

New Scientific Advances in Gastroenterology presented at the 68th Annual Meeting of the American College of Gastroenterology, Baltimore, Maryland, 2003

Children with Constipation Manifest More Toileting Anxiety than Well Kids

Experts Offer Advice for Parents with Reluctant Potty-Trainers

Researchers at the Cleveland Clinic Foundation Department of Pediatric Gastroenterology & Nutrition report that children with functional constipation have significantly more anxiety specific to toileting behavior than well children, without displaying significant general anxiety.

Anxiety specific to toileting behavior is hypothesized to play an important role in the development and maintenance of constipation. Constipation represents the chief complaint in 3 percent of pediatric outpatient visits and 10 to 25 percent of pediatric gastroenterology visits.

For their study, Rita Steffen, M.D., FACP, Tariq Ahmad, M.D. and Gerard Banez, Ph.D. studied 98 children (51 boys and 47 girls) between the ages of 6 and 18. Researchers examined whether children with functional constipation have more defecation anxiety than well children, and also compared constipated children to children with asthma, as a comparison to children with a chronic medical condition. Children participating in this research completed self-report measures of defecation anxiety and general anxiety, while their parents rated their children's defecation anxiety.

By self-report and parent report, children with functional constipation were found to have significantly more anxiety specific to toileting behavior than well children, and by parent report to have more defecation anxiety than a normative group of children with asthma. The researchers observed that children with constipation did not manifest clinically significant general anxiety, but noted that defecation anxiety and general anxiety were positively correlated.

"Constipated kids were not generally anxious overall, but among those with defecation anxiety we saw an increase in general anxiety," said Gerard

Banez, Ph.D., a child psychologist at the Cleveland Clinic Foundation. "It's important to note that we cannot infer any causality, only that those constipated children with greater defecation anxiety also exhibited increased general anxiety."

What Can Parents Do to Help Children with Constipation

According to Dr. Banez, parents of children with chronic constipation should take their children to a pediatrician to rule out any medical causes. Parents should also talk to a pediatrician about defecation anxiety if a child seems to be withholding stool, is tearful at the urge to use the toilet, or manifests vigorous resistance to using the toilet.

Parents should address their children's refusal to toilet by promoting what Dr. Banez calls "positive toilet sitting." Have the child sit on the toilet 3 to 5 times a day for a brief time, starting with as short a period as 30 seconds and gradually increasing to 5 minutes. He notes that it is acceptable during this phase for children to wear underwear or diapers. The goal is to learn to sit on the toilet and relax. Many constipated children are fearful of pain, resulting from a history of painful bowel movements. That fear can be generalized to sitting on the toilet.

Dr. Banez stresses the importance of diet changes to promote a soft, well-formed stool, including dietary fiber and possibly stool softeners.

A consistent toileting routine, on a schedule of 2 to 3 times a day for approximately 5 to 10 minutes, especially after meals, is another important strategy to help constipation in children according to Dr. Banez. Parents might consider offering incentives to constipated children for using the toilet, and reward them for going on their own.

Diet May Play Role in IBS and Dyspepsia

Studies Link Fructose and Fat to IBS Symptoms

Two recent studies attempt to unravel the role that diet plays in gastrointestinal disorders such as irritable bowel syndrome (IBS) and dyspepsia. The preliminary findings suggest that both fructose and fat contribute to

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symptoms of IBS, a disorder affecting about 10 to 15 percent of the American population.

For several years, University of Iowa researchers have been investigating how fructose, the simple sugar found in honey and many fruits, may play an important role in some of the symptoms of IBS, a leading cause of referral to a gastroenterologist. IBS is characterized by abdominal discomfort, bloating, and change in bowel habits (constipation and/or diarrhea).

Although lactose intolerance is well-known, fructose intolerance is just beginning to be recognized. Young K. Choi, M.D., and colleagues from the University of Iowa Hospitals and Clinics (Iowa City, IA) found previously that one-third to one-half of patients with IBS symptoms are fructose intolerant.

