patients with nonulcer

dyspepsia. Friedman proposes endoscopy for patients older than 45 years of age; those with a family history of stomach cancer; and those with unexplained weight loss, vomiting, dysphagia, gastrointestinal bleeding, or anemia. In younger patients seropositive for *H. pylori*, elimination of this organism will benefit those who have—or will develop—peptic ulcer disease. Eradication may also help one in five patients with nonulcer dyspepsia.

Gastrointestinal Bleeding

Important recent papers in the area of gastrointestinal bleeding focused on how best to prevent upper gastrointestinal bleeding in patients who require mechanical ventilation and on the value of hormonal therapy for those with chronic bleeding of unknown origin.

Ranitidine Prevented Upper Gastrointestinal Bleeding More Reliably Than Sucralfate in Patients on Mechanical Ventilation

Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med*. 1998;338:791-7.

Critically ill patients requiring mechanical ventilation have an elevated risk for a stress ulcer and upper gastrointestinal bleeding. This blinded, placebo-controlled study of 1200 such patients showed that clinically important hemorrhage (a decrease in the hemoglobin level > 2 g, decreasing blood pressure, tachycardia, and the need for 2 units of transfused blood) occurred in 3.8% of patients given prophylaxis with the cytoprotective drug sucralfate but in only 1.7% of those given the H_2 -receptor antagonist ranitidine. The relative risk with ranitidine therapy was 0.44. Reducing the chance of bleeding did not, however, translate into fewer cases of ventilator-related pneumonia or reduced mortality rates. The authors estimate that one significant bleeding episode would be prevented for about every 50 patients given ranitidine.

Hormonal Therapy Prevented Recurrences of Occult Gastrointestinal Bleeding

Barkin JS, Ross BS. Medical therapy for chronic gastrointestinal bleeding of obscure origin. *Am J Gastroenterol*. 1998;93:1250-4.

This study looked at a not-uncommon problem: the patient who has had recurrent gastrointestinal bleeding for more than a year; has negative results on esophagogastroduodenoscopy, colonoscopy, small-

bowel study, or enteroclysis; and has been repeatedly admitted to the hospital for transfusion. Forty-three such patients, most of them elderly, participated in this study. Angiography identified arteriovenous malformations in the stomach or proximal small bowel in 25 patients; these malformations were then cauterized. In 18 other patients, no bleeding site could be found. Thirty-eight patients received Ortho-Novum (Ortho-McNeil Pharmaceuticals, Raritan, New Jersey; 1 mg of norethindrone and 0.05 mg of mestranol) twice a day, and the remaining 5 patients received only estrogen. The results were striking: None of the 38 patients in the combination therapy group had rebleeding episodes as long as they continued to receive the prescribed dosage, but all 5 patients given estrogen alone had recurrent bleeding. Eleven patients had side effects that included gynecomastia, hot flashes, and penile or testicular atrophy. Nevertheless, 7 of these patients chose to continue treatment; 1 of them had recurrent bleeding episodes.

A recent study by Rockey and colleagues (5) sought to establish the prevalence of upper and lower gastrointestinal lesions in patients with a positive result on guaiac-based testing for occult fecal blood. Both esophagogastroduodenoscopy and colonoscopy were performed in 248 patients who had more than one positive test result. Actively bleeding patients and those with iron-deficiency anemia were not included. Esophagogastroduodenoscopy demonstrated lesions in 71 patients (29% of the total sample), half of whom were symptomatic. The most frequent lesions were esophagitis, gastric and duodenal ulcer, and gastritis. The yield of colonoscopy was 22%, and less than half these patients had symptoms. Adenomas greater than 1 cm in size and cancer were the most frequent findings (5). Use of an immunochemical test for human hemoglobin after the guaiac-based test might help distinguish colonic from upper gastrointestinal bleeding.

Inflammatory Bowel Disease

Recent reports addressed several aspects of inflammatory bowel disease. Topics included the clinical course of Crohn disease over more than three decades, a possible genetic mechanism for venous thrombosis in patients with inflammatory bowel disease, and two novel medical approaches to treating Crohn disease.

Outlook Is Still Guarded for Patients with Colorectal Crohn Disease

Lapidus A, Bernell O, Hellers G, et al. Clinical course of colorectal Crohn's disease: a 35-year fol-

low-up of 507 patients. *Gastroenterology*. 1998;114:1151-60.

