WWW.GIHEPNEWS.COM

VOL. 12 NO. 2 FEBRUARY 2018

GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

COURTESY DR. JAMES COLLINS

The ability of certain *C. difficile* ribotypes to metabolize trehalose has made them epidemic, found Dr. James Collins and coauthors.

Food additive makes *C. difficile* more virulent

BY IAN LACY
Frontline Medical News

The ability *of Clostridium difficile* ribotype 027 (RT027) to metabolize the sugar trehalose, a common food additive, has increased the virulence of *C. difficile* infections, a study showed.

"Out of several carbon sources identified that supported CD2015 growth [epidemic RT027 isolate], we found the disaccharide trehalose increased the growth yield of CD2015 by approximately fivefold, compared with a non-RT027 strain," according to James Collins, PhD, of Baylor University, Houston, and his colleagues. The increased growth of the epidemic strain of *C. difficile* observed by Dr. Collins and his team demonstrates that trehalose is a robust carbon source for the *C. difficile* bacterium.

After Dr. Collins and his team determined that trehalose is an excellent food source for *C. difficile*, they tested whether trehalose metabolism affected disease severity.

In one experiment, mice with humanized microbiota were infected with two strains of RT027, either R20291 (n = 27) or R20291-delta treA (n = 28), a phosphotrehalase enzyme (TreA) deletion mutant that cannot metabolize trehalose. Mice were then given 5 mM

See **Additive** · *page 4*

Cystic fibrosis patients need earlier, more frequent CRC screening

BY MICHELE G. SULLIVAN
Frontline Medical News

Adults with cystic fibrosis (CF) should undergo screening colonoscopy for colorectal cancer every 5 years beginning at age 40 years, unless they have had a solid organ transplant – in which case, screening should begin at age 30 years. For both groups, screening intervals should be shortened to 3 years if any adenomatous polyps are recovered.

The new screening recommendation is 1 of 10 set forth by the Cystic Fibrosis Foundation, in conjunction with the American Gastroenterological Association. The document reflects the significantly increased risk of colorectal cancer among adults with the chronic lung disorder, Denis Hadjiliadis, MD, and his colleagues wrote in the February issue of Gastroenterology. CF patients face up to a 10-fold risk of colorectal cancer, compared with the general population; the risk approaches a 30-fold increase among CF patients who have undergone a lung transplant.

In addition to making recommendations on screening intervals and protocols, the document asks clinicians to reframe their thinking of CF as a respiratory-only disease.

"Physicians should

See **CF** · *page 7*

One in five CD patients have major complications after stopping infliximab

BY AMY KARON
Frontline Medical News

About 20% of patients whose Crohn's disease was stable and remitted on infliximab-antimetabolite combination therapy developed major complications within 7 years after infliximab withdrawal, according to research published in the February issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2017.09.061).

About 70% of patients remained free of both infliximab restart failure and major complications, said Catherine Reenaers,

See **Infliximab** · *page 5*

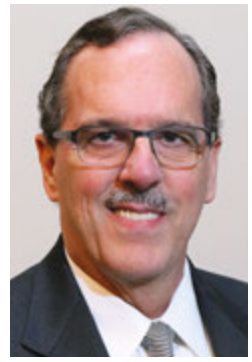
INSIDE

GI & HEPATOLOGY NEWS
151 Fairchild Ave.,
Suite 2,
Plainview, NY 11803-1709

CHANGE SERVICE REQUESTED

Presorted Standard
U.S. Postage
PAID
Permit No. 384
Lebanon Jct. KY

LETTER FROM THE EDITOR: *The New Gastroenterologist* goes digital, In Focus debuts


DR. ALLEN


DR. KATONA

GI & Hepatology News is one of the most widely read publications focused on the gastroenterology community and is the official newspaper of the AGA. *The New Gastroenterologist* is the AGA publication targeted to trainees and early-career physicians. Recognizing the strength of both digital and print communication, the AGA has consolidated its communication media.

John I. Allen, MD, MBA, AGAF
Editor in Chief
GI & Hepatology News

When *The New Gastroenterologist* debuted almost 3 years ago, it provided a mechanism for the AGA to condense and disseminate information in a single publication for those of us in training or in the early stages of our careers. Since then, *The New Gastroenterologist* has become a valuable resource for the AGA community and beyond. It is with great excitement that in 2018 *The New Gastroenterologist* will switch to a primarily digital format. Content will be distributed in quarterly e-newsletters, which will allow for easier distribution via social media. This will allow for the creation of a website archive of past articles that can be easily queried and accessed.

Additionally, *The New Gastroenterologist* will debut an "In Focus" series of concise updates on pertinent topics in our field. These In Focus articles will be published on a quarterly basis in *GI & Hepatology News* and will undoubtedly be practical and informative features that will be of interest to all AGA members, regardless of their career stage. The first In Focus article, which appears in this issue of *GI & Hepatology News*, is written by Nitin K. Ahuja, MD, MS, and James C. Reynolds, MD, AGAF, and provides an enlightening overview of the evaluation and management of chronic constipation.

I hope that everyone enjoys this new format of *The New Gastroenterologist*. As always, if you have any feedback, have interest in contributing, or have ideas that you would like to hear about, please contact me (bryson.katona@uphs.upenn.edu) or Managing Editor Ryan Farrell (rfarrell@gastro.org).

Bryson Katona, MD, PhD
Editor in Chief
The New Gastroenterologist

DDSEP eight
Digestive Diseases Self-Education Program

DDSEP 8 Quick quiz

Q1. Which of the following conditions is associated with hypergastrinemia and elevated gastric pH?
A. MEN-1 syndrome
B. *H. pylori* pangastritis
C. Obstructive mass in the pyloric channel
D. Chronic renal failure
E. Retained antrum status-post Billroth II

Q2. A 76-year-old man presents with 2 days of epigastric abdominal pain radiating to the back accompanied by nausea, vomiting, fevers, and chills. His past medical history is notable for diabetes, hypertension, coronary artery disease, and prescription for clopidogrel and aspirin, as well as atrial fibrillation, for which he is on warfarin. Vital signs at presentation are temperature of 39.1°C, blood pressure of 88/58 mm Hg, and a heart rate of 110 beats per minute. Labs reveal a WBC count of 15,000/mm^3, total bilirubin of 4.0 mg/dL, alkaline phosphatase of 234 IU/L, AST 120 IU/L, ALT 131 IU/L, and an INR of 2.7. An abdominal ultrasound reveals a common bile duct dilated to 1.5 cm.
Following fluid resuscitation and initiation of antibiotics, what is the next most appropriate step?
A. ERCP with sphincterotomy
B. MRCP
C. ERCP with stent placement
D. Continue intravenous antibiotics with no further intervention
E. Percutaneous biliary drain

The answers are on page 26.

WWW.GIHEPNEWS.COM
GI & HEPATOLOGY NEWS
THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

FRONTLINE MEDICAL COMMUNICATIONS

GI & Hepatology News is the official newspaper of the American Gastroenterological Association (AGA) Institute and provides the gastroenterologist with timely and relevant news and commentary about clinical developments and about the impact of health care policy. Content for **GI & Hepatology News** is developed through a partnership of the newspaper's medical board of editors (Editor in Chief and Associate Editors), Frontline Medical Communications Inc. and the AGA Institute Staff. "News from the AGA" is provided exclusively by the AGA, AGA Institute, and AGA Research Foundation. All content is reviewed by the medical board of editors for accuracy, timeliness, and pertinence. To add clarity and context to important developments in the field, select content is reviewed by and commented on by external experts selected by the board of editors.

POSTMASTER Send changes of address (with old mailing label) to GI & Hepatology News, Subscription Service, 151 Fairchild Ave., Suite 2, Plainview, NY 11803-1709.

The AGA Institute headquarters is located at 4930 Del Ray Avenue, Bethesda, MD 20814, ginews@gastro.org.

Editorial Offices 2275 Research Blvd, Suite 400, Rockville, MD 20850, 240-221-2400, fax 240-221-2548

GI & Hepatology News (ISSN 1934-3450) is published monthly for $230.00 per year by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Phone 973-206-3434, fax 973-206-9378

Scan this QR Code to visit gihepnews.com

Frontline Medical Communications Society Partners
VP/Group Publisher; Director, FMC Society Partners Mark Branca
Editor in Chief Mary Jo M. Dales
Executive Editors Denise Fulton, Kathy Scarbeck
Editor Lora T. McGlade
Creative Director Louise A. Koenig
Director, Production/Manufacturing Rebecca Slebodnik
National Account Manager Artie Krivopal, 973-206-2326, cell 973-202-5402, akrivopal@frontlinemedcom.com
Digital Account Manager Rey Valdivia, 973-206-8094, rvaldivia@frontlinemedcom.com
Senior Director of Classified Sales Tim LaPella, 484-921-5001, tlapella@frontlinemedcom.com
Advertising Offices 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609 973-206-3434, fax 973-206-9378

FRONTLINE MEDICAL COMMUNICATIONS

Chairman Stephen Stoneburn
President/CEO Alan J. Imhoff
CFO Douglas E. Grose

President, Digital Douglas E. Grose
Chief Digital Officer Lee Schweizer
Vice President, Digital Publishing Amy Pfeiffer

President, Custom Solutions JoAnn Wahl
Vice President, Custom Programs Carol Nathan
Vice President, Custom Solutions Wendy Raupers

Senior Vice President, Finance Steven J. Resnick
Vice President, Human Resources & Facility Operations Carolyn Caccavelli

Vice President, Marketing & Customer Advocacy Jim McDonough
Vice President, Operations Jim Chicca
Vice President, Sales Mike Guire
Vice President, Society Partners Mark Branca
Circulation Director Jared Sonners
Corporate Director, Research & Communications Lori Raskin
Editor in Chief Mary Jo M. Dales

In affiliation with Global Academy for Medical Education, LLC

Vice President, Medical Education & Conferences Sylvia H. Reitman, MBA
Vice President, Events David J. Small, MBA

#1 MOST PRESCRIBED, BRANDED BOWEL PREP KIT[1]

FIVE-STAR EFF1CACY WITH SUPREP®

Distinctive results in all colon segments

- SUPREP Bowel Prep Kit has been FDA-approved as a split-dose oral regimen[3]
- 98% of patients receiving SUPREP Bowel Prep Kit had "good" or "excellent" bowel cleansing[2*†]
- >90% of patients had no residual stool in all colon segments[2*†]
  - These cleansing results for the cecum included 91% of patients[2*†]

Aligned with Gastrointestinal Quality Improvement Consortium (GIQuIC) performance target of ≥85% quality cleansing for outpatient colonoscopies.[4]

SUPREP® BOWEL PREP KIT
(sodium sulfate, potassium sulfate and magnesium sulfate) Oral Solution

(17.5g/3.13g/1.6g) per 6 ounces

*This clinical trial was not included in the product labeling. †Based on investigator grading.

References: 1. IMS Health, NPA Weekly, May 2017. **2.** Rex DK, DiPalma JA, Rodriguez R, McGowan J, Cleveland M. A randomized clinical study comparing reduced-volume oral sulfate solution with standard 4-liter sulfate-free electrolyte lavage solution as preparation for colonoscopy. *Gastrointest Endosc.* 2010;72(2):328-336. **3.** SUPREP Bowel Prep Kit [package insert]. Braintree, MA: Braintree Laboratories, Inc; 2012. **4.** Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc.* 2015;81(1):31-53.

Braintree LABORATORIES, INC

HH13276AT-U May 2017

Strains spread with trehalose

Additive *from page 1*

of trehalose ad libitum in their drinking water. Researchers observed that the mice infected with R20291-delta treA had much lower mortality rates than the R20291 group (33.3% vs. 78.6%). These findings were then reinforced with a second experiment using mice with humanized microbiota, in which trehalose addition increased mortality in RT027 mice, compared with RT027-infected mice that were not given dietary trehalose.

While Dr. Collins and his team demonstrated the effect of trehalose on *C. difficile* in mice, they also conducted a limited analysis of ileostomy effluent from three human donors. The researchers found that, in two of three samples, treA was strongly induced in CD2015, but not in another ribotype, CD2048. This demonstrates that amounts of trehalose found in food are high enough to be metabolized by certain epidemic strains of *C. difficile* in humans.

Prior to 2000, trehalose use was limited by a relatively high cost of production. A production innovation that utilized a novel enzymatic method brought the price of trehalose to approximately $3 per kilogram, making it a commercially viable food supplement. After being considered "generally recognized as safe" by the U.S. Food and Drug Administration in 2000 and approved for use in Europe, the trehalose concentrations in food skyrocketed from around 2% to 11.25%, and trehalose became widely used in several foods, including ice cream, pasta, and ground beef.

Dr. Collins and his associates said that there is considerable evidence that the widespread use of dietary trehalose has contributed to the spread of epidemic *C. difficile* ribotypes. First, strains RT027 and RT078 have always had the ability to metabolize trehalose, as evidenced by outbreaks of nonepidemic *C. difficile* in the 1980s. But no epidemic outbreaks were reported until after 2003, several years after trehalose was approved by the FDA. Second, RT027 and RT078 are phylogenetically distant, but independently evolved the ability to metabolize low levels of trehalose. Third, increased severity of the RT027 strain, which metabolizes trehalose in mice, is consistent with increased virulence of RT078 and RT027 in human patients.

"On the basis of these observations, we propose that the widespread adoption and use of the disaccharide trehalose in the human diet has played a significant role in the emergence of these epidemic and hypervirulent strains," Dr. Collins and his colleagues wrote in in Nature.