“A fructose-restricted diet significantly improved symptoms in patients with IBS and fructose intolerance,” said Dr. Choi. “Fructose intolerance is yet another piece of the IBS puzzle, whose treatment—when adhered to—confers significant benefits.” For this study, the University of Iowa researchers tested 80 patients with suspected IBS and found that 30 were fructose intolerant. Patients were taught about eliminating fructose from their diet, and after one year, 26 were interviewed to assess their symptoms. Only one-half of the patients complied with the fructose-restricted diet.

For those who were compliant, symptoms (such as abdominal pain, bloating, and diarrhea) declined significantly ($P < 0.05$) from their reported symptoms before the diet modification. Also, the prevalence of IBS in this group declined. For the group that did not comply with the diet modification, bowel symptoms stayed the same over the study period. Given the modest number of patients, additional confirming studies would be an important prerequisite to consideration of a modification in general disease management strategies in IBS.

In the second study, Yuri A. Saito, M.D., M.P.H., and colleagues of the Division of Gastroenterology and Hepatology at Mayo Clinic and Foundation (Rochester, MN) attempted to tease out the dietary factors that may explain some of the symptoms of functional gastrointestinal disorders, such as IBS and dyspepsia. Their population-based study provides the framework for establishing whether dietary compo-

nents are the causative factors in the development of symptoms.

The investigators mailed a questionnaire to an age- and gender-stratified random sample of Minnesotans aged 20 to 50 years old. Those who reported IBS or dyspepsia or who claimed no GI symptoms had a physical exam and completed a survey on diet. Of the 221 participants who completed the diet survey, 53 cases and 58 controls were asked to record their diet for one week.

Dr. Saito and colleagues found that those with IBS or dyspepsia reported consuming a significantly higher proportion of fat in their diet (33.0 percent for those with GI disorders, 30.7 percent for controls, $P < 0.05$). No significant differences were found for protein, fiber, iron, calcium, niacin, or vitamins B₁, B₂, B₆, B₁₂, C, D, or E. “Future studies are needed to determine whether fat intake causes gastrointestinal symptoms,” said Dr. Saito.

University of Rochester Conducts Largest Single-Center Study of Living Donor Liver Transplantation

Their Success Beats U.S. National Average

A recent study showed that living donor liver transplantation (LDLT) is associated with a lower rate of serious complications and rejection and may have a slightly higher survival than orthotopic liver transplant, which uses livers from cadavers. This study represents the largest single-center investigation of LDLT in the United States.

Of the 92 patients who underwent LDLT at Rochester, 92 percent survived 6 months, and 86 percent did not experience significant complications. Study authors Bradford Sampson, M.D., Parvez S. Mantry, M.D., and Uma Sundaram, M.D., of the Digestive Diseases Unit at the University of Rochester (Rochester, NY) also found that while the national rate for vascular complications was 9.8 percent, their corresponding rate was only 2.2 percent.

“A critical shortage of cadaveric organs for adults in need of liver transplants has led to the development

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of living donor liver transplantation,” explained Dr. Mantry.

The healthy donor must undergo an operation that takes several hours, and after surgery, the person may have to remain in the hospital for a week or longer. Eventually, the liver regenerates the part that was surgically removed. The recipient also undergoes a lengthy operation; first the diseased liver is removed and then the donor's healthy liver section is transplanted.

African Americans Benefit from Screening Colonoscopy

High Prevalence of Premalignant Polyps Found in Average-Risk Patients

Researchers at Howard University College of Medicine (Washington, D.C.) found a high prevalence of premalignant polyps among their asymptomatic, average-risk African American patients. This study underscores the need for greater diligence for screening this population—to remove polyps before cancer has a chance to develop.