This 35-year follow-up of 507 patients with colorectal Crohn disease extended from 1955 through 1989. The left side of the colon was involved in 26% of cases and the entire colon was involved in 31%; 40% of patients had segmental disease. Two prominent prognostic features were the presence of fistulas, which increased the likelihood of surgery (relative risk, 1.7), and disease limited to the left colon, which made surgery less likely (relative risk, 0.6). Disease extended to the small bowel in nearly one fourth of patients (24%), a finding that contradicts the common belief that initial colonic disease will remain limited to that site. Half of all patients had surgical resection within 10 years of diagnosis, and half of these were left with an ileostomy. Two thirds of patients had relapse within 5 years after diagnosis, but those who remained free of relapse during this time were likely to remain in remission. Fifteen deaths were related to Crohn disease.

Gene Mutation Is a Warning Sign of Venous Thrombosis in Patients with Inflammatory Bowel Disease

Liebman HA, Kashani N, Sutherland D, et al. The factor V Leiden mutation increases the risk of venous thrombosis in patients with inflammatory bowel disease. *Gastroenterology*. 1998;115:830-4.

Thromboembolism is reported in up to 6% of patients with inflammatory bowel disease. A possible association with mutation of the factor V Leiden gene was sought in 11 patients with inflammatory bowel disease who had arterial or venous thrombosis and 51 matched controls with no history of thrombosis. The factor V Leiden mutation leads to loss of an activated protein C cleavage site that is required to rapidly inactivate factor Va. Its inheritance increases the risk for thrombosis in patients with various congenital or acquired prothrombotic states. In Liebman and colleagues' study, the factor V Leiden mutation was identified in 4 of the 11 patients with a history of thrombosis (36%) and in only 2 of the 51 controls (4%). The investigators believe that screening for this coagulation defect is warranted whenever a patient with inflammatory bowel disease has a personal or family history of venous thromboembolism.

Sulfasalazine remains a mainstay of treatment for both Crohn disease and ulcerative colitis. In addition, 5-aminosalicylic acid analogues, which may be given orally, in suppository form, or by enema, are very popular. Long-term corticosteroid therapy is used less often today because of concern about side effects, especially metabolic bone disease. Metroni-

dazole is an option for long-term treatment but may cause peripheral neuropathy or alter taste sensation. The immunosuppressive drugs 6-mercaptopurine and azathioprine have a steroid-sparing action and can prevent or at least delay recurrences of Crohn disease. Methotrexate appears to be effective only in the short term. Cyclosporine is used as rescue therapy for very severe ulcerative colitis when steroids have failed; about half of patients will respond to this therapy, and approximately 40% of the responders will remain in remission if 6-mercaptopurine is also administered over the long term. A recent study of several hundred patients with Crohn disease given prophylaxis for 6 to 12 months after surgery showed that 41% of those receiving 5-aminosalicylic acid and at least half of those given low-dose 6-mercaptopurine therapy did not have recurrence, compared with 31% of placebo recipients (6).

Anti-Tumor Necrosis Factor Antibody Suppressed Active Inflammation in Crohn Disease

Baert FJ, D'Haens GR, Peeters M, et al. Tumor necrosis factor α antibody (infliximab) therapy profoundly down-regulates the inflammation in Crohn's ileocolitis. *Gastroenterology*. 1999;116:22-8.

A study cited in the 1998-1999 Update in *Gastroenterology* (7) showed that a brief course of treatment with antibody against tumor necrosis factor (TNF) lessened and even eliminated symptoms of active Crohn disease. Nearly one fourth of antibody-treated patients and 8% of those given a placebo were in sustained remission after 3 months (8).

To determine the effects of anti-TNF- α , or infliximab, on the mucosal changes of Crohn ileocolitis, Baert and colleagues gave a single infusion of 5 to 20 mg/kg of body weight to 13 patients whose disease was resistant to steroids; 5 others received placebo. Not only did total histologic activity scores decline significantly 4 weeks after antibody treatment (with a reduction in mononuclear cells and near absence of neutrophils), but 4 patients regained a totally normal-appearing mucosa. Furthermore, colonic epithelial cells no longer expressed HLA-DR, and far fewer mononuclear cells in the lamina propria were still positive for TNF and in-

terleukin-4 (Table 2). A global reduction in CD4⁺ and CD8⁺ T lymphocytes was also noted. Because TNF is a key cytokine promoting mucosal inflammation in Crohn disease, antibody treatment reverses the process whereby numerous injurious cytokines are upregulated.

A different approach to Crohn disease exploits the fact that intracellular adhesion molecule-1, which helps activate leukocytes and promotes their migration, is upregulated in the inflamed mucosa of Crohn disease. An antisense oligonucleotide, ISIS 2302, which selectively inhibits the cytokine-induced expression of intracellular adhesion molecule-1, led to remission in 7 of 15 patients with active disease who received 13 alternate-day intravenous infusions; in contrast, remission occurred in only 1 of 5 placebo recipients (9). Five of the actively treated patients remained in remission 6 months later. Treatment also had a steroid-sparing effect and was well tolerated. The antisense oligonucleotide works by hybridizing to a sequence of the human intracellular adhesion molecule-1 message, reducing the cell-specific message content and thereby reducing expression of the cytokine.