The authors of the study had no relevant financial disclosures to report.

ilacy@frontlinemedcom.com

SOURCE: Collins J et al. Nature. 2018 Jan 3. doi: 10.1038/nature25178.

AGA Resource

The AGA FMT National Registry will allow physicians and patients to report back on outcomes of fecal microbiota transplantation. Learn more at www.gastro.org/FMTRegistry.

FROM THE AGA JOURNALS

Some will relapse

Infliximab *from page 1*

MD, PhD, of Centre Hospitalier Universitaire de Liège (Belgium), and her associates. Significant predictors of major complications included upper gastrointestinal disease at the time of infliximab withdrawal, white blood cell count of at least 5.0 x 10^9 per L, and hemoglobin level under 12.5 g per dL. "Patients with at least two of these factors had a more than 40% risk of major complication in the 7 years following infliximab withdrawal," the researchers reported.

Little is known about long-term outcomes after patients with Crohn's disease withdraw from infliximab. Therefore, Dr. Reenaers and her associates retrospectively studied 102 patients with Crohn's disease who had received infliximab and an antimetabolite (azathioprine, mercaptopurine, or methotrexate) for at least 12 months, had been in steroid-free clinical remission for at least 6 months, and then withdrew from infliximab. Patients were recruited from 19 centers in Belgium and France and were originally part of a prospective cohort study of infliximab withdrawal in Crohn's disease (Gastroenterology. 2012;142[1]:63-70.e5).

About half of patients relapsed and restarted infliximab within 12 months, which is in line with other studies, the researchers noted. Over a median follow-up of 83 months (interquartile range, 71-93 months), 21% (95% confidence interval, 13.1%-30.3%) of patients had no complications, did not restart infliximab, and started no other biologics. In all, 70.2% of patients (95% CI, 60.2%-80.1%) had no major complications and did not fail to respond after restarting infliximab.

Eighteen patients (19%; 95% CI, 10%-27%) developed major complications: 14 who required surgery and 4 who developed new complex perianal lesions. In a multivariable model, the strongest independent predictor of major complications was leukocytosis (hazard ratio, 10.5; 95% CI, 1.3-83; *P* less than .002), followed by upper gastrointestinal disease (HR, 5.8; 95% CI, 1.5-22) and low hemoglobin level (HR, 4.1; 95% CI, 1.5-21.8; *P* less than .01). The 13 patients who lacked these risk factors had no major complications of infliximab withdrawal. Among 72 patients who had at least one risk factor, 16.3% (95% CI, 7%-25%) developed major complications over 7 years. Strikingly, among 17 with at least two risk factors, 43% (95% CI, 17%-69%) developed major complications over 7 years, the researchers noted.

Complications emerged a median of 50 months (interquartile range, 41-73 months) after patients received their last infliximab infusion, highlighting the need for close long-term monitoring even if patients show no signs of early clinical relapse after infliximab withdrawal, the investigators said. "One strength of this cohort was the homogeneity of the population," they stressed. "Most studies of anti–tumor necrosis factor withdrawal after clinical remission were limited by heterogeneous populations, variable lengths of infliximab treatment before discontinuation, and variable use of immunomodulators and corticosteroids. In [our] cohort, the population was homogenous, infliximab withdrawal was standardized, and the disease characteristics at the time of stopping were collected prospectively." Although follow-up times varied, less than 5% of patients were followed for less than 3 years, they noted.

The researchers did not acknowledge external funding sources. Dr. Reenaers disclosed ties to AbbVie, Takeda, MSD, Mundipharma, Hospira, and Ferring.

ginews@gastro.org

SOURCE: Reenaers C et al. Clin Gastro Hepatol. 2018 February (in press).

The option of stopping a biologic agent is an attractive prospect for most Crohn's disease (CD) patients in stable clinical remission. The STORI trial, published in 2012, was among the earliest and select few studies addressing withdrawal of biologic therapy in CD among patients in sustained clinical remission with combination therapy (infliximab and thiopurine/methotrexate) for at least 6 months. Almost 50% of patients experienced disease relapse within a year of stopping infliximab in the trial.

Reenaers et al. recently published long-term follow-up of the original STORI cohort. After a median follow-up time of 7 years; four out of five patients previously in clinical remission with combination therapy experienced worsening disease activity following withdrawal of infliximab. While the majority (70%) were able to resume infliximab and recapture disease response without any untoward adverse effects; one in five patients experienced major disease-related complications such as complex perianal disease or need for abdominal surgery. Upper GI tract involvement, high white blood cell count, and low hemoglobin concentration were associated with increased likelihood of a major complication. Notably, median time to a major complication was almost 4 years.

These results are similar to long-term relapse rates reported in other studies of withdrawal of therapy in CD. While biomarkers such as C-reactive protein, fecal calprotectin, along with endoscopic disease activity are reliable predictors of short-term relapse; clinical factors such as family history of CD, disease extent, stricturing or penetrating disease, and cigarette smoking are more relevant predictors of long-term disease activity. It is important to consider both types of predictors when considering withdrawal of therapy in CD.

Lastly, while the majority of patients who relapse following withdrawal of a biologic agent will do so within a year or 2, a subset may not experience disease-related complications for several years – underscoring the need for long-term follow-up.

Manreet Kaur, MD, is assistant professor in the division of gastroenterology and hepatology; medical director, Inflammatory Bowel Disease Center; and medical director, faculty group practice, Baylor College of Medicine, Houston. She is on the advisory boards of Pfizer and Salix and the speaker's bureaus of Takeda and Abbvie.

Gluten-free diet tied to heavy metal bioaccumulation

BY AMY KARON
Frontline Medical News

A gluten-free diet (GFD) was associated with significantly elevated blood levels of mercury, lead, and cadmium and with significantly increased urinary levels of arsenic in a large cross-sectional population-based survey study.

After researchers controlled for demographic characteristics, "levels of all heavy metals remained significantly higher in persons following a gluten-free diet," compared with those who did not, Stephanie L. Raehsler, MPH, of Mayo Clinic in Rochester, Minn., wrote with her associates in an article published in the February issue of Clinical Gastroenterology and Hepatology.

The purported (unproven) benefits of a GFD have propelled them into the mainstream outside the settings of celiac disease, dermatitis herpetiformis, and wheat allergy. GFDs have been linked to nutritional deficits of iron, ferritin, zinc, and fiber, to increased consumption of sugar, fats, and salt, and to bioaccumulation of mercury, the investigators noted.

High intake of rice, a staple of many GFDs, also has been associated with elevated urinary excretion of arsenic (PLoS One. 2014 Sep 8;9[9]:e104768). To further characterize these relationships, the researchers analyzed data for 2009 through 2012 from 11,354 participants in the National Health and Nutrition Examination Survey (NHANES). Blood levels of lead, mercury, and cadmium were available from 115 participants who reported following a GFD, and data on urinary arsenic levels were available from 32 such individuals.

In the overall study group, blood mercury levels averaged 1.37 mcg/L (95% confidence interval, 1.02-1.85 mcg/L) among persons on a GFD and 0.93 mcg/L (95% CI, 0.86-1.0 mcg/L) in persons not on a GFD (*P* = .008). Individuals on a GFD had significantly higher total blood levels of lead (1.42 vs. 1.13 mcg/L; *P* = .007) and cadmi-

Continued on following page

FROM THE AGA JOURNALS

Study eyed natural history of branch-duct IPMNs

BY AMY KARON
Frontline Medical News

Branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs) grew at a median annual rate of 0.8 mm in a retrospective study of 1,369 patients.

While most of these cysts were "indolent and dormant," some grew rapidly and developed "other worrisome features," reported Youngmin Han of Seoul (South Korea) National University reported and associates in the February issue of Gastroenterology. Therefore, clinicians should plan follow-up surveillance based on initial cyst size and growth rate, they concluded.

Based on their findings, the researchers recommended surgery for young, fit, asymptomatic patients who have BD-IPMNs with a diameter of least 30 mm or with thickened cyst walls or those who have a main pancreatic duct measuring 5-9 mm. Surgery also should be considered when patients have lymphadenopathy, high tumor marker levels, or an abrupt change in pancreatic duct caliber with distal pancreatic atrophy or a rapidly growing cyst, they said.

For asymptomatic patients

Continued on following page

Continued from previous page

um (0.42 vs. 0.34; *P* = .03), and they had significantly higher urinary levels of total arsenic (15.2 vs. 8.4 mcg/L; *P* = .003). These significant differences persisted after researchers controlled for age, sex, race, and smoking status.

Among 101 individuals on GFDs who had no laboratory or clinical indication of celiac disease, blood levels of mercury were significantly elevated, compared with those not on a GFD (1.40 vs. 0.93 mcg/L; *P* = .02), as were blood lead concentrations (1.44 vs. 1.13 mcg/L; *P* = .01) and urinary arsenic levels (14.7 vs. 8.3 mcg/L; *P* = .01). Blood cadmium levels also were higher (0.42 vs. 0.34 mcg/L), but this difference was not significant (*P* = .06).

Individuals who reported eating fish or shellfish in the past month had higher blood mercury levels than those who did not, regardless of whether they were on a GFD. However, only two individuals in the study exceeded the toxicity threshold for mercury and neither was on a GFD, the researchers said. For most individuals on a GFD, levels of all heavy metals except urinary arsenic stayed under the recognized limits for toxicity, they noted.

The number of respondents following a GFD was small, but the investigators followed NHANES recommendations on sampling weights and sample design variables. Also, although the NHANES included only one question on GFDs, trained interviewers were used to help minimize bias. "Studies are needed to determine the long-term effects of accumulation of these elements in persons on a GFD," the researchers concluded.

The Centers for Disease Control and Prevention provided partial funding. The researchers reported no conflicts of interest.

ginews@gastro.org

SOURCE: Raehsler S et al. Clin Gastro Hepatol. 2018 (in press).

FROM THE AGA JOURNALS

Not just a pulmonary disease

CF *from page 1*

recognize that CF is a colon cancer syndrome," wrote Dr. Hadjiliadis, director of the Adult Cystic Fibrosis Program at the University of Pennsylvania, Philadelphia, and his coauthors.

The increased colorectal cancer risk has become increasingly evident as CF patients live longer, Dr. Hadjiliadis and the panel wrote.

"The current median predicted survival is 41 years, and persons born in 2015 have an estimated average life expectancy of 45 years. The increasing longevity of adults with CF puts them at risk for other diseases, such as gastrointestinal cancer."

In addition to the normal age-related risk, however, CF patients seem to have an elevated risk profile unique to the disease. The underlying causes have not been fully elucidated but may have to do with mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), which are responsible for the excess thickened mucosal secretions that characterize CF. CFTR also is a tumor-suppressor gene in the intestinal tract of mice, and is important in gastrointestinal epithelial homeostasis. "Absence of CFTR is associated with dysregulation of the immune response, intestinal stem cells, and growth signaling regulators," the authors noted.

In response to this observed increased risk of colorectal cancers among CF patients, the Cystic Fibrosis Foundation convened an 18-member task force to review the extant literature and compile colorectal cancer screening recommendations for CF patients who show no signs of such malignancies. The team reviewed 1,159 articles and based its findings on the 50 most relevant. The papers comprised observational studies, case-control studies, and case reports.

The American Gastroenterological Association reviewed and approved all of the recommendations:

- Screening decisions should be a collaborative process between the CF patient and clinician, taking into account comorbidities, safety, and quality of life. This should include a discussion of expected lifespan; patients with limited lifespan won't benefit from screening for a slow-growing cancer. Patients should also consider that the colonoscopy prep for CF patients is somewhat more complex than for non-CF patients. "Given these complexities, the task force agreed that individuals with CF and their providers should … carefully assess the risks and benefits of CRC screening and its impact on the health and quality of life for the adult with CF."
- The decision team should include an endoscopist. An endoscopist with CF training is preferred, but the panel noted these specialists are rare.
- Colonoscopy is the preferred method of screening for CF patients, since it can both detect and remove polyps. "This is one of the main reasons why colonoscopy is the screening procedure of choice for other high-risk groups," the panel noted.
- There is insufficient evidence to recommend alternative screening methods in CF patients, including CT, colonography, stool-based tests, or flexible sigmoidoscopy.
- In CF patients without signs of CRC, screening should commence at 40 years and be repeated every 5 years as long as the results are negative.
- Any CF patient who has had adenomatous polyps on a screening colonoscopy should have a repeat colonoscopy within 3 years, unless clinical findings support more frequent screening.
- For any adult CF patient older than 30 years who has undergone a solid organ transplant, screening colonoscopy should commence within 2 years of transplantation. "Although the absolute risk of CRC in individuals with CF is extremely low for patients younger than 30 years, the risk … greatly increases after lung transplantation," to 25-30 times the age-adjusted baseline, the panel wrote. "Increased post-transplantation survival means that many transplant patients will enter older age groups where there is an increased risk of cancer." Screening should be performed after recovery and within 2 years, unless there was a negative colonoscopy in the 5 years before transplant.
- Thereafter, patients who have had a solid organ transplant should undergo colonoscopy every 5 years, based on their life expectancy. "In cases where the expected survival time is limited (less than 10 years), screening should not be performed. For adults appropriately selected, lung transplantation usually increases survival probability. Therefore, a lung transplantation candidate with a short life expectancy is likely to become a screening candidate before and after transplantation at the appropriate ages described here, because the potential survival increases to approximately 10 years."
- Colonoscopy should be repeated every 3 years in CF patients with transplants with a history of adenomatous polyps. This interval may be as short as 1 year for patients with high-risk, large, or multiple polyps.
- CF patients should undergo more intense bowel prep for colonoscopy, with three-four washes of a minimum of 1 liter of purgative per wash; the last wash should occur 4-6 hours before the procedure. Split-prep regimens (several smaller-volume washes) are better than a single larger-volume wash. The panel suggested a sample CF-specific regimen available from the Minnesota Cystic Fibrosis Center.