“Colon cancer is the second leading cause of cancer-related death within the United States,” said Duane T. Smoot, M.D., FACP, of the Gastroenterology Section of the Department of Medicine at Howard University College of Medicine. “Recent data have shown a slight increase in the number of deaths related to colorectal cancer in African Americans.”

Dr. Smoot and his colleagues enrolled 100 African American men and women in their study. All were over 50 years old and had not been recently screened for colorectal cancer. They were considered average risk because they did not have a history of colorectal cancer in a first-degree relative, a history of colorectal polyps, or other known colorectal problems. Of the 82 participants who underwent colonoscopy for the study, 26 were found to have either colorectal cancer or premalignant polyps.

Of the 62 polyps removed and examined by the pathologist, two polyps were determined to be malignant, 35 were premalignant, and 25 were benign. In this small study, the distribution of patients with polyps was similar for all age groups.

“This study shows that average-risk African Americans have a relatively high likelihood of colonic adenomas which does not appear to increase with age,” said Dr. Smoot. “These data further support colon cancer screening in this population while patients are in their 50s, utilizing tests that examine the entire colon, such as colonoscopy.”

Study Supports Usefulness of Colonoscopy

Asymptomatic Women Just as Likely as Symptomatic Women to Have Colorectal Cancer

A study reviewing historical colonoscopy results found no statistically significant differences in the rates of cancer or other abnormalities between women who had symptoms of colorectal cancer and those who did not. This study by researchers from the University of Pennsylvania Medical Center points to the importance of colorectal screening for all adults over 50.

Gastroenterologists use the colonoscopy procedure both for colorectal cancer screening (in the absence of symptoms) and for the diagnosis of colorectal abnormalities when a patient presents with problems. The researchers analyzed the clinical findings from 415 women who had a colonoscopy for any reason (either screening or diagnosis).

“Most symptoms are poor predictors for the presence of colonic neoplasia,” said Radhika Srinivasan, M.D., FACP, the lead investigator.

Their retrospective cross-sectional study of women who had a colonoscopy in 2002 found that common symptoms of colorectal cancer, including a change in bowel habits, anemia and/or blood in the stool, did not significantly increase the likelihood that cancer would be found; women without symptoms were just as likely to have cancer.

“Colon cancer can occur without any symptoms,” warns Dr. Srinivasan. “Our study involved women, but both men and women at average risk for colorectal cancer should be screened starting at age 50.”

Colorectal cancer is the second leading cause of cancer deaths in the United States, second only to lung cancer. The ACG recommends that for average-risk

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individuals, colorectal cancer screening tests begin at age 50. The preferred approach is a screening colonoscopy every 10 years, but an alternate strategy consists of a stool test for blood every year and flexible sigmoidoscopy every 3 to 5 years. For high-risk individuals, screening colonoscopy may begin earlier and is performed more frequently. Those at high risk include those with a personal history of colorectal cancer or adenomatous polyps; family history of colorectal cancer; nonhereditary polyposis; or a predisposing condition such as inflammatory bowel disease. (Medicare provides for surveillance colonoscopy no more frequently than once every two years for those at high risk.) For both average- and high-risk individuals, all potential pre-cancerous polyps must be removed.

“More education, awareness, and media focus regarding screening colonoscopy should be directed at both patients and gastroenterologists,” said Prem Chattoo, D.O., of St. Vincent’s Hospital at the Manhattan-New York Medical College. Dr. Chattoo and colleagues selectively polled 133 gastroenterologists at Digestive Disease Week, and they found that most of the gastroenterologists over age 50 had had a screening colonoscopy. Of the doctors who had not undergone colonoscopy, only one had had an alternate strategy (flexible sigmoidoscopy and barium enema).

“Our results demonstrate that 70 percent of the study group [gastroenterologists over age 50] had a screening colonoscopy, compared to approximately 15 percent of patients in the general population over the age of 50,” said Dr. Chattoo. “The study findings suggest that gastroenterologists do practice what they preach.”

Researchers Identify Molecular Alterations in Patients with Irritable Bowel Syndrome

New Research Demonstrates Abnormal Serotonin Signaling in IBS

Novel research shows that alterations in serotonin signaling in the gastrointestinal (GI) tract are present in patients with Irritable Bowel Syndrome (IBS). These data shed light on the alterations in gut motility, secretion and sensation, as well as the clinical manifestations of IBS that include abdominal discomfort or pain, bloating, constipation and/or diarrhea.

The study findings were presented by two lead investigators from the University of Vermont, Peter Moses, M.D., associate professor of Medicine and Director of Clinical Research in the Digestive Diseases, and Gary Mawe, Ph.D., professor of anatomy and neurobiology.

“Serotonin is a critical signaling molecule necessary for normal gut function—when released, it causes gut motility and secretion, and triggers signals to the brain and spinal cord,” said Moses. “Our finding that key elements of serotonin signaling are changed in IBS lends credibility to the notion that IBS is not simply a psychological or social disorder as was once thought, but instead is due to altered gut biochemistry and interactions between the gut and the brain.”

Serotonin (5-HT) is a naturally occurring neurotransmitter and signaling molecule. Ninety-five percent of all serotonin is localized in the GI tract where it plays a key role in the motor, sensory and secretory functions of the gut. For some time, scientists have suspected that alterations in serotonin may contribute to abnormal conditions in the GI tract.

“Now we have a perspective on molecular changes in the intestines of individuals with IBS that we did not have before,” said Mawe. “We identified a significant decrease in the serotonin transporter in cells that form the inner lining of the bowel—the same serotonin transporter that is located in cells in the brain. In the gut, this transporter acts as a sponge to remove serotonin once it is released, and therefore stops its actions. Because the transporter is diminished in IBS, serotonin stays around longer, and this can lead to changes in motility, secretion and sensitivity.”

The study examined tissue obtained from 43 healthy controls and 32 patients with IBS and 22 patients with inflammatory bowel disease (IBD). IBS patients were defined strictly using ROME II diagnostic criteria. Each biopsy was evaluated by five parameters: immunohistochemical staining, histological assessment, serotonin content, serotonin release and the measurement of mRNA encoding. The study also examined the molecular components of serotonin signaling, including the serotonin re-uptake system. Specifically, the investigators measured serotonin content, the endocrine cell

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Obesity and Hepatitis C

A retrospective review was performed of all patients at a single center with chronic hepatitis C, treated with antiviral medications from 1989 to 2000. All patients were classified into one of three groups, according to BMI. A total of 253 patients were treated with either Interferon monotherapy or Interferon in combination with Ribavirin. Patients were excluded if predetermined clinical characteristics were unavailable, using logistic regression, and after adjusting for the examined variable (age, sex, history of alcohol consumption, cirrhosis on pretreatment biopsy and BMI), likelihood ratio tests showed significant differences in response to treatment, according to BMI, genotype, and cirrhosis. Those with genotypes 2 or 3 had odds ratio for success of 11.7, compared with those of genotype 1. Cirrhotic patients had an odds ratio of 0.15, compared with noncirrhotic patients. Obese patients had an odds ratio of 0.23, compared with normal and overweight patients. Hepatic steatosis was not an independent risk factor for response to antiviral treatment.

It was concluded that obesity, only when defined as a BMI greater than 30kg/m² is an independent negative predictor of response to hepatitis C treatment and independent of genotype and cirrhosis. (Bressler BL, Guindi M, Tomlinson G, Heathcote J. "High Body Mass Index is an Independent Risk Factor For Non-Response to Antiviral Treatment in Chronic Hepatitis C." *Hepatology*, 2003; Vol. 38, pp. 639-644.)

Early Viral Response in Hepatitis C Therapy

Retrospective data from a recent international clinical trial, comparing pegylated Interferon Alpha-2B plus Ribavirin with standard Interferon and Ribavirin was evaluated retrospectively to determine whether EVR could predict treatment outcome. Treatment responses in the 511 subjects were randomized to pegylated Interferon Alpha-2B at a dose of 1.5 mg/kg each week and 800 mg per day of oral Ribavirin. The subgroup of patients received pegylated Interferon Alpha-2A at a dose of 1.5mcg per week, and with a dose of Ribavirin that was at least 10.6 mg/kg per day (a so-called weight-based dosing regimen). Also studied for comparison were 505 subjects randomized to standard

Interferon at 3,000,000 units three times per week, plus 1000mg of Ribavirin for a pretreatment weight less than 75 kg., and 1200 mg for a weight of 75 kg or more. All subjects were treated for 48 weeks.

For the accuracy of different degrees of viral inhibition during the early weeks of treatment (early virologic response—EVR), in identifying patients who would not respond to therapy, the best definition of EVR was a reduction in HCV RNA by at least 2 logs after the first 12 weeks of treatment, compared with baseline. Between 69 and 76 percent of patients achieved this threshold, depending on the treatment regimen and SVR occurred in 67 to 80 percent of these patients. Patients who did not receive EVR did not respond to further therapy. If treatment is stopped in patients without EVR, drug costs would have been reduced by more than 20 percent.

It was concluded that patients who failed to achieve EVR will not clear a virus, even if an additional 9 months of therapy is received, and therapy can be confidently discontinued in these cases. (Davis GL, Wong JB, McHutchison JG, et al. "Early Virologic Response to Treatment With PEG Interferon Alpha-2B Plus Ribavirin in Patients With Chronic Hepatitis C." *Hepatology*, 2003; Vol. 38, pp. 645-662.)

6-MP in IBD

The office and hospital records of 410 patients with inflammatory bowel disease treated with 6-MP from 1980 to 1999 were reviewed and all toxicity was recorded. There was a low incidence of early drug-related allergic reactions (3.9%), and pancreatitis (1.2%). Desensitization to either 6-MP or azathioprine was often successful with the same or other drug. Significant leukopenia was observed in 11.5%, sometimes caused purposefully. Infectious complications occurred at different times during treatment with 6-MP in 14%, including pneumonia in 3.9% and herpes zoster in 3%. The author has now established diabetes as a 6-MP related complication. No significant difference in the incidence of neoplasm was seen from earlier studies or from patients not treated with 6-MP.

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number, serotonin release and presence of serotonin transporters (SERT). Serotonin transporters are regulatory molecules that control the activity of serotonin within nerve endings in the GI tract to coordinate motility, visceral sensitivity and intestinal secretion.

In patients with IBS, the study found a significant decrease in serotonin content and significantly higher endocrine cell (EC) populations in patients with IBS compared to controls, while the release of serotonin from EC cells was not significantly different. In terms of the way the body inactivates serotonin signaling, or the serotonin re-uptake system, SERT mRNA and SERT immunoreactivity were markedly reduced. This reduction led to a decrease in the capacity to remove

serotonin from intracellular space once it was released, thus increasing serotonin availability.

The study was sponsored through a research grant from Novartis Pharmaceuticals, maker of Zelnorm (tegaserod maleate) for IBS-C. In addition to Moses and Mawe, members of the study team included Matthew Coates, Christine Mahoney, David Linden, Joanna Sampson and Eric Newton of the University of Vermont; Michael Gershon and Jason Chen of the Department of Anatomy and Cell Biology at Columbia University; Keith Sharkey of the Department of Physiology and Biophysics at the University of Calgary, and Michael Crowell of the Clinical Research Department at Novartis Pharmaceuticals. ■

FROM THE LITERATURE

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Three lymphomas and two leukemias were identified, not greater in incidence than the overall IBD disease population.

It was concluded that the study supported the long-term safety of 6-MP in the management of patients with inflammatory bowel disease. Earlier development of a neoplasm in a patient predisposed, without a change in incidence remains possible. (Warman JI, Korelitz BI, Fleisher MR, Janardhanam R. "Cumulative Experience With Short- and Long-Term Toxicity to 6-Mercaptopurine in the Treatment of Crohn's Disease and Ulcerative Colitis." *Journal of Clinical Gastroenterology*, 2003; Vol. 37 (3), pp. 220-225.)

B₁₂ Treatment on Gastric Emptying With *H. pylori* Infection

Thirty-Four *H. pylori*-positive patients who had low serum levels of B₁₂, but no other factors associated with altered gastric motility and prolonged gastric emptying time were studied. Each patient underwent a

radionuclide gastric emptying study before and after 3-months of B₁₂ replacement therapy. Dyspepsia scores were calculated pre-therapy and post-therapy, using a semiquantitative scale.

The mean gastric emptying time before B₁₂ treatment was significantly longer than after treatment. The mean dyspepsia score was also significantly improved by treatment of the *H. pylori* gastritis.

It was concluded that B₁₂ deficiency appeared to play an important role in the development of gastric dysmotility and its clinical consequences in patients with *H. pylori* gastritis. Replacement therapy will improve gastric emptying in some patients with dyspepsia. (Gumurdulu Y, Serin E, Ozer B, et al. "The Impact of B₁₂ Treatment on Gastric Emptying Time in Patients With *Helicobacter Pylori* Infection." *Journal of Clinical Gastroenterology*, 2003, Vol. 37, (3), pp. 230-233.)

Murray H. Cohen, D.O., editor of "From the Literature" is a member of the Editorial Board of *Practical Gastroenterology*.

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BOOK REVIEWS

An Internist's Illustrated Guide to Gastrointestinal Surgery

Wu GU, Aziz K, and Whalen GF
Humana Press, 2003
ISBN: 1-58829-023-9; \$99.50

Although this hardcover text is geared towards the general internist, it is also an excellent guide for medical residents and gastroenterology fellows. This book covers surgery involving the alimentary tract, from the esophagus to the rectum, liver, biliary tract, and pancreas as well as those including the peritoneum, abdominal aorta and portal venous system. Each chapter reviews epidemiology, history, pathophysiology, evaluation and treatment in a concise manner.

The most helpful sections for internists cover the standard of care for workup of common disorders and possible complications after therapy and also provide clear diagrams that delineate the anatomical changes from surgery. The text is easy to read and the depth of information given on the surgeries is appropriate for general review. Other useful sections for fellows and internists include tables that list indications and contraindications for procedures (for those who will be completing consults and those who will be requesting them).

One chapter that seems particularly relevant to those who practice in the clinic setting is the section on bariatric surgery. This section covers clearly the initial screening criteria prior to referral for the increasingly popularized gastric bypass surgery and banded gastroplasty. Also included is an overview of diagrams, expected results and potential complications.

For those who practice in the general hospital setting, sections I found clinically informative are the chapters on percutaneous enterostomy tubes and pancreatic pseudocyst management. Again, diagrams and descriptions of types of tubes used, indications, con-

traindications, and complications are covered. There is even a small summary of costs at the end of each chapter. In addition to the illustrations, which are extremely helpful, there are intraoperative black and white photographs as well as a handful of CT scan and radiographic images. The images are all labeled and have markings which point out the specific findings. For fellows, the photograph of the different types of esophageal stents, sizes, manufacturers, and diameters provide nice detail.

The only weakness that I could find is that most of the references were drawn from surgical journals in the 1990s. Other references may be necessary for greater depth into medical treatment of disease but this text is a practical and succinct review of GI surgery.

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PEARLS OF GASTROENTEROLOGY

It's More Than Just a Pretty Picture

Answer: The endoscopic photograph shows a large benign gastric ulcer with a PPI tablet (pantoprazole) sitting at the base of the ulcer.