Controlling Flatus

Passing colonic gas is a ubiquitous and vexing condition. The average American passes 600 to 2000 mL of intestinal gas in 24 hours. The process is amplified by eating a wide range of vegetables, including cabbage, asparagus, and beans of all types. Lactose-containing foods, bran cereals, and whole wheat bread are other culprits. Hydrogen sulfide (H₂S) is the major sulfurous gas produced by bacteria in the human colon and is also one of the chief malodorous components of flatus. The many dietary and endogenous sources of sulfur make limiting its delivery to the colon impractical. Although antibiotics could be used to eliminate microorganisms producing H₂S, bacterial resistance and overgrowth are possible sequelae. An alternative approach would be to administer a substance that binds H₂S, as bismuth does in vitro.

Bismuth Compound Controlled Flatus Odor by Reducing Hydrogen Sulfide in the Colon

Suarez FL, Furne JK, Springfield J, et al. Bismuth subsalicylate markedly decreases hydrogen sulfide release in the human colon. *Gastroenterology*. 1998;114:923-9.

This study measured gas production by homogenates of human and rat feces when incubated with or without bismuth subsalicylate. An inverse dose-dependent relation was seen between the concen-

Table 2. Change in Biopsy Results after Infliximab Treatment or Placebo

Variable	Infliximab Group	Placebo Group
Histologic score	Decrease	No change
Polymorphonuclear cell count	Decrease	No change
Mucosal architecture	Normal	No change
Tumor necrosis factor level	Decrease	No change
Intracellular adhesion molecule-1 level	Decrease	No change
Interleukin-4 level	Decrease	No change

tration of bismuth subsalicylate and the amount of H₂S released. Consistent with these findings, fecal release of H₂S over 24 hours of incubation was reduced more than 95% when 10 healthy persons took bismuth subsalicylate (524 mg four times daily) for 3 to 7 days. Baseline levels of H₂S release returned 5 days after discontinuation of bismuth therapy.

Bismuth might also prove useful in preventing possible adverse effects of H₂S on the colonic mucosa. A recent report indicates that bismuth subsalicylate can lead to marked clinical improvement in patients with collagenous colitis, a condition that is often difficult to treat effectively (10). One drawback is the possible development of neurotoxicity when bismuth is used over the long term, but non-toxic doses may suppress H₂S production. As an alternative, a preparation that releases bismuth in the distal ileum or colon could be given, or bismuth could be administered in enema form.

Pancreatitis

Some patients with cystic fibrosis develop pancreatitis, and cystic fibrosis is the most common inherited disorder of the exocrine pancreas. Mutations of the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) result in dysfunction of the lungs, sweat glands, and pancreas but have seldom been directly implicated in clinical pancreatitis. These mutations are not uncommon; 1 in every 2000 live births is affected.

Mutation of a Cystic Fibrosis Gene Was Strongly Associated with Chronic Pancreatitis

Cohn JA, Friedman KJ, Noone PG, et al. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. *N Engl J Med.* 1998;339:653-8.

This study used DNA testing to determine whether an abnormal *CFTR* genotype predisposes patients who lack conventional findings of cystic fibrosis to development of idiopathic pancreatitis. Ten of 27 patients with chronic pancreatitis of unknown origin (37%) did have at least one abnormal *CFTR* allele. The number of mutations detected—8—was substantially greater than the number expected. In 3 patients, both alleles were altered. Although these patients lacked the typical pulmonary abnormalities of cystic fibrosis, each of them did have abnormal *CFTR*-mediated chloride ion transport in the nasal mucosa. The 5T allele, which reduces the level of functional *CFTR*, was about twice as frequent as expected. Pancreatography yielded abnormal findings in 22 of the 25 patients examined.

These findings imply that *CFTR* mutations may increase the risk for pancreatitis in persons exposed

to alcohol or certain drugs and that genetic testing could identify those who are at risk. These patients did not have the lung changes expected in cystic fibrosis, and many of them were in their thirties or older when pancreatitis was diagnosed. A large majority (22 of 27) were women. In general, 60% to 70% of patients in the United States with chronic pancreatitis are chronic alcoholics, and 5% to 10% of patients with chronic pancreatitis have diverse predisposing conditions, including radiation exposure, cancer, and past trauma. Twenty percent to 25% of cases are considered idiopathic. A companion study, which sought *CFTR* mutations in 134 consecutive patients with chronic pancreatitis (11), supports a policy of screening for cystic fibrosis whenever small-duct pancreatitis is found in a woman or a nonalcoholic person, although the actual consequences of such screening remain to be determined.