The new document reflects expert consensus on the currently available data, the panel said. As more data emerge, the recommendations might change.

"It is possible that different subpopulations will need more or less frequent schedules for rescreening and surveillance. Our recommendations are making an effort to balance the risk of missing advanced colorectal cancer and minimizing the burden and risk of too frequent examinations."

None of the panel members had any financial disclosures.

msullivan@frontlinemedcom.com

SOURCE: Hadjiliadis D et al. Gastroenterology. 2017 Dec 28. doi: org/10.1053/j.gastro.2017.12.012.

Continued from previous page

whose cysts are under 10 mm and who do not have worrisome features, they recommended follow-up with CT or MRI at 6 months and then every 2 years after that. Cysts of 10-20 mm should be imaged at 6 months, at 12 months, and then every 1.5-2 years after that, they said. Patients with cyst diameters greater than 20 mm "should undergo MRI or CT or EUS [endoscopic ultrasound] every 6 months for 1 year and then annually thereafter, until the cyst size and features become stable," they added. Patients whose cysts have a diameter of 30 mm or greater "should be closely monitored with MRI or CT or EUS every 6 months. Surgical resection can be considered in younger patients or those with other combined worrisome features."

To characterize the natural history of BD-IPMN, the investigators evaluated clinical and imaging data collected between 2001 and 2016 from patients with classical features of BD-IPMN. Each patient included in the study provided 3 or more years of CT, MRI, EUS, and endoscopic retrograde cholangiopancreatography data. The researchers used regression models to estimate changes in sizes of cysts and main pancreatic ducts.

Median follow-up time was 61 months (range, 36-189 months). Cyst diameter averaged 12.8 mm (standard deviation, 6.5 mm) at baseline and 17 mm (SD, 9.2 mm) at final measurement. Larger baseline diameter was associated with faster growth (P = .046): Cysts measuring less than 10 mm at baseline grew at a median annual rate of 0.8 mm (SD, 1.1 mm), while those measuring at least 30 mm grew at a median annual rate of 1.2 mm (SD, 2.1 mm).

Worrisome features were present in 59 patients at baseline and emerged in another 150 patients during follow-up. At baseline, only 2.3% of cysts exceeded 30 mm in diameter, but 8.0% did at final measurement. Cyst wall thickening was found in 0.5% of patients at baseline and 3.7% of patients at final measurement. Main pancreatic ducts measured 5-9 mm in 1.9% of patients at baseline and in 5.6% of patients at final measurement. Additionally, the prevalence of mural nodules rose from 0.4% at baseline to 3.1% at final measurement.

Main pancreatic ducts averaged 1.8 mm (SD, 1.0 mm) at baseline and 2.4 mm (SD, 1.8 mm) at final measurement. Compared with the values seen with smaller cysts, larger baseline

Continued on page 14

FROM THE AGA JOURNALS

Continued from page 7

cyst diameter correlated significantly with larger main pancreatic ducts, more cases of cyst wall thickening, and more cases with mural nodules (*P* less than .001 for all comparisons).

The study was funded by a grant from Korean Health Technology R&D Project of Ministry of Health and Welfare, Republic of Korea. The investigators reported having no conflicts of interest.

ginews@gastro.org

SOURCE: Han Y et al. Gastroenterology. 2018. doi: 10.1053/j.gastro.2017.10.013.

The appropriate management of branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs), a precursor cystic lesion to pancreatic cancer, has been a controversial issue since their initial description in 1982. Current national and international guidelines are primarily based on surgical series with potential selection bias and on observational studies with short surveillance periods. Consequently, there is limited information on the natural history and, more importantly, the malignant potential of BD-IPMNs.

DR. SINGHI

The study by Youngmin Han and colleagues represents a comprehensive analysis of over 1,000 patients, each with at least 3 years of follow-up for a suspected BD-IPMN. In addition, the authors identified an optimal screening method for patients based on cyst size. Their data largely validates prior reports.

However, as the authors note, limitations of their study include its retrospective design and validation of their screening protocol. Moreover, several lingering questions remain for patients with BD-IPMNs: What is the best method of measuring a BD-IPMN (for example, CT, MRI, or endoscopic ultrasound)? How long should surveillance continue? And what is the role for cytopathology and ancillary studies, such as carcinoembryonic antigen testing, and testing for other pancreatic cyst biomarkers? Indeed, further studies are needed to identify an optimal treatment algorithm, and, with the increasingly frequent detection of pancreatic cysts, a cost-effective approach to the evaluation of patients with BD-IPMNs.

Aatur D. Singhi, MD, PhD, is in the division of anatomic pathology in the department of pathology at the University of Pittsburgh Medical Center. He has no conflicts of interest.

VIP an unwelcome contributor to eosinophilic esophagitis

BY NEIL OSTERWEIL
Frontline Medical News

Vasoactive intestinal peptide (VIP) appears to play an important role in the pathology of eosinophilic esophagitis (EoE) by recruiting mast cells and eosinophils that contribute to EoE's hallmark symptoms of dysphagia and esophageal dysmotility, investigators reported in the February issue of Cellular and Molecular Gastroenterology and Hepatology (doi: 10.1016/j.jcmgh.2017.09.006).

Blocking one of three VIP receptors – chemoattractant receptor-homologous molecule expressed on Th2 (CRTH2) – could reduce eosinophil infiltration and mast cell numbers in the esophagus, wrote Alok K. Verma, PhD, a postodoctoral fellow at Tulane University in New Orleans, and his colleagues.

"We suggest that inhibiting the VIP–CRTH2 axis may ameliorate the dysphagia, stricture, and motility dysfunction of chronic EoE," they wrote in a research letter to Cellular and Molecular Gastroenterology and Hepatology.

They hypothesized that VIP may be a chemoattractant that draws eosinophils into perineural areas of the muscular mucosa of the esophagus.

To test this idea, they looked at VIP expression in samples from patients both with and without EoE and found that VIP expression was low among controls (without EoE); they also found that eosinophils were seen to accumulate near VIP-expressing nerve cells in biopsy samples from patients with EoE.

When they performed in vitro studies of VIP binding and immunologic functions, they found that eosinophils primarily express the CRTH2 receptor rather than the vasoactive intestinal peptide receptor 1 (VPAC-1) or VPAC-2. They also demonstrated that VIP's effects on eosinophil motility was similar to that of eotaxin and that, when they pretreated eosinophils with a CRTH2 inhibitor, esoinophil motility was hampered.

The investigators next looked at biopsy specimens from patients with EoE and found that eosinophils that express CRTH2 accumulated in the epithelial mucosa.

To see whether VIP and its interaction with the CRTH2 receptor might play a role in mast cell recruitment, they performed immunofluorescence analyses and confirmed the presence of the CRTH2 receptor on tryptase-positive mast cells in the esophageal mucosa of patients with EoE.

"These findings suggest that, similar to eosinophils, mast cells accumulate via interaction of the CRTH2 receptor with neurally derived VIP," they wrote.

Finally, to see whether a reduction in peak eosinophil levels in patients with EoE with a CRTH2 antagonist – as seen in prior studies – could also ameliorate the negative effects of mast cells on esophageal function, they looked at the effects of CRTH2 inhibition in a mouse model of human EoE.

They found that, in the mice treated with a CRTH2 blocker, each segment of the esophagus had significant reductions in both eosinophil infiltration and mast cell numbers (*P* less than .05 for each).

The work was supported in part by grants from the National Institutes of Health and the Tulane Edward G. Schlieder Educational Foundation. Senior author Anil Mishra, PhD, disclosed serving as a consultant for Axcan Pharma, Aptalis, Elite Biosciences, Calypso Biotech SA, and Enumeral Biomedical. The remaining authors disclosed no conflicts of interest.

ginews@gastro.org

SOURCE: Verma AK et al. Cell Mol Gastroenterol Hepatol. 2018;5[1]:99-100.e7.

The rapid increase in the incidence of pediatric and adult EoE draws attention to the importance of studying the mechanisms underlying this condition. The lack of preventive or curative therapies for EoE further underscores the importance of research that addresses gaps in our understanding of how eosinophilic inflammation of the esophagus is regulated on the molecular and cellular level. EoE is classified as an allergic immune disorder of the gastrointestinal tract and is characterized by eosinophil-rich, chronic Th2-type inflammation of the esophagus.

In this publication, the laboratory of Anil Mishra, PhD, showed that VIP serves as a potent chemoattractant for eosinophils and promotes accumulation of these innate immune cells adjacent to nerve cells in the muscular mucosa. Increased VIP expression was documented in EoE patients when compared to controls, and the authors identified the chemoattractant receptor homologous molecule expressed on Th2 lymphocytes (CRTH2) as a main binding receptor for VIP. Interestingly, CRTH2 was not only found to be expressed on eosinophils but also on tissue mast cells – another innate immune cell type that significantly contributes to the inflammatory tissue infiltrate in EoE patients. Based on the human findings, the authors tested whether VIP plays a major role in recruiting eosinophils and mast cells to the inflamed esophagus and whether CRTH2 blockade can modulate experimental EoE. Indeed, EoE pathology improved in animals that were treated with a CRTH2 antagonist.

These observations suggest that inhibiting the VIP-CRTH2 axis may serve as a therapeutic intervention pathway to ameliorate innate tissue inflammation in EoE patients.

Edda Fiebiger, PhD, is in the department of pediatrics in the division of gastroenterology, hepatology and nutrition at Boston Children's Hospital, as well as in the department of medicine at Harvard Medical School, also in Boston. She had no disclosures.

For first-line constipation therapy, stick with the leader

The AGA recommends PEG laxatives (like MiraLAX) as a first-line constipation treatment[1]

- ✔ 96% patient satisfaction rate*
- ✔ #1 GI-recommended laxative for over 10 years

Start with MiraLAX for proven relief of occasional constipation.

MiraLAX®
Polyethylene Glycol 3350, Powder for Solution, Osmotic Laxative

Doctor recommended, patient approved

*Survey of 300 consumers, 2017.

Use as directed on product labeling or as directed by your doctor.

Reference: 1. Clinical decision support tools. American Gastroenterological Association website. http://campaigns.gastro.org/algorithms/constipation/index.html. Accessed May 12, 2017.

Tough patient cases from 2017

AGA's member-only online networking platform, the AGA Community, was the hub for clinical case scenarios in 2017. About 100 deidentified patient cases were submitted to the forum, generating over 475 private and public responses from your peers.

Here are summaries of the three cases that sparked the most discussion among AGA members. You can view all discussions in the forum at community.gastro.org/discussions.

#3 "Esophageal hyperkeratosis" (February 2017)

Patient scenario: Patient was having dysphagia. EGD showed circumferential thickening of esophageal lining in the lower half of the esophagus causing partial obstruction; lumen diameter was 7 mm (scope was able to pass with mild resistance). Human papillomavirus (HPV) stain was negative. Multiple biopsies were negative for malignancy, so the practice did not recommend esophagectomy and believed the symptoms were consistent with hyperkeratosis of esophagus. Endoscopic cryotherapy was being considered.

Biopsies showed mild chronic inflammation, duodenitis, and negative for *H. pylori*. The patient was started on a proton pump inhibitor (PPI). One month later, patient reported early satiety, a 40-pound weight loss over last few months, nausea and vomiting, with minimal improvement while using the PPI. A CT scan of the abdomen and pelvis showed diffuse thickening of the stomach, but was otherwise unremarkable.

Question: Has anyone come across a case like this?

#2 Thickened stomach (May 2017)

Patient scenario: A 74-year-old male presented early satiety, anemia, and dyspepsia. EGD showed diffuse moderate erythema of the stomach sparing the antrum, and two small superficial duodenal ulcers. Biopsies showed mild chronic inflammation, duodenitis, and negative for *Helicobacter pylori*. The patient was started on a proton pump inhibitor (PPI).

One month later, patient reported early satiety, a 40-pound weight loss over last few months, nausea and vomiting, with minimal improvement while using the PPI. A CT scan of the abdomen and pelvis showed diffuse thickening of the stomach, but was otherwise unremarkable.

One month after that, a repeated EGD showed moderate erythema with enlarged gastric folds, cobblestone of mucosa, again all sparing the antrum. The colonoscopy results were unremarkable. Gastric biopsies showed mild chronic inflammation. Endoscopic ultrasound showed a thickened gastric wall to 14 mm (normal 5 mm) and fine-needle aspiration showed normal gastric foveolar epithelium. The patient received a PEG-J tube to maintain nutrition, and then had a laparoscopic-assisted full-thickness gastric biopsy, which showed benign hypertrophic gastric smooth muscle tissue.

Serum protein electrophoresis and urine protein electrophoresis test results were normal, with total IgG and IgA normal, total IgM low at 31 (normal 60-265), albumin low, other proteins normal, and immunofixation negative. Prealbumin was low at 5 (normal 15-45). Albumin initially normal and over a couple of days low at 2.6 (normal 3.4-5.0). Total protein initially

Continued on following page

Insurance barriers should not hinder step therapy treatment for IBD

As part of Crohn's and Colitis Awareness Week 2017 (Dec. 1-7), AGA participated in a congressional briefing sponsored by Takeda and the California Life Sciences Association highlighting advances in inflammatory bowel disease (IBD) therapies, as well as the barriers that patients face in receiving proper treatment for managing their disease.

Physician perspective

Michael Weinstein, MD, representing AGA and the Digestive Health Physicians Association, discussed how treatment options have changed considerably since he began practicing in the 1980s when the only treatment options were immunosuppressive drugs or high-dose steroids that led to dangerous side effects. He highlighted the burden that physicians face with prior authorization practices, especially step therapy in which a patient is required to fail several therapies before being granted coverage to the preferred, physician-prescribed therapy. These insurance protocols can have dire effects on patient care and can be very disruptive to patients who may be so ill that they cannot work or go to school. Dr. Weinstein stated that the burden step therapy places on his practice requires him to have a full-time employee just to navigate the various insurance policies. Many small practices do not have the resources to handle these burdens.

Patient perspective

Members of Congress and congressional staff heard compelling testimony from Kate Detwiler, an IBD patient who spoke of her family history of IBD, her experience with the disease, and how disruptive it has been to find the best provider and treatments to manage her disease. She and Dr. Weinstein both stressed the financial burdens that the disease puts on families and how limiting it can be to patients who are starting out in their careers or school.

Legislator perspective

Rep. Brad Weinstrup, R-Ohio, and Rep. Raul Ruiz, D-Calif., addressed the briefing as the lead sponsors of HR 2077, the Restoring Patient's Voice Act, which would provide patients and providers with a clear, equitable, and transparent appeals process when subject to step therapy protocols. Both Rep. Wenstrup and Rep. Ruiz are physicians and have seen the real-life consequences of these policies and their impact on patient care. Both representatives stressed that this is a bipartisan, commonsense solution to ensuring that patients have access to the care that they need when they need it.

AGA continues to advocate for support and passage of HR 2077 and thanks those members who have contacted their members of Congress to request their support. If you haven't already, please call on your legislator to support this legislation. We will continue to work to garner additional support for the bill in this Congress.

ginews@gastro.org

Registration open for DDW® 2018 and 2018 AGA Postgraduate Course

Digestive Disease Week® (DDW), taking place in Washington, D.C., June 2-5, is the gold standard digestive disease meeting. Attend to learn monumental developments in science and medicine, meet leaders in the field, network with colleagues, and attain practical takeaways that you can implement in your career. Visit www.ddw.org to register, and for general meeting information, details about the host city, and much more.

On the DDW website, you can also register for the AGA Postgraduate Course taking place during DDW, June 2-3. The 2018 AGA Postgraduate Course will provide a comprehensive look at the latest medical, surgical, and technological advances over the past 12 months that aim to keep you up to date in a field that is rapidly changing. Each presenter will turn abstract ideas into concrete action items that you can immediately implement in your practice. At the end of the course, the take-home points will be compiled and distributed with the eSyllabus.

ginews@gastro.org

Continued from previous page

normal and over a couple of days was low at 6.3 (normal 6.8-8.8). Gastrin level was insignificant on the PPI, in the 400s. Zollinger Ellison gastrin not impressive, and the patient is HIV negative.

Question: With a negative biopsy and other test results, Menetrier's, malignancy, sarcoidosis, eosinophilic gastroenteritis, and amyloidosis can be ruled out. What could the diagnosis be?

#1 IBD and prior hep B (July 2017)

Patient scenario: A 53-year-old male diagnosed with ulcerative colitis (UC) at outside hospital after presenting with abdominal pain, perforation of sigmoid colon. He underwent total colectomy with ileostomy, which showed he has remnant rectum, and the path of colon showed UC with sigmoid stricture. There is no malignancy or dysplasia, and the terminal ileum included in the resection was normal. He had complicated post-op course with enterocutaneous fistula.

He underwent takedown of ileostomy, small bowel resection and ileostomy revision. Path showed segmental small bowel showing viable mucosa with acute serositis and serial adhesions. Ileal mucosa was normal. Rectum has inflammation, and he has symptoms of mucus, urgency, and blood. He had rectal burning and did not tolerate CANASA® suppository. He did not seem to improve with hydrocortisone suppository either.

In trying to decipher next treatment step, hepatitis panel was done, which showed positive hepatitis B core antibody (IgM). Hepatitis B viral load was undetectable. Hepatitis B surface antibody test (HBsAb) quantitative was 6 (not quite the range for immunity of greater than 10). Hepatitis B "e" antigen (HBeAg) negative and hepatitis B "e" antibody (HBeAb) positive. This patient's hep B core total was positive and hep B surface antigen was negative.

Question: How would you treat this patient? Would you use Imuran?

Share your difficult patient case for the GI community to help you solve at community.gastro.org/quickpost.

ginews@gastro.org

Support GI research through the AGA Research Foundation

The way we diagnose and treat patients is thanks to years of research. Decades of research and discoveries by dedicated investigators have revolutionized the care of many digestive disease patients. As the charitable arm of the American Gastroenterological Association (AGA), the AGA Research Foundation contributes to this tradition of discovery.

DR. LYNCH

Federal research funding is at risk. Promising early-stage investigators find it increasingly difficult to secure funding and many leave the field because they are unable to sustain a research career. The foundation provides a key source of funding at a critical juncture in a young investigator's career.

Your tax-deductible donation will make a critical difference in retaining talented GI scientists, like Kristle Lynch, MD, 2017 AGA–June and Donald O. Castell, MD, Esophageal Clinical Research Award Recipient, whose research will impact the future care of patients.

"As a clinical researcher, funding for investigation is critical in scientific breakthroughs to promote more efficient and robust patient care. My project will provide novel insights into the role of distensibility in the treatment of patients with esophageal eosinophilia, potentially resulting in more efficient treatment selection and disease management."

Join others in donating to the AGA Research Foundation to help protect the next generation of investigators. Make your gift at www.gastro.org/donateonline.

ginews@gastro.org

Metabolic/bariatric surgery reduces CVD risk in teens

BY IAN LACY
Frontline Medical News

Weight loss caused by metabolic and bariatric surgery (MBS) independently predicts the normalization of dyslipidemia, elevated blood pressure, hyperinsulinemia, diabetes, and elevated high-sensitivity C-reactive protein (hs-CRP) in severely obese adolescents, according to results of a longitudinal, multicenter prospective study.

In the study of 242 severely obese adolescents undergoing MBS between Feb. 28, 2007, and Dec. 30, 2011, Marc Michalsky, MD, of Nationwide Children's Hospital, Columbus, Ohio, and his colleagues found that, with every 10% increase in weight loss, patients were 24%, 11%, 14%, 13%, and 19% more likely to resolve dyslipidemia, elevated blood pressure, hyperinsulinemia, diabetes, and elevated hs-CRP, respectively.


MOODBOARD/THINKSTOCK

'The identification of specific predictors of CVD-RF [cardiovascular disease risk factors] normalization and/or remission on the basis of sex, race, preoperative BMI, and age at surgery may serve to improve future study design and insights regarding the optimization of treatment strategies.'

Lower body mass index levels were linked with significantly lower blood pressures, compared with the higher BMI scores (BMI less than 50 in kg/m^2, 30% vs. BMI greater than or equal to 60, 63%; *P* less than .001). At a 3-year follow-up, the difference between blood pressure numbers was almost indistinguishable between low and high BMI groups (15% vs. 18%).

One of the most important facets of this study is the predictive nature of different patient risk factors on the future remission of cardiovascular disease symptoms.

For example, "the evidence suggests that better long-term outcomes may be anticipated among individuals undergoing MBS at lower BMI levels (i.e., less than 50)," they reported in the journal Pediatrics. "Increasing age at the time of MBS was associated with a reduced likelihood of dyslipidemia remission and normalization of hs-CRP," which was true even in the narrow age range of this group of adolescents.

"The identification of specific predictors of CVD-RF [cardiovascular disease risk factors] normalization and/or remission on the basis of sex, race, preoperative BMI, and age at surgery may serve to improve future study design and insights regarding the optimization of treatment strategies," wrote Dr. Michalsky and his colleagues. "Collectively, these data demonstrate a reduction in the risk for development of CVD in adulthood and offer additional, compelling support for MBS in adolescents."

Dr. Inge has worked as a consultant for Standard Bariatrics, UpToDate, and Independent Medical Expert Consulting Services; all of these companies are unrelated to this research. John B. Dixon, PhD, has received support for his research through a National Health and Medical Research Council research fellowship. Anita Courcoulas, MD, has received grants from various health care groups and companies. All other authors had no relevant financial disclosures. The study was funded by a variety of institutional grants and the National Institutes of Health.

ilacy@frontlinemedcom.com

SOURCE: Michalsky M et al. Pediatrics. 2018 Jan 8. doi: 10.1542/peds.2017-2485.

AGA Resource
GIs are uniquely positioned to lead a care team to help patients with obesity achieve a healthy weight. The AGA Obesity Practice Guide provides a comprehensive, multidisciplinary process to personalize innovative obesity care for safe and effective weight management.

Bariatric surgery comes with some risk of complications

BY HEIDI SPLETE
Frontline Medical News

Bariatric surgery has been demonstrated to improve a host of obesity-related comorbidities, but the operation carries a risk of complications that should be acknowledged by clinicians and understood by patients, a large cohort study has shown.

Gunn Signe Jakobsen, MD, of Vestfold Hospital Trust, Tønsberg, Norway, and her colleagues wrote in an article published in JAMA, "Few studies report long-term complication rates. ... No large-scale clinical practice–based study has compared the long-term association of bariatric surgery and specialized medical obesity treatment with obesity-related somatic and mental comorbidities, nor the irrespective complication rates."

The investigators compared outcomes from 932 patients who underwent bariatric surgery and 956 who underwent specialized medical treatment that involved either individual or group lifestyle intervention programs, both outpatient and at a center. The study population included 1,249 women and 639 men with an average age of 44 years and an average baseline body mass index of 44 kg/m^2.

The surgery patients were more likely than the medical treatment patients to have remission of hypertension (absolute risk 32% vs. 12%, respectively), and less likely to develop new-onset hypertension (absolute risk 4% vs. 12%, respectively).

Diabetes remission was significantly higher among surgery patients, compared with medical treatment patients (58% vs. 13%) as was the likelihood of dyslipidemia remission (43% vs. 13%). Surgery patients also were less likely to develop new-onset diabetes or dyslipidemia than the medical treatment patients.

The surgery patients were significantly more likely than the medical treatment patients to have low ferritin levels; to develop new-onset depression, anxiety, and sleep disorders; and to require treatment with opioids.

However, more patients who underwent bariatric surgery had low ferritin levels, compared with the medical treatment patients (26% vs. 12%). The surgery patients were significantly more likely than the medical treatment patients to develop new-onset depression (adjusted relative risk, 1.5; 95% confidence interval, 1.4-1.7), anxiety and sleep disorders (aRR, 1.3; 95% CI, 1.2-1.5), and treatment with opioids (aRR, 1.3; 95% CI, 1.2-1.4). In addition, bariatric patients were more likely to have at least one additional gastrointestinal surgical procedure (aRR, 2.0; 95% CI, 1.7-2.4), an operation for intestinal obstruction (aRR, 10.5; 95% CI, 5.1-21.5), abdominal pain (aRR, 1.9; 95% CI, 1.6-2.3), and gastroduodenal ulcers (aRR, 3.4; 95% CI 2.0-5.6).

The study was limited by several factors, including selection bias of younger, heavier patients in the bariatric surgery group, the lack of data on actual weight loss, incomplete laboratory data, and a relatively homogeneous white population, the researchers noted. However, the nearly 100% follow-up over approximately 6 years adds to the strength of the findings, which suggest that "the risk for complications should be considered in the decision-making process," for obese patients considering bariatric surgery, they said.

Dr. Jakobsen was supported by the Vestfold Hospital Trust, with no financial conflicts to disclose.

ginews@gastro.org

SOURCE: Jakobsen G et al. JAMA. 2018 Jan 16;319(3):291-301.

WWW.GIHEPNEWS.COM

GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

Mutations on LRRK2 gene modify risks for both Crohn's and Parkinson's

BY MICHELE G. SULLIVAN
Frontline Medical News

Crohn's and Parkinson's diseases seem to share a common genetic risk pathway, mediated by mutations in a gene that modify disease risk in both directions.

A multidisciplinary collaboration of researchers have discovered that the Crohn's risk variant N2081D in the leucine-rich repeat kinase 2 (LRRK2) gene lies close to variant G2019S, the major genetic risk factor for both sporadic and familial Parkinson's. However, protective mutations also occur in the LRRK2 gene, and Ken Y. Hui, MD, of Yale University, New Haven, Conn., and his associates identified and reported two that, when combined, significantly decrease the risk of Crohn's (Sci Transl Med. 2018. doi: 10.1126/scitranslmed.aai7795).

The team first discovered the association in an exome sequencing study of 50 Crohn's patients of Ashkenazi Jewish descent. This identified more than 4,000 potentially high-yield mutations, which they then examined in a pure Ashkenazi cohort of 1,477 Crohn's patients and 2,614 healthy controls.

In this phase, the researchers found that N2081D in LRRK2 was associated with a 73% increased odds of Crohn's. The LRRK2 N551K variant was associated with protection against Crohn's, reducing odds for the disease by 35% (odds ratio, 0.65), as was R1398H, which conferred a 29% reduction in the likelihood of developing the disease (OR, 0.71). It has been known that these two mutations can combine to provide a protective genetic signature, and the team investigated this compound interaction as well.