The Short-Bowel Syndrome

Bile Acid Replacement Improved Fat Absorption in a Patient with Refractory Short-Bowel Syndrome

Gruy-Kapral C, Little KH, Fordtran JS, et al. Conjugated bile acid replacement therapy for short-bowel syndrome. *Gastroenterology.* 1999;116:15-21.

Decreased secretion of bile acids is part of the explanation for inadequate absorption of fat in patients with the short-bowel syndrome. The obvious remedy—replacing deficient bile acids—has been avoided because of concern that it may worsen diarrhea. Gruy-Kapral and colleagues' experience with a single patient, whose condition was resistant to treatment and who could not receive parenteral nutrition, showed that either of two preparations promoted fat and calcium absorption and permitted a significant gain in body weight, from 80 to 98 pounds in 4 months. One preparation was a mixture of conjugated bile acids prepared from ox bile, and the other was cholylsarcosine, a synthetic conjugated bile acid. Ileostomy water intake did not change substantially during this bile acid replacement therapy, which would seem to be an effective adjunctive measure in selected patients with the short-bowel syndrome.

Celiac Disease

New Serologic Test Reliably Diagnosed Celiac Sprue

Sulkanen S, Halttunen T, Laurila K, et al. Tissue transglutininase autoantibody enzyme-linked immunosorbent assay in detecting celiac disease. *Gastroenterology.* 1998;115:1322-8.

Dieterich W, Laag E, Schopper H, et al. Autoantibodies to tissue transglutaminase as predictors of celiac disease. *Gastroenterology*. 1998;115:1317-21.

On the assumption that tissue transglutaminase is a major (if not the only) endomysial antigen in celiac disease, these studies used an enzyme-linked immunosorbent assay to quantify tissue transglutaminase autoantibody in untreated patients. In the two series, which enrolled a total of 242 patients, 95% and 98%, respectively, tested positive for tissue transglutaminase antibody, compared with less than 10% of controls. Similarly, more than 90% of patients in both studies were positive for endomysial antibody. These findings support the notion that tissue transglutaminase is the target antigen for endomysial antibody and suggest a useful serologic test for diagnosing celiac disease.

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References

1. Blustein PK, Beck PL, Meddings JB, Van Rosendaal GM, Bailey RJ, Lalor E, et al. The utility of endoscopy in the management of patients with gastroesophageal reflux symptoms. *Am J Gastroenterol*. 1998;93:2508-12.
2. Clavé P, González A, Moreno A, López R, Farré A, Cussó X, et al. Endogenous cholecystokinin enhances postprandial gastroesophageal reflux in humans through extrasplanchnic receptors. *Gastroenterology*. 1998;115:597-604.
3. Kuipers EJ, Lundell L, Klinkenberg-Knol EC, Havu N, Festen HP, Liedman B, et al. Atrophic gastritis and *Helicobacter pylori* infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med*. 1996;334:1018-22.
4. Friedman LS. *Helicobacter pylori* and nonulcer dyspepsia [Editorial]. *N Engl J Med*. 1998;339:1928-30.
5. Rockey DC, Koch J, Cello JP, Sanders MP, McQuaid K. Relative frequency of upper gastrointestinal and colonic lesions in patients with positive fecal occult-blood tests. *N Engl J Med*. 1998;339:153-9.
6. McLeod RS, Wolff BG, Steinhart AH, Carryer PW, O'Rourke K, Andrews DF, et al. Risk and significance of endoscopic/radiological evidence of irregular Crohn's disease. *Gastroenterology*. 1997;113:1823-7.
7. Greenberger NJ. Update in gastroenterology. *Ann Intern Med*. 1998;129:309-16.
8. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor α for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med*. 1997;337:1029-35.
9. Yacyshyn BR, Bowen-Yacyshyn MB, Jewell L, Tami JA, Bennett CF, Kisner DL, et al. A placebo-controlled trial of ICAM-1 antisense oligonucleotide in the treatment of Crohn's disease. *Gastroenterology*. 1998;114:1133-42.
10. Fine KD, Lee EL. Efficacy of open-label bismuth subsalicylate for the treatment of microscopic colitis. *Gastroenterology*. 1998;114:29-36.
11. Sharer N, Schwarz M, Malone G, Howarth A, Painter J, Super M, et al. Mutation of cystic fibrosis gene in patients with chronic pancreatitis. *N Engl J Med*. 1998;339:645-52.