After repeated analyses in large, unique case-control cohorts and tissue samples, they determined that the N2081D allele increased the odds of Crohn's by 70% in the Ashkenazi subjects and by 60% in non-Ashkenazi subjects. The allele was associated with a 10% increased likelihood of Parkinson's among the Ashkenazi cohort and a 30% increased likelihood among the non-Ashkenazi cohort.

"Our study strongly implicates the contribution of LRRK2 in Crohn's disease risk," they concluded. "The LRRK2 N2081D risk allele and the N551K/R1398H protective alleles, as well as numerous other variants within the LRRK2 locus, revealed shared genetic effects between Crohn's and Parkinson's risk, providing a potential biological basis for clinical co-occurrence. Our findings suggest that LRRK2 may be a useful target for developing drugs to treat Crohn's disease."

The research was supported by a variety of grants from the National Institutes of Health, the National Science Foundation, and other foundations. Five of the authors reported consulting for pharmaceutical companies or companies selling genetic information products. None of the other authors had relevant disclosures.

msullivan@frontlinemedcom.com

SOURCE: Hui K et al. Sci Transl Med. 2018. doi: 10.1126/scitranslmed.aai7795.

CMV colitis mortality unpredictable

BY LUCAS FRANKI
Frontline Medical News

Cytomegalovirus (CMV) colitis has mortality rates similar in immunocompetent patients to that in immunocompromised patients, according to Puo-Hsien Le, MD, and associates.

In a retrospective study, the investigators analyzed data from 42 immunocompetent patients and 27 patients who were immunocompromised because of HIV infection, solid organ or bone marrow transplantation, immunosuppressive drug use, chemotherapeutic agent use within 6 months, or other reasons. In-hospital mortality was 26.2% in immunocompetent patients and 25.9% in immunocompromised patients.

Immunocompetent patients were more likely to present with melena while immunocompromised patients were more likely to present with diarrhea. The number of days until diagnosis was the only independent predictor of in-hospital mortality according to the analysis, with patients who were diagnosed within 9 days of admittance having a significantly higher survival rate.

"Contrary to data published up to this point, we found that CMV colitis was not rare and that it could be fatal in immunocompetent hosts, especially those patients with specific comorbidities associated with immune dysfunction, critical illness, or IBD." the investigators concluded.

lfranki@frontlinemedcom.com

SOURCE: Le PH et al. Ther Clin Risk Manag. 2017 Dec 15;13:1585-93.

DDSEP eight
Digestive Diseases Self-Education Program

Quick quiz answers

Q1. Answer: B

Rationale
Hypergastrinemia is normally a physiologic response to hypochlorhydria. When hypergastrinemia occurs in the setting of acidic gastric pH, it is considered inappropriate. Gastrinoma is a component of MEN-1 syndrome that results in abnormal gastrin release and acid hypersecretion. Gastric outlet obstruction may lead to stomach distention and persistent stimulation by retained food, causing increased gastrin release and acid secretion. Chronic renal failure leads to a decrease in clearance of gastrin from the circulation, resulting in hypergastrinemia. This increase in circulating gastrin results in stimulation of parietal cells to release acid into the gastric lumen. Therefore, the hypergastrinemia associated with chronic renal failure is inappropriate, given the high serum gastrin level despite low intragastric pH. Retained antrum results when a small portion of antrum is left attached to the duodenal bulb (afferent loop) during a Billroth II surgical procedure. As a result, the G cells from the retained antrum are displaced from the stomach and excluded from the inhibitory effects of gastric acid. The lack of negative feedback leads to persistently high gastrin release and resultant acid production. *H. pylori* pangastritis results in suppression of acid secretion, leading to a high intragastric pH. Therefore, it represents an appropriate cause for hypergastrinemia.

Reference
1. Murugesan S.V., Varro A., Pritchard D.M. Review article: Strategies to determine whether hypergastrinaemia is due to Zollinger-Ellison syndrome rather than a more common benign cause. Aliment Pharmacol Ther. 2009;29:1055-68.

Q2. Answer: C

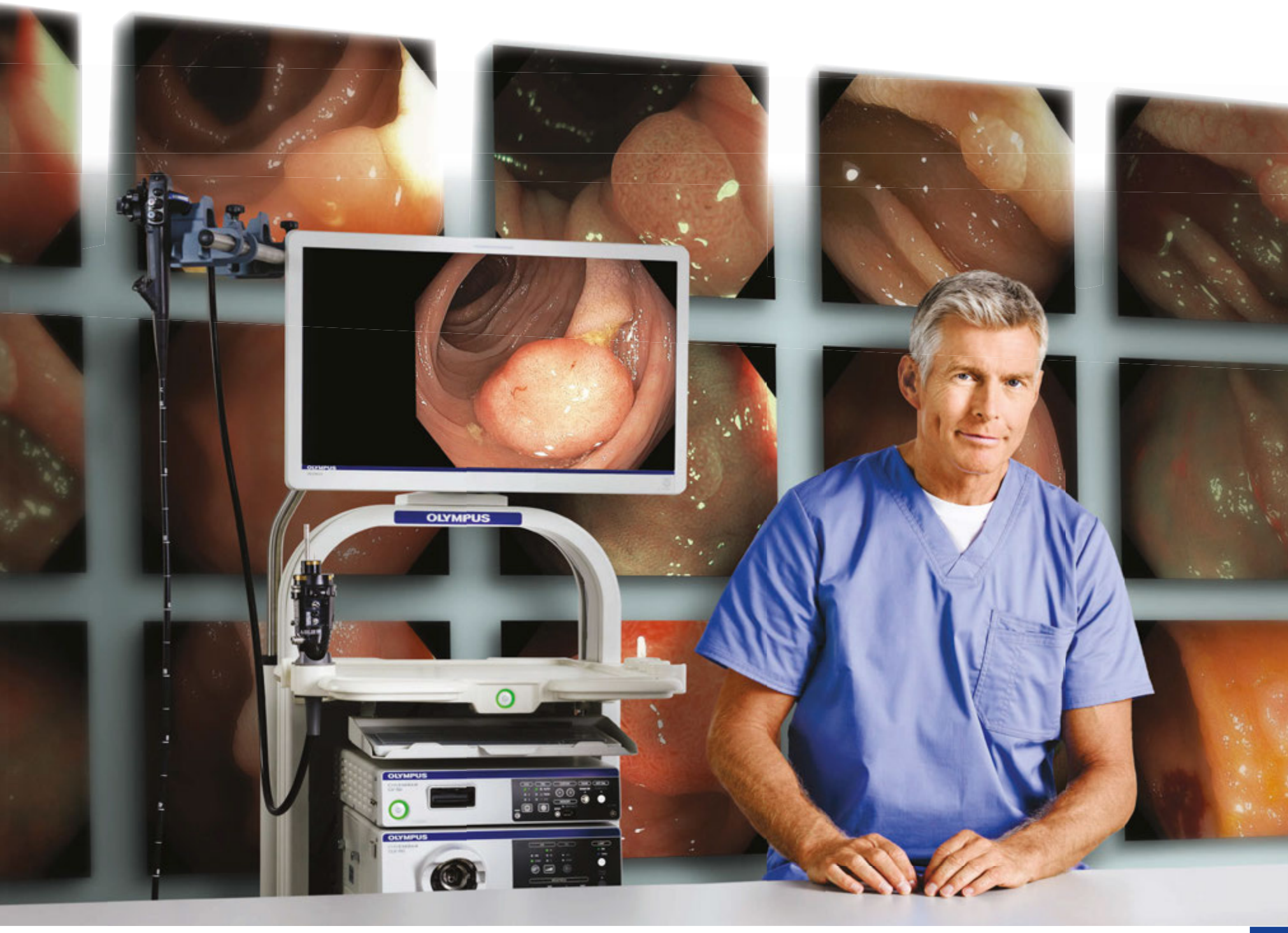
Rationale
The patient has ascending cholangitis. After stabilization and initiation of antibiotics, the next most appropriate step is ERCP. The patient is high risk for postsphincterotomy bleeding as he is on three antithrombotic agents. The most prudent course of action is ERCP with stent placement. ERCP and stent placement is not contraindicated in patients on antithrombotic agents. This will allow for confirmation of the diagnosis as well as therapy for the obstruction. Once the patient has recovered, he can return on an elective basis, off antithrombotic agents, for definitive management of the common bile duct stone. MRCP would allow for a diagnosis; however, it is not therapeutic, and in the setting of cholangitis, management of the obstruction is necessary. Continued medical management neither provides information regarding diagnosis nor treats the obstruction. Percutaneous biliary drain would provide appropriate drainage but, as he is at a high risk for bleeding, ERCP with stent placement is a better therapeutic option in this patient.

References
1. Committee, ASGE Standards of Practice, et al. Management of anti-thrombotic agents for endoscopic procedures. Gastrointest Endosc. 2009;70(6):1060-70.
2. Boustiere C., Veitch A., Vanbiervliet G., et al. Endoscopy and antiplatelet agents. Endoscopy. 2011;43(5):445-61.

ginews@gastro.org

OLYMPUS®

Your Vision, Our Future



Be the one who sees it all

The enhanced visual breadth, sharper image clarity, and exceptional responsiveness of the **EVIS EXERA III** platform puts you in control of every endoscopy procedure. With industry-leading technology and trusted support, Olympus helps you maximize what you can achieve in endoscopy.

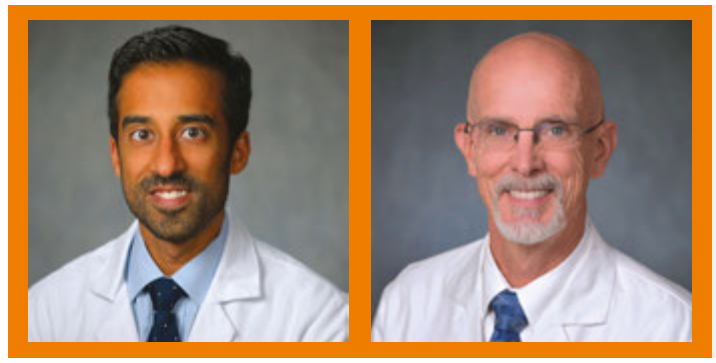
Contact your Olympus Sales Representative or call 800-848-9024.

 | www.medical.olympusamerica.com | OAIGI0118AD24647

In Focus
Brought To You By The New Gastroenterologist

Chronic constipation: Practical approaches and novel therapies

BY NITIN K. AHUJA, MD, MS, AND JAMES C. REYNOLDS, MD, AGAF



Dr. Ahuja (left) is assistant professor of clinical medicine, division of gastroenterology; Dr. Reynolds is professor of clinical medicine, and director of the program in neurogastroenterology and motility, division of gastroenterology, Perelman School of Medicine, University of Pennsylvania, Philadelphia.

While constipation is one of the most common symptoms managed by practicing gastroenterologists, it can also be among the most challenging. As a presenting complaint, constipation manifests with widely varying degrees of severity and may be seen in all age groups, ethnicities, and socioeconomic backgrounds. Its implications can include chronic and serious functional impairment as well as protracted and often excessive health care utilization. A growing number of pharmacologic and nonpharmacologic interventions have become available and proven to be effective when appropriately deployed. As such, health care providers and particularly gastroenterologists should strive to develop logical and efficient strategies for addressing this common disorder.

TABLE 1
Selected causes of constipation

Mechanical
Benign and malignant tumor
Stricture (e.g., inflammatory, ischemic, anastomotic)
Endometriosis
Uterine fibroids
Volvulus
Metabolic
Diabetes mellitus
Thyroid abnormalities
Mitochondrial disorders
Heavy metal toxicity
Neurological
Multiple sclerosis
Parkinson's disease
Spinal cord injury
Severe cognitive dysfunction
Connective tissue disorders
Systemic sclerosis
Amyloidosis
Mixed connective tissue disease, overlap syndrome
Medications
Opioids
Anticholinergics (e.g., selected antiemetics, antispasmodics)
Calcium-channel blockers
Antihistamines
Antidepressants
Anticonvulsants
Diuretics
Motility/functional
Dietary change
Immobility
Colonic inertia
Hirschsprung's disease
Dyssynergic defecation
Irritable bowel syndrome
Chronic idiopathic constipation

Frontline Medical News

Clinical importance

While there are a variety of etiologies for constipation (Table 1), a large proportion of chronic cases fall within the framework of functional gastrointestinal disorders, a category with a substantial burden of disease across the population. Prevalence estimates vary, but constipation likely affects between 12% and 20% of the North American population.[1] Research has demonstrated significant health care expenditures associated with chronic constipation management; U.S. estimates suggest direct costs on the order of hundreds of millions of dollars per year, roughly half of which are attributable to inpatient care.[2] The financial burden of constipation also includes indirect costs associated with absenteeism as well as the risks of hospitalization and invasive procedures.[3]

Physical and emotional complications can be likewise significant and affect all age groups, from newborns to patients in the last days of life. Hirschsprung's disease, for example, can lead to life-threatening sequelae in infancy, such as spontaneous perforation or enterocolitis, or more prolonged functional impairments when it remains undiagnosed. Severe constipation in childhood can lead to encopresis, translating in turn into ostracism and impaired social functioning. Fecal incontinence associated with overflow diarrhea is common and debilitating, particularly in the elderly population.

The potential mechanical complications of constipation lead to its overlap with a variety of other gastrointestinal complaints. For example, the difficulties of passing inspissated stool can provoke lower gastrointestinal bleeding from irritated hemorrhoids, anal fissures, stercoral ulcers, or prolapsed rectal tissue. Retained stool can also lead to upper gastrointestinal symptoms such as postprandial bloating or early satiety.[4] Delayed fecal discharge can promote an increase in fermentative microbiota, associated in turn with the production of short-chain fatty acids, methane, and other gaseous byproducts.

The initial assessment

History

Taking an appropriate history is an essential step toward achieving a successful outcome. Presenting concerns related to constipation can range from hard, infrequent, or small-volume stools; abdominal or rectal pain associated with the process of elimination; and bloating, nausea, or early satiety. A sound diagnosis requires a keen understanding of what patients mean when they indicate that they are constipated, an accurate assessment of its impact on quality of life, and a careful inventory of potentially associated complications.

The presence or absence of alarm symptoms such as weight loss or anemia certainly merit specific investigation. An inventory of medications that might predispose to constipation is prudent.

It is critical to define the duration of the problem. Not infrequently, patients will focus on recent events while failing to reveal that altered bowel habits or other functional symptoms have been problematic for years. Reminding the patients to "begin at the beginning" can aid enormously in contextualizing their complaints. Individuals with longstanding symptoms and previously negative evaluations are much less likely to present with a new organic disease than are those in whom symptoms have truly arisen de novo.

The presence or absence of alarm symptoms such as weight loss or anemia certainly merit specific investigation. An inventory of medications that might predispose to constipation (e.g., opiates, calcium channel blockers, loop diuretics, and anticholinergic agents) is likewise prudent. A history salient for multiple, prolonged, or complicated vaginal deliveries or other perineal trauma would also be relevant to the risk of underlying pelvic floor disorder.

Defining constipation by frequency of bowel eliminations alone has proved inaccurate at predicting actual severity. This is in part because the bowel movement frequency varies widely in healthy individuals (anywhere from thrice daily to once every 3 days) and in part because the primary indicator of effective evacuation is not frequency but volume – a much more difficult quantity for patients to gauge.[5] The Bristol Stool Scale is a simple, standardized tool that more accurately evaluates the presence or absence of colonic dysfunction. For example, patients passing Type 1-2 (hard or lumpy) stools often have an element of constipation that needs to be addressed.[6] However, the interpretation of stool consistency assessments is still aided by awareness of both frequency and volume. A patient passing multiple small-volume Type 6-7 (loose or

watery) stools may be the most constipated, presenting with overflow or paradoxical diarrhea attributable to fecal impaction.

Physical examination

An expert physical exam is another essential aspect of the initial assessment. Alarm features can be elicited in this context as well via signs of pallor, weight loss, blood in the stool, physical abuse, or advanced psychological distress. Attention should also be paid to signs of a systemic disorder that might be associated with gastrointestinal dysmotility including previously unrecognized signs of Raynaud's syndrome, sclerodactyly, amyloidosis, surgical scars, and joint hypermobility.[7,8] Abdominal bloating, a frequently vague symptomatic complaint, can be correlated with the presence or absence of distention as perceived by the patient and/or the examiner.[9]

Any initial evaluation of constipation should also include a detailed digital rectal exam. A complete examination should include a careful visual assessment of the perianal region for external lesions and of the degree and directional appropriateness of pelvic floor excursion (perineal elevation and descent) during squeeze and simulated defecation maneuvers, respectively. Digital examination should include palpation for the presence or absence of pain as well as stool, blood, or masses in the rectal vault, as well as an assessment of sphincter tone at baseline, with squeeze, and with simulated defecation. Rectal pressure generation with the latter maneuver can also be qualitatively assessed. Research has suggested moderate agreement between the digital rectal examination and formal manometric evaluation in diagnosing dyssynergic defecation, underscoring the former's utility in guiding initial management decisions.[10]

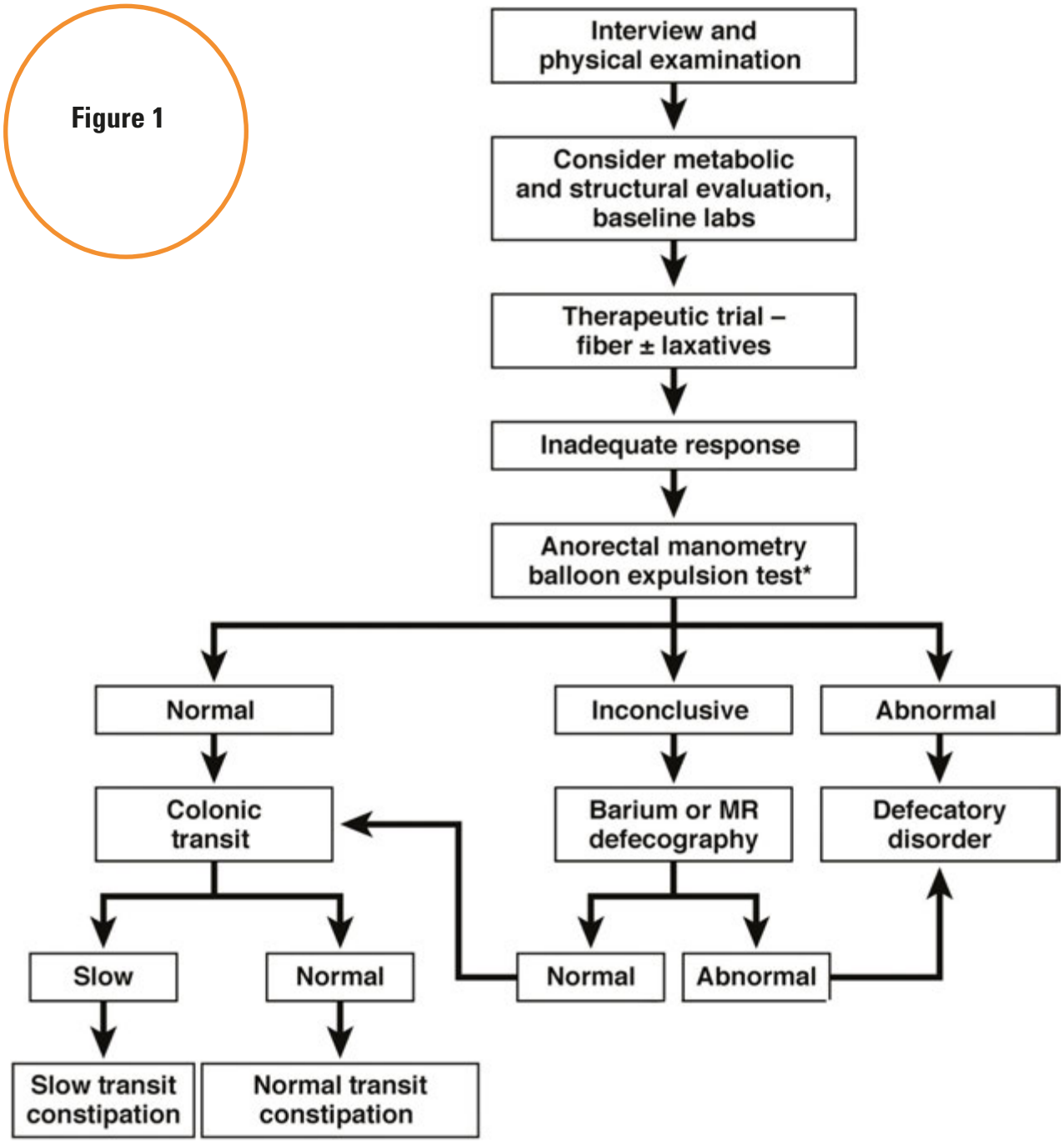
Testing

It is reasonable to exclude metabolic, inflammatory, or other secondary etiologies of constipation in patients in whom history or examination raises suspicion. Likewise, colonoscopy should be considered in patients with alarm features or who are due for age-appropriate screening. That said, in the absence of risk factors or ancillary signs and symptoms, a detailed diagnostic work-up is often unnecessary. The AGA's Medical Position Statement on Constipation recommends a complete blood count as the only test to be ordered on a standard basis in the work-up of constipation.[11]

In patients new to one's practice, the diligent retrieval of prior records is one of the most efficient ways to avoid wasting health care resources. Locating an old abdominal radiograph that demonstrates extensive retained stool can not only secure the diagnosis for vague symptomatic complaints but also obviate the need for more extensive testing. One should instead consider how symptom duration and the associated changes in objective measures such as weight and laboratory parameters can be used to justify or refute the need for repeating costly or invasive studies.

It is important to consider the potential contribution of defecatory dyssynergy to chronic constipation early in a patient's presentation, and to return to this possibility in the future if initial therapeutic interventions are unsuccessful. An abnormal qualitative assessment on digital rectal examination should trigger a more formal characterization of the patient's defecatory mechanics via anorectal manometry (ARM) and balloon expulsion testing (BET). Likewise, a lack of response to initial pharmacotherapy should prompt suspicion for outlet dysfunction, which can be queried with functional testing even if a rectal examination is qualitatively unrevealing.

Figure 1



Courtesy AGA Institute

Figure 1. Treatment algorithm for chronic constipation. MR, magnetic resonance. This figure was published in American Gastroenterological Association, Bharucha A.E., Dorn S.D., Lembo A., Pressman A. American Gastroenterological Association medical position statement on constipation. Gastroenterology. 2013;144:211-7. Copyright Elsevier/AGA.

Initial approach to the chronically constipated patient

The aforementioned AGA Medical Position Statement provides a helpful algorithm regarding the diagnostic approach to constipation (Figure 1). In the absence of concern for secondary etiologies of constipation, an initial therapeutic trial of dietary, lifestyle, and medication-based intervention is reasonable for mild symptoms. Patients should be encouraged to

Continued on page 32

Continued from page 29

strive for 25-30 grams of dietary fiber intake per day. For patients unable to reach this goal via high-fiber foods alone, psyllium husk is a popular supplement, but it should be initiated at modest doses to mitigate the risk of bloating. Fiber may be supplemented with the use of osmotic laxatives (e.g., polyethylene glycol) with instructions that the initial dose may be modified as needed to optimal effectiveness. Selective response to rectal therapies (e.g., bisacodyl or glycerin suppositories) over osmotic laxatives may also suggest utility in early queries of outlet dysfunction.

An abdominal radiograph can be helpful not only to diagnose constipation but also to assess the stool burden present at the time of beginning treatment. For patients presenting with a significant degree of fecal loading, an initial bowel cleanse with 4 liters of osmotically balanced polyethylene glycol can be a useful means of eliminating background fecal impactions that might have mitigated the effectiveness of initial therapies in the past or that might reduce the effectiveness of daily laxative therapy moving forward.

Patients with a diagnosis of defecatory dyssynergy made via ARM/BET should be referred to pelvic floor physical therapy with biofeedback. Recognizing that courses of therapy are highly individualized in practice, randomized controlled trials suggest symptom improvement in 70%-80% of patients, with the majority also demonstrating maintenance of response.[12] Biofeedback appears to be an essential component of this modality based on meta-analysis data and should be requested specifically by the referring provider.[13]

Table 2. Pharmacologic agents for constipation

Osmotic laxatives	Peripherally acting mu-opioid receptor antagonists
Polyethylene glycol Lactulose Glycerin suppositories	Naloxegol Methylnaltrexone Naldemedine
Secretory stimulants	**Serotonin (5HT4) agonists**
Guanylate cyclase agonists Linaclotide Plecanatide Chloride-channel activators Lubiprostone	Prucalopride (not available in United States)

Frontline Medical News

Pharmacologic agents

For those patients with more severe initial presentations or whose symptoms persist despite initial medical management, there are several pharmacologic agents that may be considered on a prescription basis (Table 2). Linaclotide, a minimally absorbed guanylate cyclase agonist, is approved by the Food and Drug Administration for patients with irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC). Improvements in constipation tend to occur over a slightly shorter timeline than in abdominal pain, though both have been demonstrated in comparison to placebo.[14,15] Plecanatide, a newer agent with a similar mechanism of action, has demonstrated improvements in bowel movement frequency and was recently approved for CIC.[16] Lubiprostone, a chloride-channel agonist, has demonstrated benefit for IBS-C and CIC as well, though its side effect profile is more varied, including dose-related nausea in up to 30% of patients.[17]

For patients with opioid-induced constipation who cannot wean from the opioid medications, the peripheral acting mu-opioid receptor antagonists may be quite helpful. These include injectable as well as oral formulations (e.g., methylnaltrexone and naloxegol, respectively) with additional agents under active investigation in particular clinical subsets (e.g., naldemedine for patients with cancer-related pain).[18,19]

Prucalopride, a selective serotonin receptor agonist, has also demonstrated benefit for constipation; it is available abroad but not yet approved for use in the United States.[20] Prucalopride shares its primary mechanism of action (selective agonism of the 5HT4 serotonin receptor) with cisapride, a previously quite popular gastrointestinal motility agent that was subsequently withdrawn from the U.S. market because of arrhythmia risk.[21] This risk is likely attributable to cisapride's dual binding affinity for potassium channels, a feature that prucalopride does not share; as such, cardiotoxicity is not an active concern with the latter agent.[22]

Still other pharmacologic agents with novel mechanisms of action are currently under investigation. Tenapanor, an inhibitor of a particular sodium/potassium exchanger in the gut lumen, mitigates intestinal sodium absorption, which increases fluid volume and transit. A recent phase 2 study demonstrated significantly increased stool frequency relative to placebo in patients with IBS-C.[23] Elobixibat, an ileal bile acid transport inhibitor, promotes colonic retention of bile acids and, in placebo-controlled studies, has led to accelerated colonic transit and an increased number of spontaneous bowel movements in patients with CIC.[24]

While there are not many practical distinctions at present in the therapeutic management of slow-transit versus normal-transit constipation, the use of novel medications with an explicitly prokinetic mechanism of action may be reasonable to consider in the setting of a documented delay in colonic transit.

Persistent constipation

In cases of refractory constipation (in practical terms, symptoms that persist despite trials of escalating medical therapy over at least 6 weeks), it is worth revisiting the question of etiology. Querying defecatory dyssynergy via ARM/BET, if not pursued prior to trials of newer pharmacologic agents, should certainly be explored in the event that such trials fail. Inconclusive results of ARM and BET testing, or BET abnormalities that persist despite a course of physical therapy with biofeedback, may raise suspicion for pelvic organ prolapse, which may be formally evaluated with defecography. Additional testing for metabolic or structural predispositions toward constipation may also be reasonable at this juncture.

Formal colonic transit testing via radio-opaque markers, scintigraphy, or the wireless motility capsule is often inaccurate in the setting of dyssynergic defecation and should be pursued only after this entity has been excluded or successfully treated.[25] While there are not many practical distinctions at present in the therapeutic management of slow-transit versus normal-transit constipation, the use of novel medications with an explicitly prokinetic mechanism of action may be reasonable to consider in the setting of a documented delay in colonic transit. Such delays can also help justify further specialized diagnostic testing (e.g., colonic manometry), and, in rare refractory cases, surgical intervention.

Consideration of colectomy should be reserved for highly selected patients with delayed colonic transit, normal defecatory mechanics, and the absence of potentially explanatory background conditions (e.g., connective tissue disease). Clear evidence of an underlying colonic myopathy or neuropathy may militate in favor of a more targeted surgical intervention (e.g., subtotal colectomy) or guide one's clinical evaluation toward alternative systemic diagnoses.

A diverting loop ileostomy with interval assessment of symptoms may be useful to clarify the potential benefits of colectomy while preserving the option of operative reversal. Proximal transit delays should be definitively excluded before pursuing colonic resections given evidence that multisegment transit delays portend significantly worse postoperative outcomes.[26]

Conclusion

Constipation is a common, sometimes confusing presenting complaint and the variety of established and emergent options for diagnosis and therapy can lend themselves to haphazard application. Patients and providers both are well served by a clinical approach, rooted in a comprehensive history and examination, that begins to organize these options in thoughtful sequence.

See references online

CLINICAL CHALLENGES AND IMAGES

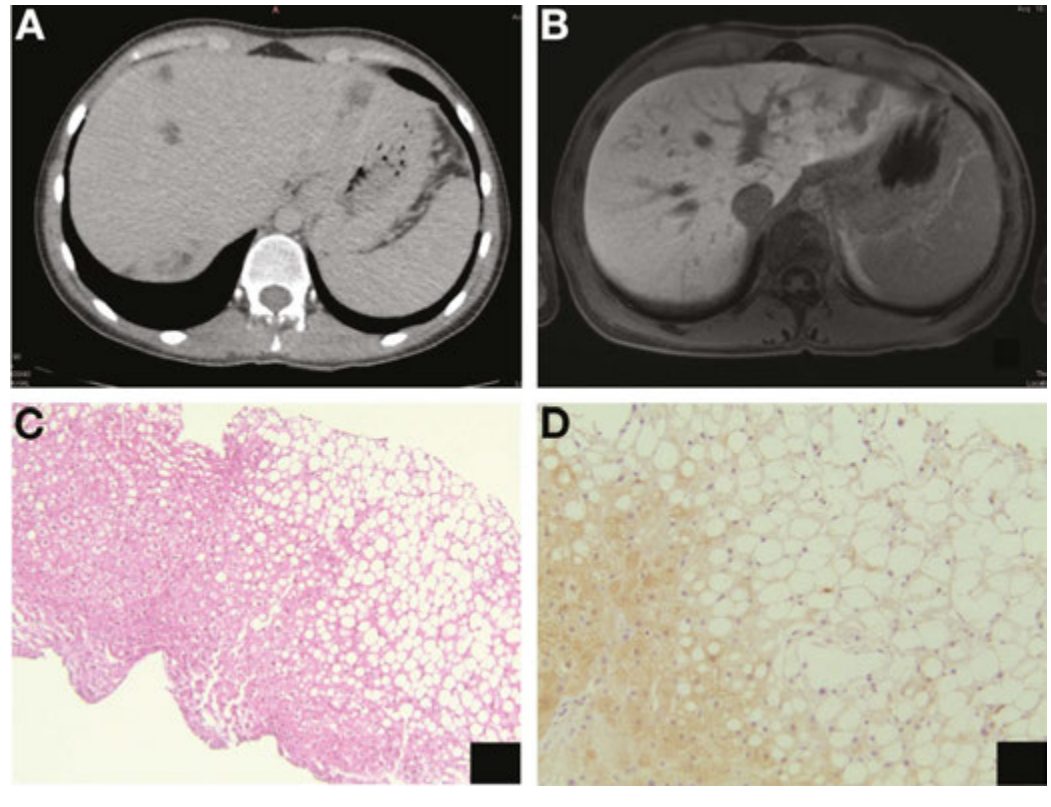
What is your diagnosis?

By Claudio De Vito, MD, PhD, Laura Rubbia-Brandt, MD, PhD, and Christian Toso, MD, PhD. Published previously in Gastroenterology (2016;151[1]32, 33).

A 22-year-old woman with no past medical history was investigated for hypoglycemia episodes. A nodule located in the head of the pancreas was identified, with radiologic features of a neuroendocrine neoplasm. The overall clinical presentation was consistent with an insulinoma. No distant lesion was detected. She underwent a Whipple procedure, and the histopathologic examination reported a 2.2-cm, well-differentiated neuroendocrine tumor (insulinoma) G2 (4% Ki-67 index), with no lymphovascular invasion or lymph node metastasis (0 of 30 lymph nodes).

Six months later the patient was asymptomatic and a follow-up scan, completed by magnetic resonance imaging and dihydroxyphenylalanine positron-emission tomography–CT, revealed multiple bilobar steatotic liver areas but no sign of metastasis (Figures A, B). No hypermetabolic activity was identified by positron-emission tomography. A CT-guided biopsy of one lesion showed steatotic hepatocytes with a loss of liver fatty acid–binding protein (L-FABP), and no evidence for neuroendocrine tumor metastasis (Figures C [stain: hematoxylin and eosin] and D [L-FABP immunostaining]).

See the diagnosis on page 34.



AGA Institute

FDA: Gadolinium retention prompts GBCA class warning

BY SHARON WORCESTER
Frontline Medical News

Gadolinium-based contrast agents (GBCAs) used for MRI will now carry a warning regarding their potential retention in the bodies and brains of treated patients, according to the Food and Drug Administration.

The FDA is requiring the new class warning, along with other safety measures, based on evidence showing that trace amounts of gadolinium can be retained in the body for months to years after treatment.

"Gadolinium retention has not been directly linked to adverse health effects in patients with normal kidney function, and the FDA has concluded that the benefit of all approved GBCAs continues to outweigh any potential risk," an FDA MedWatch safety alert stated. "However, after additional review and consultation with the Medical Imaging Drugs Advisory Committee, the FDA is requiring several actions to alert health care professionals and patients about gadolinium retention after an MRI using a GBCA, and actions that can help minimize problems."

Specifically, the agency will require that patients receiving GBCAs first receive a Medication Guide and that GBCA manufacturers conduct human and animal studies to further assess GBCA safety. At this time, the only known adverse health effect of gadolinium retention is nephrogenic systemic fibrosis, which affects a small subgroup of patients with pre-existing kidney failure. No causal association has been established between gadolinium retention and reported adverse events in those with normal kidney function.

The FDA recommended that health care professionals consider the retention characteristics of GBCAs for patients who may be at higher risk for retention, including those requiring multiple lifetime doses, pregnant women, children, and patients with inflammatory conditions, but stressed that, although repeated GBCA imaging studies should be minimized when possible, they should not be avoided or deferred when they are necessary. In the safety alert, the FDA noted that administration of the GBCAs Dotarem (gadoterate meglumine), Gadavist (gadobutrol), and ProHance (gadoteridol) produce the lowest gadolinium levels in the body, and the three agents leave similar gadolinium levels in the body.

The agency encourages reports of adverse events or side effects related to the use of GBCAs to its MedWatch Safety information and Adverse Event Reporting Program. Reports can be submitted online at www.fda.gov/MedWatch/report or by calling 1-800-332-1088 to request a preaddressed form that can be mailed or faxed to 1-800-FDA-0178.

sworcester@frontlinemedcom.com

CLINICAL CHALLENGES AND IMAGES

The diagnosis

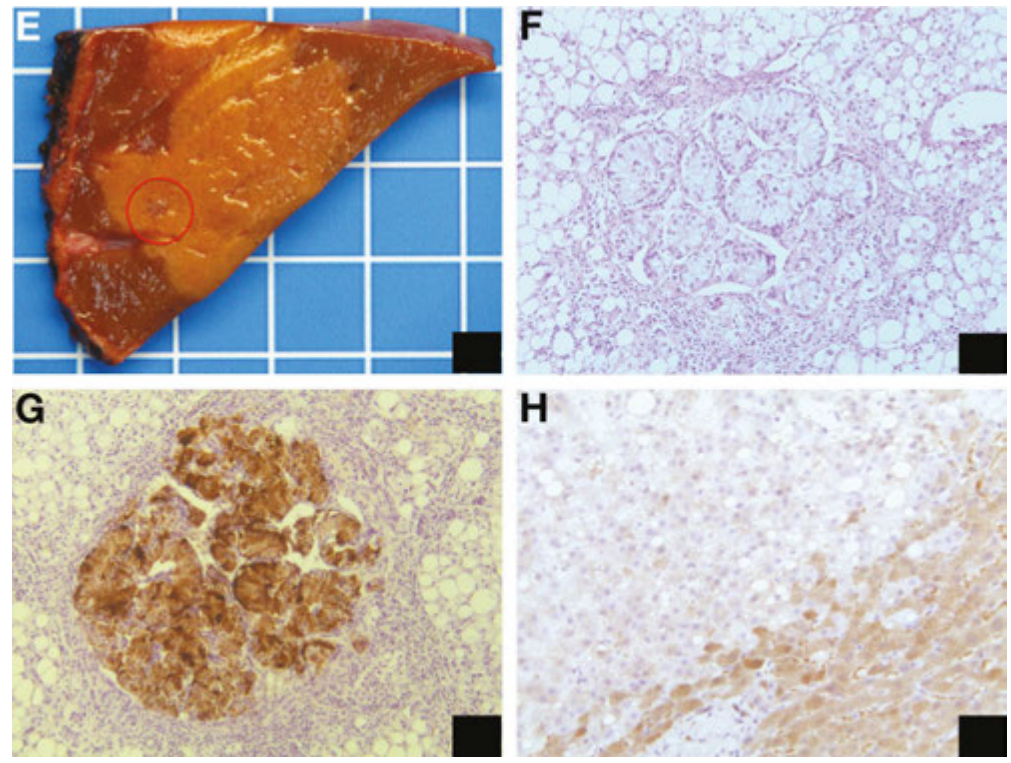
Answer to "What's your diagnosis?" on page 33: Metastatic insulinoma surrounded by steatotic hepatocytes

The loss of L-FABP expression in steatotic hepatocytes is the hallmark of HNF1alpha-inactivated liver adenoma,[1] and clearly suggested this diagnosis. However, the emergence of multiple steatotic lesions over a short period of time was uncommon for liver adenomas. Despite the absence of radiologically detectable metastasis, this diagnosis could not be ruled out, and the patient underwent a surgical liver biopsy (tip of the right lobe). The specimen showed a 0.2-cm greyish nodule surrounded by a steatotic map-like area of 3.5 cm in the largest dimension (Figure E). Histopathologic examination showed neuroendocrine cells (Figures F [hematoxylin and eosin staining] and G [insulin immunostaining]), confirming the diagnosis of metastatic insulinoma surrounded by steatotic hepatocytes.

The key interest of the case is the reduction of L-FABP expression in the steatotic hepatocytes (Figure H [L-FABP immunostaining]), which was an unexpected finding and could have led to an incorrect diagnosis of HNF1α-inactivated liver adenoma.

In contrast with other functional neuroendocrine tumors, insulinomas are frequently benign tumors, and only about 10% of patients develop metastasis. In the liver, they are often surrounded by microscopic or radiologically detectable steatotic areas thanks to the paracrine effect of insulin. Such a feature has been previously described both with liver insulinoma metastases[2] and after pancreatic islet transplantation.[3] The reduction of L-FABP expression within the steatotic hepatocytes seems to be less frequent because it was not observed in an additional patient with G3 insulinoma (neuroendocrine carcinoma) metastases and in three pancreatic islet recipients (data not shown).

The present patient with multiple liver G2 insulinoma metastases illustrates 1) the potential of foci of steatosis to represent early signs of insulinoma liver metastasis, and 2) the presence of a reduction or even a loss of L-FABP expression in other liver lesions than HNF1alpha-inactivated liver adenoma.



Acknowledgment
Claudio De Vito's current affiliation is Institute of Liver Studies, King's College Hospital, London, UK.

The authors thank A.M.J. Shapiro from the University of Alberta, Edmonton, and A. Quaglia from the King's College Hospital, London for sharing the liver samples of transplanted pancreatic islets and G3 insulinoma metastasis. They are also grateful to the members of the Geneva Hepato-Biliary and Pancreatic Center for the discussion of the case.

References

1. Bioulac-Sage P., Cubel G., Taouji S., et al. Immunohistochemical markers on needle biopsies are helpful for the diagnosis of focal nodular hyperplasia and hepatocellular adenoma subtypes. Am J Surg Pathol. 2012;36:1691-9.
2. Sohn J., Siegelman E., Osiason, A. Unusual patterns of hepatic steatosis caused by the local effect of insulin revealed on chemical shift MR imaging. AJR Am J Roentgenol. 2001;176:471-4.
3. Toso C., Isse K., Demetris A.J., et al. Histologic graft assessment after clinical islet transplantation. Transplantation. 2009;88:1286-93.

ginews@gastro.org

For GI Endoscopic Resections

Visit eleviewUS.com • 888-ARIES-08

Contains Methylene Blue

Conquer polyps with lift that lasts

Eleview™ submucosal injection agent

- Provides an immediate and long-lasting cushion[1] that holds for up to 45 minutes[2]
- Increases visibility of target lesion margins[1]
- Designed to lower the risk of perforation[1]
- Appropriate for challenging polyps regardless of size, location, or type

Lasts for up to 45 minutes[2]

Eleview™ submucosal injectable composition is intended for use in gastrointestinal endoscopic procedures for submucosal lift of polyps, adenomas, early-stage cancers, or other gastrointestinal mucosal lesions, prior to excision with a snare or endoscopic device.

Important Safety Information

WARNINGS AND PRECAUTIONS

- The endoscopist injecting Eleview™ must be experienced in the administration technique.
- The safety of Eleview™ has not been established in pregnant or lactating women, or in children under 18 years of age.

CONTRAINDICATIONS

Patients with known sensitivity to any of the components contained in Eleview™.

ADVERSE REACTIONS

Rarely, local bleeding and/or inflammatory reaction could occur which may or may not be associated with Eleview™.

Please see Instructions for Use for complete Important Safety Information.

References: 1. Eleview™ Instructions for Use, Aries Pharmaceuticals, Inc. April 2017. **2.** Data on File, Aries Pharmaceuticals, Inc.

ARIES Pharmaceuticals, Inc.
Member of Cosmo Pharmaceuticals NV Group
aries-pharma.com

Lift that lasts
Eleview™

COMMENTARY: Warn patients about the risk of OTC overdose

BY CHARLES MEL WILCOX, MD

Roughly 8 in 10 Americans routinely reach for over-the-counter (OTC) pain pills to relieve headaches, backaches, sore muscles, fevers, or colds, according to a national poll by the American Gastroenterological Association (AGA). Most are unaware that these medications, if used incorrectly, can be just as dangerous as prescription drugs.

In my GI practice, I often see cases of accidental OTC pain medicine overdose that have caused stomach bleeding, ulcers, liver damage, and even liver failure. And, I am not alone – the poll found that gastroenterologists see, on average, nearly two patients per week with complications from OTC pain pills.

The nation's attention is focused on the opioid crisis, with good reason, but we cannot forget about the risks associated with OTC pain medicines. While it may seem harmless to take more OTC medications than indicated, the body is not capable of absorbing higher doses of pain medicine ingredients at a faster rate.

According to the AGA's survey, many people are confident they can manage symptoms on their own, without consulting a doctor. Yet, the same poll found that 39% of Americans knowingly took more than the recommended dosage. In most cases, they falsely believed that taking more OTC pain medicine than what was indicated on the label would help them "feel better faster."

I treated a woman in her 20s who recently had dental surgery. She was taking Lortab, which is a combination of acetaminophen and hydrocodone, an opioid. But when she still felt pain, she took additional OTC acetaminophen to try to find faster relief. When I saw her, her liver tests were abnormal, her acetaminophen level was elevated, and she was feeling nauseated. In trying to get faster pain relief, she unintentionally overdosed on OTC pain medicine.

DR. WILCOX

To help patients avoid this kind of medication mishap, it's vital that health care providers initiate conversations at every visit about the dangers of OTC pain medicine overdose. The following tips have helped me advise my patients and educate them on the associated risks:

- Encourage your patients to read and follow all medicine labels, even on OTC drugs – every time they reach for into the medicine cabinet.
- Talk to your patients about the two main types of oral OTC pain medicines and make sure they know to take only one product at a time containing the same type of active ingredient.
- Ask about all medicines your patients take, including OTC medicines, as they may not know to tell you.
- Patients may not realize that their current health situation, age, and/or medical history can impact their risk for OTC pain medicine overdose. Let them know that products that worked in the past may no longer be the right choice for them.

If more health care providers emphasized the dangers of incorrect usage of OTC pain medicines, we could easily help patients avoid the dangerous side effects of taking too much.

Dr. Wilcox is professor of medicine in the division of gastroenterology and hepatology at the University of Alabama at Birmingham and a chair of AGA's Gut Check: Know Your Medicine campaign.

Waiving Medicare coinsurance for positive colorectal screening likely beneficial

BY GREGORY TWACHTMAN
Frontline Medical News

Waiving coinsurance for Medicare beneficiaries who have a screening colonoscopy when it results in a polyp removal or follows a positive fecal screening test would likely have a favorable balance of health and cost impact.

Currently, Medicare covers colorectal screening at no charge to the patient, but if a polyp is removed upon discovery during the procedure, the patient would then be subject to Medicare's coinsurance payments for both the colonoscopy and the removal.

"We estimated that waiving coinsurance would be cost-effective if screening rates increased from 60.0% to 60.6%, assuming a willingness-to-pay threshold of $50,000 per QALY [quality-adjusted life-year] gained – which suggests that the waiver would likely have a very favorable balance of health and cost impact," Elisabeth F.P. Peterse, of Erasmus University Medical Center, Rotterdam, The Netherlands, and her colleagues wrote in new research appearing in the December 2017 issue of Health Affairs.

Researchers used the Microsimulation Screening Analysis-Colon model to estimate the cost-effectiveness of waiving coinsurance for every component of colorectal cancer screening. They estimated that, currently, using the colonoscopy regimen with coinsurance, 12.8 colorectal cancer deaths occurred per 1,000 people aged 65 years and 124.1 QALYs were gained per 1,000 people aged 65 years. The total number of procedures per 1,000 Medicare beneficiaries was 1,132, of which 410 (36%) were potentially subject to coinsurance requirements.

"We estimated that the total lifetime costs for [the Centers for Medicare & Medicaid Services], which included colorectal cancer screening, surveillance, and treatment with coinsurance, to be $2.675 million per 1,000 sixty-five-year-olds," Ms. Peterse and her colleagues wrote. Researchers noted that, if the coinsurance was waived but there was no follow-on increase in the screening rate, the benefits of screening would not change but the total cost of screening and treatment would increase to $2.726 million per 1,000 people aged 65 years.

However, "an assumed 5-percentage-point increase in the rates of first colonoscopy screening and surveillance decreased the number of colorectal cancer deaths by 0.9 (6.4 percent), accompanied by an increase of $33,000 (1.2 percent) in total costs, with a cost per QALY gained (or cost-effectiveness ratio) of $4,086."

They added that estimated screening benefits were similar when fecal testing was the primary screening method.

"In general, [fecal testing] screening was associated with lower number of procedures subject to coinsurance," the researchers added. "If [fecal testing] screening becomes more popular in the United States, following trends observed in several settings, the costs of waiving coinsurance would be even lower." The researchers also suggest that it could lead to reducing disparities of colorectal cancer in the United States as well.

AGA has been working for years to try to fix this issue, and supports the bipartisan Removing Barriers to Screening Act, which would correct this inequity for Medicare beneficiaries and remove the financial barriers that may prevent a patient from undergoing a screening. AGA is hopeful that the growing support for the legislation on both sides of the aisle will help get the bill passed this year. To learn more about this issue, visit www.gastro.org/take-action/top-issues/patient-cost-sharing-for-screening-colonoscopy. To help your patients undertand this issue, AGA has created "What to Expect: Paying for Your Colonoscopy," which can be downloaded at www.gastro.org/patient-care/procedures/Colonoscopy_CoPay__WhatToKnowFactSheet.pdf to be shared in your office.

gtwachtman@frontlinemedcom.com

SOURCE: Peterse EFP et al. Health Affairs. 2017 Dec;36(12):2151-9.

Malpratice premiums continue downward slide

BY ALICIA GALLEGOS
Frontline Medical News

Malpractice premiums continue to inch down but wide disparities in total cost still linger across states.

Internists, general surgeons, and obstetrician-gynecologists experienced a respective 1% drop in their medical liability premiums last year, according to the 2017 Medical Liability Monitor Annual Rate Survey. The rate drop follows an ongoing trend of decreasing premiums over the last decade.

"The takeaways for doctors are really all good ones in that the rates remain very stable," said Paul A. Greve Jr. senior vice president/senior consultant for Willis Towers Watson Health Care Practice and coauthor of the 2017 MLM Survey report. "The market for physician coverage remains very competitive because there are so many players involved for what is really a shrinking number of buyers, so the groups and individual physicians that are buying are seeing favorable pricing."


"The takeaways for doctors are really all good ones in that the rates remain very stable," said Paul A. Greve Jr.

Premiums differed vastly across geographic area, consistent with previous years. Southern Florida internists for example, paid $47,707 for malpractice insurance last year, while their Minnesota colleagues paid $3,375. For ob.gyns., premiums ranged from $214,999 in southern New York to $16,240 in central California. General surgeons in Southern Florida paid $190,829 in 2016, while those in Wisconsin paid $10,868.

Overall, no states experienced a premium rate change in the double digits, and physicians in only five states – Hawaii, Kansas, Michigan, Montana, and Ohio – saw premium decreases of more than 5%. No states experienced rate increases of more than 5%.

Fewer claims filed by plaintiffs' attorneys is one factor contributing to the continued stability of malpractice premiums, according to analysts. However, there are signs that high verdicts are on the rise, said Michael Matray, editor of the Medical Liability Monitor and chief content officer for Cunningham Group. Survey data show claims closing at greater than $1 million are increasing.

"There is data that indicates claim severity has experienced a slight uptick," Mr. Matray said in an interview. "It obviously hasn't affected rates, yet. This could be due to the positive effect state-level tort reforms have had – where plaintiff attorneys are only bringing cases that are a slam dunk and carry a larger dollar value."

Continued practice consolidation and the increase in the number of employed physicians also helped keep premiums steady, Mr. Greve said in an interview. Consolidation means fewer buyers and a more competitive market, which helps keep premiums low and stable.

The jury is still out on how the move to value-based care might impact medical malpractice insurance payments. There is concern that the methods required to determine health care value could unwittingly increase malpractice risk, Mr. Matray said.

"To support value-based reimbursement models, a health care system must manage a vast network of public and private data used by various entities in order to monitor quality and cost," Mr. Matray said. "The collection of that data requires using electronic health record technology that many physicians find onerous. This leads to physician burnout and dangerous EHR workarounds, such as copy-and-paste practices where previous EHR entries are cloned and inserted into a new progress note, as well as disabling or overriding burdensome safety alerts, to save time and increase efficiency. You can see how this would increase medical liability claim risk."


The methods required to determine health care value could unwittingly increase malpractice risk, Michael Matray said.

The MLM survey report is published yearly based on July 1 premium data from the major malpractice insurers and examines premium rates for mature, claims-made policies with $1 million/$3 million limits for internists, general surgeons, and ob.gyns.

agallegos@frontlinemedcom.com

INDEX OF ADVERTISERS

CMS launches advanced APM with bundled payments

BY GREGORY TWACHTMAN
Frontline Medical News

The Centers for Medicare & Medicaid Services is launching a new voluntary bundled payment demonstration project that for the first time will qualify as an advanced alternative payment model under the Quality Payment Program.

The Bundled Payments for Care Improvement Advanced (BPCI Advanced) "builds on the earlier success of bundled payment models and is an important step in the move away from fee-for-service and towards paying for value," CMS Administrator Seema Verma said in a statement. "Under this model, providers will have an incentive to deliver high-quality care."

The program will provide a single retrospective payment and one risk track, with a 90-day clinical episode duration. It will cover 29 in-patient episodes and three outpatient clinical episodes.

Medicare-certified acute care hospitals and physician group practices are eligible to take part in the BPCI Advanced, according to Medicare documentation. They will be categorized either as "conveners" – entities that bring together multiple parties for the purpose of coordinating care, as well as apportioning financial risks – or as "nonconveners" – those who bear financial risk for themselves only.

Both categories of participants may enter into agreements with individual physicians and nonphysician providers to furnish care under the bundled payment model.

The program will provide a single retrospective payment and one risk track, with a 90-day clinical episode duration. It will cover 29 in-patient episodes and three outpatient clinical episodes. Payment will be tied to performance on quality measures.

The 29 in-patient clinical episodes cover a range of conditions, including liver disorders (excluding malignancy, cirrhosis, and alcoholic hepatitis); gastrointestinal hemorrhage or obstruction; and major bowel procedures.

Seven quality measures will be tracked as part of the payment. For all clinical episodes, measurement of all-cause hospital readmissions and advance care plan will be required. The others, including perioperative care, selection of prophylactic antibiotic, first- or second-generation cephalosporin, and AHRQ patient safety indicators, among others – will be applied to the payment as approriate.

CMS had an open-door forum for those interested in participating in BPCI Advanced on Jan. 30.

Applications for participation will be accepted through March 12.

gtwachtman@frontlinemedcom.com

WWW.GIHEPNEWS.COM

GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE