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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

NICK PIEGARI/FRONTLINE MEDICAL NEWS

Dr. Colleen Kelly is a leader of the 10-year study on short- and long-term patient outcomes associated with FMT in adults and children.

Study will follow fecal microbiota transplants

BY MICHELE G. SULLIVAN
Frontline Medical News

AT DDW 2017

CHICAGO – A 10-year registry study aims to gather clinical and patient-reported outcomes on 4,000 adult and pediatric patients who undergo fecal microbiota transplant (FMT) in the United States, officials of the American Gastroenterological Association announced during Digestive Disease Week®.

The AGA Fecal Microbiota Transplantation National Registry will be the first study to assess both short- and long-term patient outcomes associated with FMT in both adults and children, Colleen Kelly, MD, said in an interview. Most subjects will have received FMT for recurrent or refractory *Clostridium difficile* infections – the only indication for which Food and Drug Administration currently allows independent clinician action. But the investigational uses of FMT are expanding rapidly, and patients who undergo the procedure during any registered study will be eligible for enrollment, said Dr. Kelly, co-chair of the study's steering committee.

The study's primary objectives are short- and long-term safety outcomes, said Dr. Kelly of Brown University, Providence, R.I. While FMT is generally considered quite safe, short-term adverse events have been report-

See **Transplants** · *page 13*

Endoscopic weight-loss surgery cuts fat, costs, side effects

ESG becoming a popular procedure.

BY HEIDI SPLETE
Frontline Medical News

FROM DDW 2017

Obese patients who underwent endoscopic sleeve gastroplasty had significantly fewer complications and shorter hospital stays than did those who had laparoscopic sleeve gastrectomy or laparoscopic band placement, according to results from a study of 278 adults presented at Digestive Disease Week.®

Overall, 1% of patients who underwent endoscopic sleeve gastroplasty (ESG) experienced adverse events, compared with 8% of those who underwent laparoscopic sleeve gastrectomy (LSG) and 9% of those who underwent laparoscopic gastric band (LAGB) placement.

ESG, which reduces gastric volume by use of an endoscopic suturing system of full-thickness sutures through the greater curvature of the stomach, is becoming a popular weight-loss procedure for patients with a body mass index greater than 30 kg/m^2 who are poor candidates for laparoscopic surgery or who would prefer a less invasive procedure, according to Reem Z. Sharaiha, MD, of Cornell University, New York.

Dr. Sharaiha and her colleagues randomized 91 patients to ESG, 120 to

See **Surgery** · *page 17*

'Rich pipeline' of novel NASH treatments being studied

BY SARA FREEMAN
Frontline Medical News

AMSTERDAM – There is a "very, very rich pipeline" of drugs being developed for the treatment of nonalcoholic steatohepatitis (NASH), Jean-François Dufour, MD, AGAF, the head of hepatology and director of the University Clinic for Visceral Surgery and Medicine at the University of Berne (Switzerland) said at the International Liver Congress.

"We have many therapeutic options [under investigation]," Dr. Dufour noted at the Congress, which is sponsored by the European Association for the Study of the Liver. These include drugs

See **NASH** · *page 4*

News from DDW 2017 Digestive Disease Week®

in this issue

INSIDE

IBD AND INTESTINAL DISORDERS
Bile acid diarrhea is not IBS
Misdiagnosis takes a serious toll. • 14

ENDOSCOPY, PANCREAS & BILIARY TRACT
Indomethacin post ERCP
Cuts pancreatitis risk especially in patients with PSC. • 17

UPPER GI TRACT
Misoprostol for aspirin-induced bleeding
Results in mucosal healing. • 21

LIVER DISEASE
Albumin: Yes
Effective, expensive in decompensated cirrhosis. • 25

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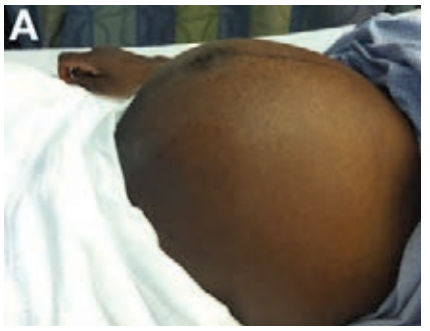
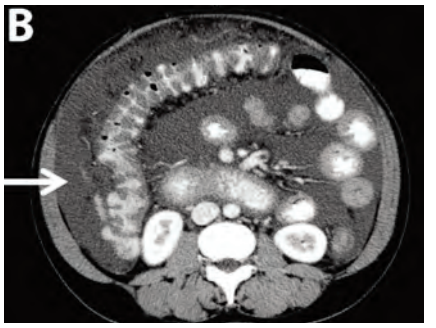
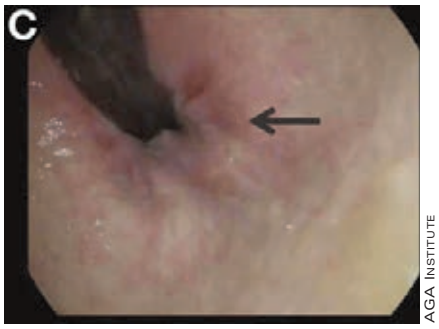
CLINICAL CHALLENGES AND IMAGES

What's your diagnosis?

By Ravi B. Parikh, MD, George A. Alba, MD, and Lawrence R. Zuckerberg, MD. Published previously in Gastroenterology (2013;144;272, 467).







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A 36-year-old woman, originally from Haiti, presented to the emergency department with 2 weeks of abdominal distention, diarrhea, and blood-tinged emesis. She had given birth to her first child by uncomplicated cesarean section 9.5 weeks earlier. There was no history of recent travel, diet change, or sick contacts. She denied alcohol, tobacco, or illicit drug use and was not taking any medications or supplements. She was allergic to chloroquine (itchiness) and had no history of atopy. She was not aware of any family history of liver disease or allergy, although her paternal history was unknown.

Upon admittance to the general medicine service, the patient was afebrile and hemodynamically stable. She did not have any stigmata of chronic liver disease. Her abdomen was distended and diffusely tender with rebound tenderness and guarding (Figure A). Serum studies were notable for white blood cell count of 14.5 x 10^3/microL, with 46% eosinophils (absolute count 6,660/mm^3). Other values, including serum human chorionic gonadotropin, were normal.

Computed tomography of the abdomen and pelvis (Figure B) showed a large amount of abdominal and pelvic ascites (arrow) with mild small bowel wall thickening. There was no evidence of organomegaly or vessel thrombosis. Subsequent diagnostic paracentesis demonstrated an exudative effusion with total nucleated cells 4,545/mL, with 82% eosinophils. Large-volume paracentesis of 4,000 mL of straw-colored fluid relieved the patient's abdominal pain. Fluid bacterial and tuberculosis cultures were negative, and cytology showed no evidence of malignancy. Peripheral blood smear was unremarkable. Stool culture, stool ova and parasites, urine culture, and blood culture were all negative.

Because of these findings, the gastroenterology service was consulted. Esophagogastroduodenoscopy and colonoscopy showed mild rectal mucosal erythema (arrow) without masses, bleeding, ulcers, or polyps (Figure C).

The diagnosis appears on page 21.

LETTER FROM THE EDITOR: It was great to be together at DDW

DR. ALLEN

Last month we had another successful Digestive Disease Week® in Chicago. Next year's DDW will be in Washington D.C., June 2-5, 2018. The science and clinical pearls presented in Chicago were excellent. Cover articles in this month's *GI & Hepatology News* from DDW include a description of the AGA's NIH-funded fecal transplant registry and results of endoscopic bariatric procedures compared to surgery.

From the AGA journals, we learn about probiotic use after antibiotics and patterns of progression in nondysplastic Barrett's. Variations in outcomes of HCC treatment and chronic liver disease are disturbing but fixable, given better resource allocation. Another article points out a resurgence of HCV among young women. We are noting this in parallel to the opioid epidemic. Finally, in our practice management section, there

Continued on page 5

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FRONTLINE MEDICAL COMMUNICATIONS

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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.

HH13276BT May 2017

Some new drugs, new uses

NASH *from page 1*

that target metabolic homeostasis, insulin resistance, inflammation, oxidative stress, or fibrosis (Liver Int. 2017 May;37:634-47).

Dr. Dufour gave an overview of the current trials that are underway in NASH. There are currently five ongoing multicenter phase III trials being undertaken with four drugs. First, there is the REGENERATE trial with Intercept's farnesoid X receptor obeticholic acid. This is a placebo-controlled trial comparing two daily doses of obeticholic acid (10 and 25 mg) on top of standard of care. The trial will recruit just over 2,000 patients with biopsy-proven stage 2-3 NASH fibrosis; the primary endpoint is the resolution of NASH without fibrosis worsening or fibrosis improvement without worsening of NASH at week 72.

Second, there is the RESOLVE-IT trial with Genfit's peroxisome proliferator-activated receptor alpha/delta agonist elafibranor. This randomized, double-blind trial hopes to recruit 2,000 patients with biopsy-proven NASH stage 1-3 fibrosis and will compare elafibranor 120 mg given once a day with placebo. The primary endpoint is the resolution of NASH without worsening of fibrosis at week 72.

Next, Tobira Therapeutics' C-C chemokine receptor type 2 and 5 antagonist cenicriviroc is being studied in the AURORA trial. Again, around 2,000 patients will be studied, but this time with stage 2-3 biopsy-proven NASH fibrosis. Cenicriviroc will be given daily at a dose of 150 mg and compared with placebo. The primary endpoint is the improvement of fibrosis by one or more stage with no worsening of steatohepatitis at 1 year.

Finally, there are the STELLA 3 and STELLA 4 trials with Gilead's apoptosis signal-regulated kinase-1 inhibitor selonsertib. Target accrual in both studies is 800 patients with STELLA 3 recruiting patients with stage 3 NASH fibrosis and STELLA 4 those with compensated cirrhosis from NASH. Both trials will compare two daily doses of selonsertib (6 and 18 mg) versus placebo. The primary endpoints are improvement of at least one or more fibrosis stage with no worsening of steatohepatitis at 48 weeks and event-free survival at week 240.

In addition, there are at least 20 phase IIb and IIa studies looking at a variety of other novel drugs with different therapeutic targets, Dr. Dufour said; many were described at the meeting.

Eric J. Lawitz, MD, AGAF, vice president of scientific and research development at the Texas Liver Institute, San Antonio reported the promising results of a "proof of concept" open-label study in which the safety and efficacy of treatment with the oral acetyl-CoA carboxylase (ACC) inhibitor, GS-0976, was examined in 10 patients with a clinical diagnosis of nonalcoholic fatty liver disease.

He reported that 12 weeks' treatment with GS-0976 suppressed de nova lipogenesis by 29%, compared with baseline (P = .022). There was also a 43% decrease in hepatic steatosis from baseline to 12 weeks (P = .006), as measured by the magnetic resonance imaging–proton-density fat fraction (MRI-PDFF). "There is a placebo-controlled phase II trial of GS-0976 in patients with NASH that is ongoing," Dr. Lawitz said.

Results of two phase II studies presented during the late-breaking

abstracts session at the meeting showed similar promising results could be achieved with drugs mimicking the activity of different fibroblast growth factors.

"Fibroblast growth factor 21 [FGF21] is a nonmitogenic hormone produced in the liver that is an important regulator of energy metabolism," said Arun J. Sanyal, MD, Virginia Commonwealth University in Richmond , who presented the findings of a study with the FGF21 inhibitor BMS-986036.

The study involved 74 patients with stage 1-3 biopsy-proven NASH fibrosis and a hepatic fat fraction of 10% or greater measured by MRI-PDFF. Patients were randomized to treatment with BMS-986036 at subcutaneously administered doses of 10 mg given once daily or 20 mg once weekly or to placebo for 16 weeks.

A significant reduction in the hepatic fat fraction was seen in patients treated with both the once-daily and once-weekly regimen of the active treatment relative to placebo, with absolute changes from baseline of –6.8% ($P = .008$) and –5.2% ($P = .0004$), respectively. "Results suggest that BMS-986036 had beneficial effects on steatosis, liver injury, and fibrosis in NASH," said Dr. Sanyal.

NGM282 is another recombinant human analog mimicking the action of an FGF, this time FGF19, and early data suggest that it also reduces hepatic steatosis and key biomarkers of NASH. Stephen Harrison, MD, the medical director of Pinnacle Clinical Research in Live Oak, Tex., reported data on 82 patients with stage 1-3 NASH fibrosis who had been treated with NGM-282 3 mg or 6 mg subcutaneously once daily or placebo for 12 weeks.

"The primary endpoint [decrease in absolute liver fat content greater than or equal to 5%] was met in 79% of NGM-282-treated subjects, with over one-third of subjects achieving normalization of liver fat content with 12 weeks of therapy," Dr. Harrison reported. One serious adverse event of acute pancreatitis occurred in a patient treated with FGF19, which was possibly thought to be treatment related.

Dr. Dufour disclosed receiving speaking and teaching fees from pharmaceutical companies. Gilead Sciences supported the study reported by Dr. Lawitz and he disclosed receiving grants and other support from the company and others. The study presented by Dr. Sanyal was financed by Bristol-Myers Squibb; funding was provided to his institution and he received support and consulting fees from many pharmaceutical companies. Dr. Harrison said he received research funding from and acted as a consultant to NGM Bio, which sponsored the study he presented.

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Continued from page 2

is an excellent article on the specific challenges facing independent GI practices.

The political front continues to be chaotic as the House passed a tax bill disguised as health care reform. We will follow these developments closely as they affect our patients' insurance coverage and lives. Personally, I spoke at multiple DDW venues stressing the need for us as physicians to be aware and involved in advocating for our patients. Visit gastro.org/take-action for ample direction about how you can be active.

John I. Allen, MD, MBA, AGAF
Editor in Chief

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FLASHBACK TO 2012

2007-**10-Year Anniversary**-2017

It's a whole new biosimilar world. In the April 2012 issue of *GI & Hepatology News* (*GIHN*) there was a small article on the issued Food and Drug Administration guidance on how to develop biosimilars. A biosimilar molecule must be structurally similar to the reference or originator product with the expectation that the safety and efficacy will be the same. The European Medicines Agency (EMA) established a legal framework for approving biologics in the European Union in 2003 and guidelines for approval in 2005 to 2006 with the first biosimilar approved in 2006 (somatropin [Omnitrope]).

The first monoclonal antibody biosimilar approved by the EMA was CT-P13 (infliximab-dyyb) in June 2013. There are now over 23 biosimilars approved for use in Europe. In 2012 there were no biosimilars on the market in the United States. This past year (2016) has been the year of the biosimilar with two of the four approved compounds used in inflammatory bowel disease – Inflectra (infliximab-dyyb, Hospira) April 2016 and Amjevita (adalimumab-atto, Amgen) September 2016 appearing.

The launch of these biosimilars raises a whole new series of questions. First and foremost for gastroenterologists – are the biosimilars truly similar in patients with inflammatory bowel disease? Adalimumab-atto was approved on the basis of two phase III studies in psoriasis and in rheumatoid arthritis and infliximab-dyyb was approved on the basis of studies in rheumatoid arthritis and ankylosing spondylitis. Other questions arise: 1. Can a patient who is doing well on the originator be safely switched to the biosimilar? 2. Can we use the same assays for drug monitoring? 3. Will use of biosimilars lead to a lower cost structure for patients and hospitals? 4. What are the regulations and guidelines for interchangeability? (*GIHN* March 2017). In the United States, development of biosimilars was slow to start but we expect to see an explosion in development of these agents in gastroenterology as the patents expire on the biologics currently in use.

Kim L. Isaacs, MD, PhD, AGAF, is professor of medicine in the division of gastroenterology and hepatology at the University of North Carolina at Chapel Hill. She is codirector of the UNC Center for Inflammatory Bowel Disease. She is an Associate Editor for GI & Hepatology News.

FROM THE AGA JOURNALS

Start probiotics within 2 days of antibiotics to prevent *Clostridium difficile* infection, study suggests

BY AMY KARON
Frontline Medical News

Starting probiotics within 2 days of the first antibiotic dose could cut the risk of *Clostridium difficile* infection among hospitalized adults by more than 50%, according to the results of a systemic review and metaregression analysis.

The protective effect waned when patients delayed starting probiotics, reported Nicole T. Shen, MD, of Cornell University, New York, and her associates. The study appears in the June issue of Gastroenterology (doi: 10.1053/j.gastro.2017.02.003). "Given the magnitude of benefit and the low cost of probiotics, the decision is likely to be highly cost effective," they added.

Systematic reviews support the use of probiotics for preventing *Clostridium difficile* infection (CDI), but guidelines do not reflect these findings. To help guide clinical practice, the reviewers searched MEDLINE, EMBASE, the International Journal of Probiotics and Prebiotics, and the Cochrane Library databases for randomized controlled trials of probiotics and CDI among hospitalized adults taking antibiotics. This search yielded 19 published studies of 6,261 patients. Two reviewers separately extracted data from these studies and examined quality of evidence and risk of bias.

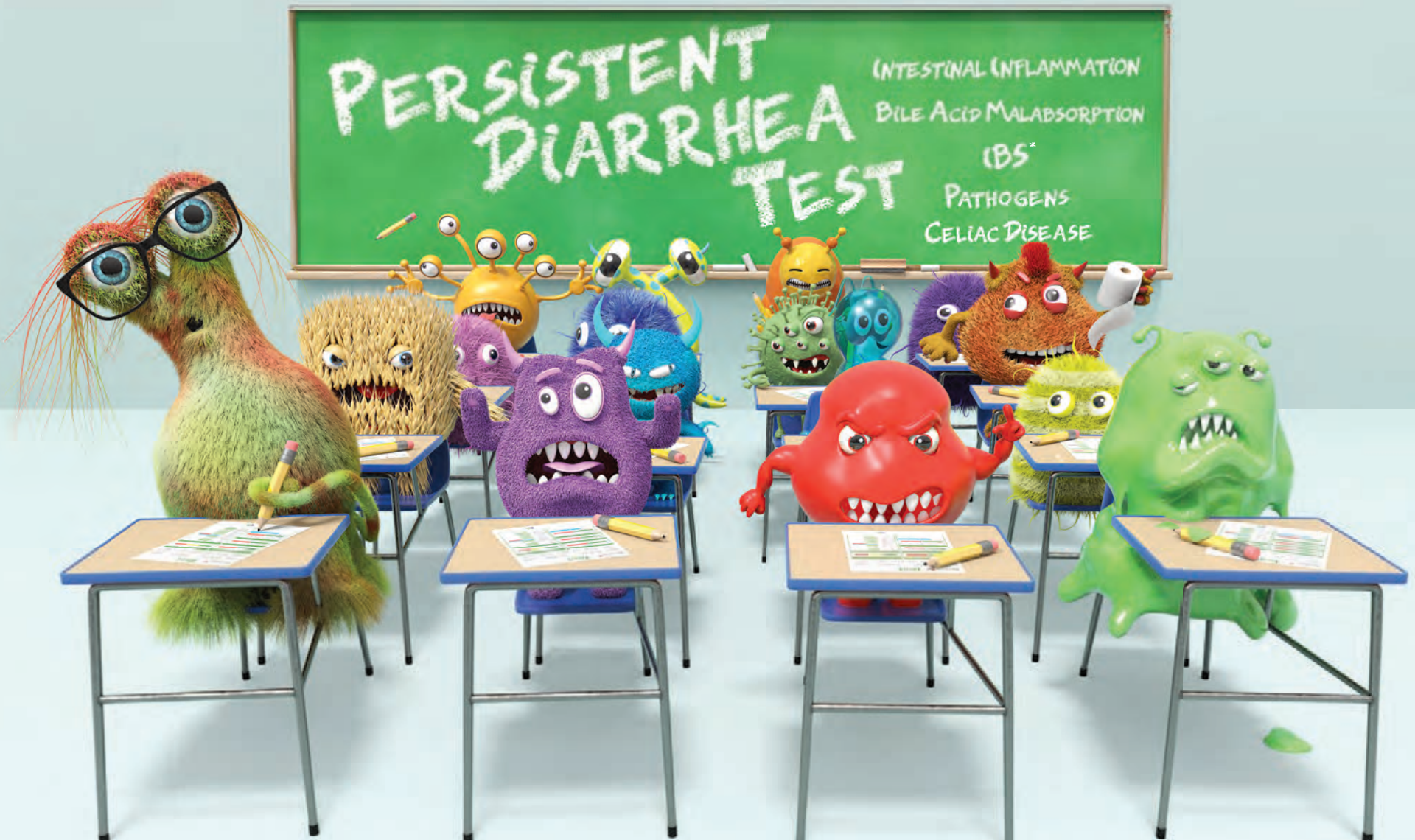
"Given the magnitude of benefit and the low cost of probiotics, the decision is likely to be highly cost effective." Importantly, probiotics were significantly effective against CDI only when started within 2 days of antibiotic initiation.

A total of 54 patients in the probiotic cohort (1.6%) developed CDI, compared with 115 controls (3.9%), a statistically significant difference (*P* less than .001). In regression analysis, the probiotic group was about 58% less likely to develop CDI than controls (hazard ratio, 0.42; 95% confidence interval, 0.30-0.57; *P* less than .001). Importantly, probiotics were significantly effective against CDI only when started within 2 days of antibiotic initiation (relative risk, 0.32; 95% CI, 0.22-0.48), not when started within 3-7 days (RR, 0.70, 95% CI, 0.40-1.23). The difference between these estimated risk ratios was statistically significant (*P* = .02).

In 18 of the 19 studies, patients received probiotics within 3 days of starting antibiotics, while patients in the remaining study could start probiotics any time within 7 days of antibiotic initiation. "Not only was [this] study unusual with respect to probiotic timing, it was also much larger than all other studies, and its results were statistically insignificant," the reviewers wrote. Metaregression analyses of all studies and of all but the outlier study linked delaying probiotics with a decrease in efficacy against CDI, with *P* values of .04 and .09, respectively. Those findings "suggest that the decrement in efficacy with delay in starting probiotics is not sensitive to inclusion of a single large 'outlier' study," the reviewers emphasized. "In fact, inclusion only dampens the magnitude of the decrement in efficacy, although it is still clinically important and statistically significant."

The trials included 12 probiotic formulas containing Lactobacillus, *Saccharomyces*, *Bifidobacterium*, and *Streptococcus*, either alone or in combination. Probiotics were not associated with adverse effects in the trials. Quality of evidence was generally high, but seven trials had missing data on the primary outcome. Furthermore, two studies lacked a placebo group, and lead authors of two studies disclosed ties to the probiotic manufacturers that provided funding.

One reviewer received fellowship support from the Louis and Rachel Rudin Foundation. None had conflicts of interest.



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NEW

FROM THE AGA JOURNALS

Persistence of NDBE does not mean low risk of EAC

BY AMY KARON
Frontline Medical News

Patients with at least five endoscopies with biopsies showing nondysplastic Barrett's esophagus were statistically as likely to progress to high-grade dysplasia or esophageal adenocarcinoma as patients with a single such biopsy, according to a multicenter prospective registry study in the June issue of Clinical Gastroenterology and Hepatology (doi: org/10.1016/j.cgh.2017.02.019).

The findings, which contradict those from another recent multicenter cohort study (Gastro. 2013;145[3]:548-53), highlight the need for more studies before lengthening the time between surveillance biopsies in patients with nondysplastic Barrett's esophagus, Rajesh Krishnamoorthi, MD, of Mayo Clinic in Rochester, Minn., wrote with his associates.

Barrett's esophagus is the strongest predictor of esophageal adenocarcinoma, but studies have reported mixed results as to whether the risk of this cancer increases over time or wanes with consecutive biopsies that indicate nondysplasia, the researchers noted. Therefore, they studied the prospective, multicenter Mayo Clinic Esophageal Adenocarcinoma and Barrett's Esophagus registry, excluding patients who progressed to adenocarcinoma within 12 months, had missing data, or had no follow-up biopsies. This approach left 480 subjects for analysis. Patients averaged 63 years of age, 78% were male, the mean length of Barrett's esophagus was 5.7 cm, and the average time between biopsies was 1.8 years, with a standard deviation of 1.3 years.

A total of 16 patients progressed to high-grade dysplasia or esophageal adenocarcinoma over 1,832 patient-years of follow-up, for an overall annual risk of progression of 0.87%. Two patients progressed to esophageal adenocarcinoma (annual risk, 0.11%; 95% confidence interval, 0.03% to 0.44%), while 14 patients progressed to high-grade dysplasia (annual risk, 0.76%; 95% CI, 0.45%-1.29%). Eight patients progressed to one of these two outcomes after a single nondysplastic biopsy, three progressed after two such biopsies, three progressed after three such biopsies, none progressed after four such biopsies, and two progressed after five such biopsies. Statistically, patients with at least five consecutive nondysplastic biopsies were no less likely to progress than were patients with only one nondysplastic biopsy (hazard ratio, 0.48; 95% CI, 0.07-1.92; $P = .32$). Hazard ratios for the other groups ranged between 0.0 and 0.85, with no significant difference in estimated risk between groups ($P = .68$) after controlling for age, sex, and length of Barrett's esophagus.

The previous multicenter cohort study linked persistently nondysplastic Barrett's esophagus with a lower rate of progression to esophageal adenocarcinoma, and, based on those findings, the authors suggested lengthening intervals between biopsy surveillance or even stopping surveillance, Dr. Krishnamoorthi and his associates noted. However, that study did not have mutually exclusive groups. "Additional data are required before increasing the interval between surveillance endoscopies based on persistence of nondysplastic Barrett's esophagus," they concluded.

The study lacked misclassification bias given long-segment Barrett's esophagus, and specialized gastrointestinal pathologists interpreted all histology specimens, the researchers noted. "The small number of progressors is a potential limitation, reducing power to assess associations," they added.

The investigators did not report funding sources. They reported having no conflicts of interest.

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Current practice guidelines recommend endoscopic surveillance in Barrett's esophagus (BE) patients to detect esophageal adenocarcinoma (EAC) at an early and potentially curable stage.


DR. WANI

Endoscopic surveillance of BE has numerous limitations. Persistence of nondysplastic BE (NDBE) has previously been shown to be an indicator of lower risk of progression to high-grade dysplasia (HGD)/EAC. However, outcomes studies on this topic have reported conflicting results.

Krishnamoorthi and his colleagues bring the issue of persistent NDBE as a potential risk stratification variable to the forefront. Using the Mayo Clinic registry, the authors found no statistically significant decrease in the risk of progression in patients with persistent NDBE. Similar results were recently reported by Nguyen and colleagues using the national Veterans Health Administration datasets.

Where do we stand with regard to persistence of NDBE and its impact on surveillance intervals? Future large cohort studies are required that address all potential confounders and include a large number of patients with progression to HGD/EAC (a challenge given the rarity of this outcome). Based on the available data, surveillance intervals cannot be lengthened in patients with persistent NDBE. Future studies also need to focus on the development and validation of prediction models that incorporate clinical, endoscopic, and histologic factors in risk stratification. Until then, meticulous examination techniques, cognitive knowledge and training, use of standardized grading systems, and use of high-definition white light endoscopy are critical in improving effectiveness of surveillance programs in BE patients.

Sachin Wani, MD, is associate professor of medicine and medical codirector of the Esophageal and Gastric Center of Excellence, division of gastroenterology and hepatology, University of Colorado at Denver, Aurora. He is supported by the University of Colorado Department of Medicine Outstanding Early Scholars Program and is a consultant for Medtronic and Boston Scientific.

Study confirms uneven VA access to liver cancer treatment

BY AMY KARON
Frontline Medical News

Only 25% of Veterans Affairs (VA) patients with potentially curable (Barcelona Clinic Liver Cancer stage 0/A) hepatocellular carcinoma (HCC) received resection, transplantation, or ablative therapy, according to the results of a national retrospective cohort study published in the June issue of Gastroenterology (doi: 10.1053/j.gastro.2017.02.040).

Furthermore, 13% of the fittest (Eastern Cooperative Oncology Group performance status 1-2) patients received no active treatment for their HCC, Marina Serper, MD, of Corporal Michael J. Crescenz VA Medical Center, Philadelphia, and Tamar H. Taddei, MD, of VA New York Harbor Health Care System, Brooklyn, N.Y., wrote with their associates in Gastroenterology.

"Delivery of curative therapies conferred the highest survival benefit, and notable geographic and specialist variation was observed in the delivery of active treatment," they added. "Future studies should further evaluate modifiable health system and provider-specific barriers to delivering high quality, multidisciplinary care in hepatocellular carcinoma [in order] to optimize patient outcomes."

HCC ranks second worldwide and fifth in the United States as a cause of cancer mortality. Gastroenterologists, hepatologists, medical oncologists, or surgeons may take primary responsibility for treatment in community settings, but little is known about how provider and health system factors affect outcomes or the likelihood of receiving active treatments, such as liver transplantation, resection, ablative or transarterial therapy,

Continued on following page

FROM THE AGA JOURNALS

Distance from transplant center predicted mortality

BY AMY KARON
Frontline Medical News

Living more than 150 miles from a liver transplant center was associated with a higher risk of mortality among patients with chronic liver failure, regardless of etiology, transplantation status, or whether patients had decompensated cirrhosis or hepatocellular carcinoma, according to a first-in-kind, population-based study reported in the June issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2017.02.023).

The findings underscore the need for accessible, specialized liver care irrespective of whether patients with chronic liver failure (CLF) are destined for transplantation, David S. Goldberg, MD, AGAF, of the University of Pennsylvania, Philadelphia, wrote with his associates. The associations "do not provide cause and effect," but underscore the need to consider "the broader impact of transplant-related policies that could decrease transplant volumes and threaten closures of smaller liver transplant centers that serve geographically isolated populations in the Southeast and Midwest," they added.

Managing chronic liver failure is complex – physicians must treat acute illness, portal hypertension and its complications, and hepatocellular carcinoma. Consequently, several studies have reported that care is best provided by experts at specialized practices, "nearly always" liver transplant centers in large urban areas, the researchers noted. For these reasons, geographic isolation might undermine survival even among the 11 of every 12 CLF patients who never undergo transplantation. Because no population-based study had explored this question, the researchers analyzed data from 16,824 patients with CLF who were included in the Healthcare Integrated Research Database between 2006 and 2014.

A total of 879 (5.2%) patients lived more than 150 miles from the nearest liver transplant center, the analysis showed. Even after controlling for etiology of liver disease, this subgroup was at significantly greater risk of mortality (hazard ratio, 1.2; 95% confidence interval, 1.1-1.3; *P* less than .001) and of dying without undergoing transplantation (HR, 1.2; 95% CI, 1.1-1.3; *P* = .003) than were patients who were less geographically isolated.

Distance from a transplant center also predicted overall and transplant-free mortality when modeled as a continuous variable, with hazard ratios of 1.02 (*P* = .02) and 1.03 (*P* = .04), respectively. "Although patients living more than 150 miles from a liver transplant center had fewer outpatient gastroenterologist visits, this covariate did not affect the final models," the investigators reported. Rural locality did not predict mortality after controlling for distance from a transplant center, and neither did living in a low-income zip code, they added.

Data from the Centers for Disease Control and Prevention indicate that age-adjusted rates of death from liver disease are lowest in New York, where the entire population lives within 150 miles of a liver transplant center, the researchers noted. "By contrast, New Mexico and Wyoming have the highest age-adjusted death rates, and more than 95% of those states' populations live more than 150 miles from a [transplant] center," they emphasized. "The management of most patients with CLF is not centered on transplantation, but rather the spectrum of care for decompensated cirrhosis and hepatocellular carcinoma. Thus, maintaining access to specialized liver care is important for patients with CLF."

Dr. Goldberg received support from the National Institutes of Health. The investigators had no conflicts.

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Continued from previous page

sorafenib, systemic chemotherapy, or radiation. Accordingly, the researchers reviewed medical records and demographic data from all 3,988 U.S. patients diagnosed with HCC between 2008 and 2010 who received care at 128 Veterans Affairs centers. Patients were followed through the end of 2014. Data were from the Veterans Outcomes and Costs Associated With Liver Disease (VOCAL) cohort study (Gastroenterology. 2017 Mar 7. doi: 10.1053/j.gastro.2017.02.040).

After diagnosis, most (54%) patients underwent only transarterial palliative therapy, and 24% received no cancer treatment. Being treated at an academically affiliated VA hospital nearly doubled the odds of receiving active therapy (odds ratio, 1.97; 95% confidence interval, 1.6-2.4; *P* less than .001), even after the researchers controlled for race, Charlson-Deyo comorbidity, and presenting Barcelona Clinic Liver Cancer stage. Evaluation by multiple specialists also significantly increased the odds of active treatment (OR, 1.60; 95% CI, 1.15-2.21; *P* = .005).

Receipt of active therapy also varied significantly by region. Compared with patients in the Northeastern United States, those in the mid-South were significantly less likely to receive active therapy (hazard ratio, 0.62; 95% CI, 0.44-0.85). Patients in the Southeast, Central, and Western United States also were less likely to receive active treatment than were those in the Northeast, but 95% CIs for these hazard ratios were nonsignificant. Virtual tumor boards could help overcome diagnostic and treatment delays, but costs, care coordination, patient factors, and compensation issues are major barriers against implementation, they noted.

Overall survival was associated with active treatment of HCC, including liver transplantation (HR, 0.22; 95% CI, 0.16-0.31), liver resection (HR, 0.38; 95% CI, 0.28-0.52), ablative therapy (HR, 0.63; 95% CI, 0.52-0.76), and transarterial therapy (HR, 0.83; 95% CI, 0.74-0.92). Reduced mortality was associated with seeing a hepatologist (HR, 0.7), medical oncologist (HR, 0.82), or surgeon (HR, 0.79) within 30 days of diagnosis (*P* less than .001 for each). Undergoing review by a multidisciplinary tumor board was associated with significantly reduced mortality (HR, 0.83; *P* less than .001), said the researchers. "Findings from the VOCAL cohort of predominantly older males with significant medical comorbidities are important in light of the aging U.S. population and a nearly 70% expected increase in cancer among older adults," they wrote.

The study was funded by unrestricted grants from Bayer Healthcare Pharmaceuticals and the VA HIV, Hepatitis and Public Health Pathogens Programs. The investigators had no conflicts.

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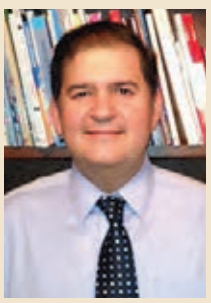
The treatment of hepatocellular carcinoma (HCC) can be challenging because of underlying chronic liver disease and cirrhosis in the majority of patients. There are important aspects of the study Dr. Serper and colleagues worth highlighting.

First, 36% of patients presented with early-stage HCC and clearly had a better overall survival. This highlights the need for surveillance of patients with cirrhosis not only in the VA but also in other health systems. Second, only a minority of patients with early-stage HCC received curative interventions. For improved outcomes, patients with early-stage disease should receive appropriate curative interventions. Third, gastroenterologists saw a large number of patients with HCC in the VA system, but, unfortunately, this led to less receipt of active therapy and a trend for a worse all-cause mortality, compared with hepatologists and other specialties. It is critical that gastroenterologists refer patients to specialties more adept at treating HCC in order to achieve better outcomes.



DR. MARRERO

Lastly, only 34% of patients with HCC were managed via a multidisciplinary tumor conference. Importantly, these patients had an increased probability of receipt of active treatment and a 17% reduction in all-cause mortality. Our group has shown that a multidisciplinary approach to treating HCC improves overall survival.

Jorge A. Marrero, MD, MS, AGAF, is professor of medicine and medical director for liver transplantation at UT Southwestern Medical Center Dallas. He has no conflicts of interest to report regarding this manuscript or commentary.

AGA recognizes 52 investigators with research funding

The AGA Research Foundation is thrilled to award 52 researchers with research funding in the 2017 award year.

"The AGA Research Foundation has a proven track record of funding young investigators who subsequently achieve great success in research. We are confident that the 2017 class will be no exception," said Robert S. Sandler, MD, MPH, AGAF, chair, AGA Research Foundation. "AGA is honored to invest in this year's award recipients and looks forward to seeing how each research project contributes to advancing the field of gastroenterology."

"The AGA Research Foundation has a proven track record of funding young investigators who subsequently achieve great success in research. We are confident that the 2017 class will be no exception."

The AGA Research Award Program serves to support talented investigators who are pursuing careers in digestive disease research. A grant from the AGA Research Foundation ensures that a major proportion of the recipient's time is protected for research.

The awards program is made possible thanks to generous donors and funders contributing to the AGA Research Foundation. Show your support for GI research.

To learn about upcoming research funding opportunities, and to view the list of this years' winners, visit www.gastro.org/awards.

This year's honorees were recognized during several AGA Research Foundation events at Digestive Disease Week® 2017, which took place May 6-9 in Chicago, IL.

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Dr. Sheila E. Crowe becomes President of AGA Institute

Sheila E. Crowe, MD, FRCPC, FACP, FACG, AGAF, of the University of California, San Diego (UCSD), began her term as 112th president of the AGA Institute immediately following Digestive Disease Week® (DDW) 2017.

A former AGA Governing Board member and chair of the AGA Council, which plans DDW, Dr. Crowe has had a successful career in research while also developing a robust clinical practice focused on celiac disease and food allergy.

"Health policy changes and the evolving demographics of our society have forced the greatest changes in clinical practice since the advent of Medicare in 1965. AGA recognizes this moment as an inspiring juncture in the evolution of medicine," said Dr. Crowe, professor of medicine and director of research in the division of gastroenterology at UCSD. "AGA has consistently adapted to change over the years, developing initiatives that provide a forward-looking vision for our members."


Dr. Sheila E. Crowe

Dr. Crowe has been in academic gastroenterology for her entire career with experience at several renowned institutions including McMaster University, the University of Texas-Galveston, the University of Virginia, and now UCSD.

In addition to her work on the AGA board and council, Dr. Crowe she has served on AGA committees related to research, education, and women. She has been appointed by AGA leadership to several key task forces, to direct key educational activities and to reevaluate our governance and organization.

To learn more about Dr. Crowe, read the *Gastroenterology* article (http://www.gastrojournal.org/article/S0016-5085[17]30337-2/fulltext) detailing her early life, academic background, history, and awards at AGA and beyond.

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DDSEP eight Quick quiz

Digestive Diseases Self-Education Program

Q1: A 56-year-old man with a history of decompensated cirrhosis due to hepatitis C, complicated by ascites, presents with abdominal distension. A therapeutic paracentesis is performed, and is positive for spontaneous bacterial peritonitis.

Which statement is true regarding spontaneous bacterial peritonitis?

A. Cultures identify bacteria in 5% of cases
B. Recurrence rate is low if infection is treated in the acute setting
C. Nosocomial infections respond well to third-generation cephalosporins
D. Patients may be completely asymptomatic

Q2: The family of a 7-year-old boy that has been followed for colitis for the past 2 years presents with many questions and concerns. He was diagnosed with colitis at age 4 when he presented with several weeks of bloody diarrhea. He is doing well on a maintenance regimen of mesalamine but the family would like to discuss what the future may hold.

Which of the following statements describes a likely outcome of colitis at this age?

A. His colitis will likely resolve by time he reaches puberty.
B. The child's colitis will likely worsen over the next several years, requiring colectomy.
C. The child will probably not reach his expected mid-parental height.
D. The child should start enteral tube feedings immediately.
E. By the time he reaches puberty, it will likely become apparent he has Crohn's disease.

The answers are on page 13.

2018 AGA Fellows Program now accepting applications

The application period for the 2018 AGA Fellows Program is now open. The program recognizes members whose accomplishments demonstrate personal commitment to the field of gastroenterology with the distinction of fellowship.

AGA Fellows receive this honor from AGA for their superior professional achievement in clinical private or academic practice and in basic or clinical research.

AGA Fellows receive:
- The privilege of using the designation "AGAF" in professional activities.
- An official certificate and pin denoting your status.
- A listing on the AGA website.

And more.

Apply today to join this international community of excellence.

Find more information, including the list of benefits and criteria for fellowship, at www.gastro.org/fellowship. The deadline for application submissions is Monday, July 31, 2017.

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Are you prepared for MACRA?

MACRA (Medicare Access and CHIP Reauthorization Act of 2015) replaces the flawed sustainable growth rate (SGR) formula and significantly changes the way Medicare pays physicians.

Many things about the Affordable Care Act (ACA; Obamacare) are likely to change under the new administration, but MACRA and the commitment to cost-effective, value-based care is here to stay. MACRA is separate from the ACA. Congress overwhelmingly passed MACRA legislation with bipartisan support. MACRA will eventually transition physicians toward more value-based payments.

It is important to understand MACRA to ensure you are doing everything required under the current rules in 2017. Ignore MACRA in 2017 and you will face an automatic reduction of 4% to your payments under Medicare in 2019.

AGA offers educational webinars and videos to help you prepare. Visit gastro.org/MACRA to learn more.

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Order the 2017 AGA Postgraduate Course resources

The 2017 AGA Postgraduate Course: The Full Scope of GI Advances resources are available for purchase. Gain access to the multitopic postgraduate course taught by world-renowned leaders with the 2017 resources, available in the following formats:

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- Online sessions: CME and MOC available through webcasts of the general session lectures and select breakout sessions.

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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

Biobank of stool samples planned

Transplants *from page 1*

ed with FMT, and some have been serious – including one death from aspiration pneumonia in a patient who received donor stool via nasogastric tube (Clin Infect Dis. 2015 Mar;61[1]:136-7). Other adverse events are usually self-limited but can include low-grade fever, abdominal pain, bloating, and diarrhea.

Scientists are only now beginning to unravel the ways the microbiome promotes both health and disease. Specific alterations, for example, have been associated with obesity and other conditions; there is concern that transplanting a new microbial population could induce a disease phenotype in a recipient who might not have otherwise been at risk.

With the planned cohort size and follow-up period, the study should be able to detect any adverse events that occur in more than 1% of the population, Dr. Kelly said. It will include a comparator group of patients who also have recurrent or refractory *C. difficile* infection from a large insurance claims database to allow comparison between patients treated with FMT and those treated with antibiotics only.

The registry study also aims to discover which method or methods of transplant delivery are best, she said. Right now, there are several methods (colonoscopy/sigmoidoscopy, enema, upper gastrointestinal endoscopy, nasogastric or nasoduodenal tube, and capsules), and no consensus on which is best. As indications for FMT expand, the approach will probably be matched to the disorder being treated, and the study may help illuminate this as well.

See related video at gihepnews.com.

For the first 2 years after transplant, clinicians will follow patients and enter data into the registry. After that, an electronic patient-reported outcomes system will automatically contact the patient annually for follow-up information by email or text message. When patients enter their data, they can access material that will help keep them up-to-date on potential adverse events.

The study will also include a biobank of stool samples obtained during the procedures, hosted by the American Gut Project and the Microbiome Initiative at the University of California, San Diego. This arm of the project will analyze the microbiome of 3,000 stool samples from recipients, both before and after their transplant.

The registry study, a project of the AGA Center for Gut Microbiome Research and Education, is funded by a $3.3 million grant from the National Institute of Allergy and Infectious Diseases. It will be conducted in partnership with the Crohn's and Colitis Foundation, Infectious Diseases Society of America, and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. It currently is accepting applications. Physicians who perform FMT for *C. difficile* infections, and centers that conduct FMT research for other potential indications, can fill out a short survey to indicate their interest at gastro.org/fmtregistry.

DDW® is jointly sponsored by the American Association for the Study of Liver Diseases (AASLD), the AGA Institute, the American Society for Gastrointestinal Endoscopy (ASGE), and the Society for Surgery of the Alimentary Tract (SSAT).

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DDSEP eight
Digestive Diseases Self-Education Program

Quick quiz Answers

Q1: Answer: D

Objective: Recognize that spontaneous bacterial peritonitis may present in an asymptomatic manner.

Discussion: It is important to recognize that patients with spontaneous bacterial peritonitis may present in various ways and may not exhibit classic abdominal pain or fevers. Patients may have atypical or no overt symptoms at all. With direct inoculation of ascitic fluid into culture bottles at bedside, cultures may identify bacteria in up to 40%-50% of cases.

Patients who survive an episode of SBP have a very high risk of recurrence (70%) within the first year of the index episode. It is therefore essential that patients recovering from SBP be started on prophylactic therapy prior to hospital discharge. Nonabsorbable (or poorly absorbable) antibiotics are most effective for such prophylaxis by selectively eliminating gram-negative organisms in the gut.

These agents reduce the rate of SBP recurrence to around 15%–20%. Nosocomial infections respond poorly (~40% of cases) to third-generation cephalosporins. Those who have been in the hospital and received antibiotics within the past 90 days should receive extended-spectrum antibiotics.

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Q2: Answer: E

Critique: Children with early-onset inflammatory bowel disease tend to present with colonic disease. Many of them eventually develop signs and symptoms consistent with Crohn's disease as they get older. They are often diagnosed as "indeterminant" colitis or even ulcerative colitis but the diagnosis often changes. The colitis does not usually improve with age and these early-onset patients often follow a complicated course. This boy may eventually require enteral tube feedings or even a colectomy; however, that cannot be predicted at this time. Provided his disease is well managed, he should reach his expected mid-parental height.

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Bile acid malabsorption as a cause of chronic diarrhea

BY LORA T. MCGLADE
Frontline Medical News

AT DDW

CHICAGO – Bile acid malabsorption increasingly is recognized as a cause of persistent, chronic diarrhea, but patients often receive suboptimal treatment because medical and public awareness is low, Julian Walters, MD, of Imperial College London, said at Digestive Disease Week®.

Members of two patient support groups in the United Kingdom were invited to complete an online survey to provide information on how this condition affects them. The first 100 responses were analyzed. Respondents were overwhelmingly female (91). More than 35 respondents were diagnosed after the age of 50 years, and 35 felt their condition had not been taken seriously by multiple practitioners prior to their eventual diagnosis, she reported.

Two-thirds of respondents had been diagnosed with irritable bowel syndrome; the majority (68) of these had more than 10 interactions with medical professionals before being properly diagnosed.

Once appropriately diagnosed, most respondents reported doing very well on drugs such as cholestyramine and colesevelam, Dr. Walters said. He stressed that mental health issues are an important part of this condition because of its pervasive effects on daily life.

Dr. Walters disclosed that he has been a consultant to or has received research funds from GE Healthcare, Intercept, Albireo, and Novartis.

Digestive Disease Week® is jointly sponsored by the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterological Association (AGA) Institute, the American Society for Gastrointestinal Endoscopy (ASGE), and the Society for Surgery of the Alimentary Tract (SSAT).

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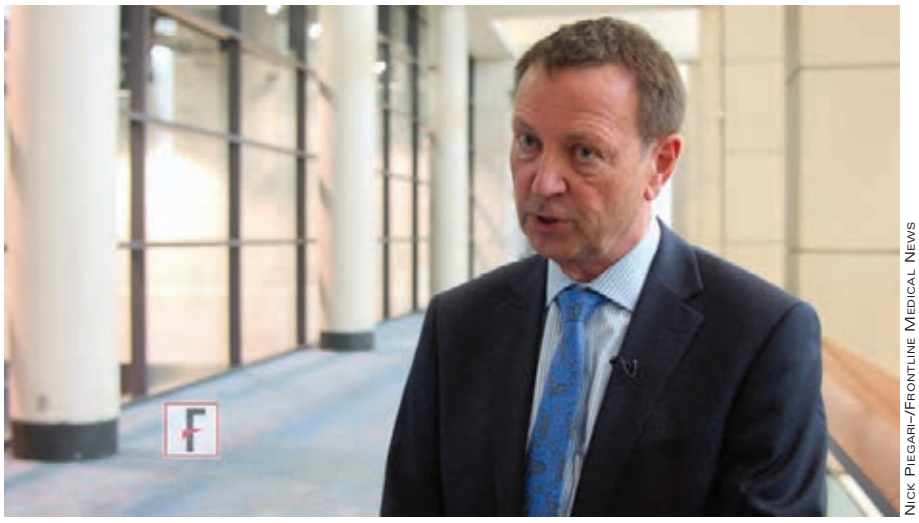

NICK PIEGARI–/FRONTLINE MEDICAL NEWS

Dr. Julian Walters discusses the survey and bile acid malabsorption in a video interview, which you can view at gihepnews.com.

Anti-TNF drugs reduce mortality in Crohn's disease

BY ROXANNE NELSON
Frontline Medical News

AT DDW

CHICAGO – As compared with prolonged use of corticosteroids, the use of anti–tumor necrosis factor (TNF) drugs was associated with reduced mortality in patients with Crohn's disease, according to new findings presented here at Digestive Disease Week®.

The reduced mortality seen in this population may be secondary to the lower rates of major adverse cardiovascular events and hip fracture that are associated with anti-TNF use as compared to corticosteroid use. However, the same reduction in mortality risk was not observed in patients with ulcerative colitis using anti-TNF drugs.

"Corticosteroids are widely used, even though they are not recommended for maintenance therapy," said James D. Lewis, MD, MSCE, professor of medicine at the University of Pennsylvania, Philadelphia, who presented the findings of his study at the meeting. "Previous studies have associated their use with an increased risk of mortality."

Anti-TNF therapy has become a cornerstone in the management of inflammatory bowel disease (IBD), and Dr. Lewis noted that these agents have been shown to be useful for induction, maintenance, and remission, and to reduce surgical and hospitalization rates.

"However, fear of adverse events and cost has deterred greater use of these agents," he told attendees.

In their study, Dr. Lewis and his colleagues compared the mortality risk with prolonged corticosteroids use versus anti-TNF drugs in patients with IBD.

They conducted a retrospective cohort study using data for 2006-2013 of a population of Medicaid and Medicare beneficiaries in the United States. The cohort included individuals who had received treatment with corticosteroids within the prior year and subsequently had been treated with either additional corticosteroid therapy for a total of greater than 3,000 mg of prednisone or equivalent within 12 months or newly initiated anti-TNF therapy.

The primary outcome of the study was all-cause mortality and secondary outcomes included common causes of death.

Dr. Lewis explained that 57 potential confounding variables were thought to be associated with the choice between corticosteroid use or anti-TNF therapy. These variables, which included demographic characteristics, medications, diagnostic tests, and comorbidities, were measured.

Among Crohn's disease patients,

Continued on following page

Antacid use in infants linked to increased fracture risk

BY TARA HAELLE
Frontline Medical News

SAN FRANCISCO – Children were more likely to experience a fracture if they were prescribed antacids before age 1 year, according to a study of military families.

The large study revealed that use of proton pump inhibitors (PPIs) before age 1 year was linked to a 22% increased risk of fracture, compared with those not prescribed antacids. Similarly, children prescribed both PPIs and H_2-blockers before age 1 year were 31% more likely to have a fracture compared to those not taking the drugs.


DR. MALCHODI

"A lot of data are coming out that proton pump inhibitors are not quite as benign as we used to think, and we are seeing that fracture risk is increased with use," U.S. Air Force Capt. Laura Malchodi, MD, a pediatrics resident at Walter Reed National Military Medical Center in Bethesda, Md., told colleagues at the Pediatric Academic Societies meeting.

Antacid use has been increasing among both adults and children, but the biggest rise has been in children under age 1 year, she said. Previous research into adult use of antacids has revealed an increased incidence of fractures, so Dr. Malchodi investigated the incidence of fractures in children under age 1 year among those who had taken PPIs, H_2-blockers, neither, or both.

"What this means for doctors is that, when you do start to think of using proton pump inhibitors or any antacid therapy in children, we should really think of limiting it to one type if possible – H_2-blockers are now preferable – and for the shortest amount of time as possible," Dr. Malchodi said of her findings.

The retrospective study's cohort comprised 874,447 children born between 2001 and 2013 who had been in the U.S. Military Health System for at least 2 years. Children who took antacids after age 1, spent more than a week in a neonatal intensive care unit, or had nonaccidental trauma (abuse) or osteogenesis imperfecta were excluded.

Ninety percent of the cohort had not received prescriptions for any antacids (789,631 children) in their first year of life, and 1.2% had received prescriptions for both PPIs and H_2-blockers before age 1 year. Of the remaining children, 7.7% had received prescriptions for H_2-blockers, and 0.8% for PPIs.

The children who had and had not been prescribed antacids were similar in median years enrolled in the system, but nearly twice as many who received antacid prescription had been preterm (6.4% vs. 3.5%, *P* less than .05). Similarly, 3.7% of those prescribed antacids had a low birth weight, compared with 2.2% of those not prescribed antacids (*P* less than .05). The median age of fracture also differed for the two groups: 3.9 years for those prescribed antacids and 4.5 years for those not (*P* less than .05).

In using medical records during their analysis, the researchers excluded follow-up visits for the same fracture within the previous 6 months. Before adjustment for covariates, boys had a slightly increased risk of fracture (hazard ratio, 1.08), and those with a previous fracture had an 85% increased risk (HR, 1.85). Compared with children not prescribed antacids, those prescribed PPIs had a 23% increased risk of fracture (HR, 1.23), and those prescribed H_2-blockers had a 13% increased risk (HR, 1.13). Those prescribed combination antacid therapy had a 32% increased risk of fractures (HR, 1.32).

Adjustment for preterm birth, low birth weight, sex, and a previous fracture barely reduced those risks: 22% increased risk for PPI use, 4% increased risk for H_2-blocker use, and 31% increased risk for using both. The vast majority of children who took antacids had been prescribed them in their first 6 months, so the researchers calculated adjusted risk by age of exposure. For H_2-blockers, no statistically significant increased risk of fracture existed in those taking them before or after 6 months old.

Those taking PPIs, however, had a 25% increased risk of fracture if they took them before 6 months old, compared with a 20% increased risk if prescribed PPIs between 6 and 12 months. Likewise, children taking both PPIs and H_2-blockers before 6 months old had a 32% increased risk of fracture, compared with a 23% increased risk between 6 and 12 months old.

Analysis of the duration of children's use of antacids revealed a dose-response relationship, with an increasing risk alongside increasing days taking the medication. For example, those on PPIs for a month or less had a 19% increased risk of fracture, compared with children not prescribed antacids, but that rose to a 23% increased risk for those taking PPIs from 60 to 150 days and to a 42% increased risk for taking them longer than 150 days.

Similarly, the risk of fracture after having taken H_2-blockers for up to a month was 14%, which increased to 22% for medication durations over 120 days. Children on combination therapy took the medication for much longer than did children prescribed either antacid. The risk of fracture was 17% greater for those taking them for up to 4 months, but that increased to a 50% greater risk for children taking both antacids for longer than 338 days.

"A couple of decades ago, we thought these medications were super safe, that there could be no problem with them," Dr. Malchodi said, suggesting that their availability over the counter for adults may contribute to that perception. "With this growing evidence, there's at least a lot more caution about using them," she said.

Because the study relied on prescriptions for antacids, the researchers could not take into account which children actually took the antacids. Another limitation was their inability to consider other potential confounders, such as socioeconomic status or comorbidities that may later increase the risk of fracture. Further, exclusion of 6 months of follow-up after one fracture may have missed new fractures in that time period. Using a military cohort, on the other hand, meant having a geographically and socioeconomically diverse population with less risk of care bias because all the children had universal health care coverage.

No external funding was used. Dr. Malchodi reported having no disclosures.

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Continued from previous page

7,694 were prolonged corticosteroid users and 1,879 were new to anti-TNF therapy. Among patients with ulcerative colitis, 3,224 were long-term corticosteroid users and 459 were new anti-TNF users.

The researchers found that the weighted annual incidences of death per 1,000 Crohn's disease treated patients were 21.4 for those using anti-TNF therapy and 30.1 for those with prolonged corticosteroid use. For those with ulcerative colitis, these figures were 23.0 and 30.9, respectively.

The risk of death was statistically significantly reduced in Crohn's disease patients who used anti-TNF therapy (odds ratio, 0.78; 95% confidence interval, 0.65-0.93). However, the benefit was not as pronounced in ulcerative colitis.

"We did not see the same effect for ulcerative colitis but for mortality, it was in the same direction, with a hazard ratio of 0.87," he said.

Among the Crohn's disease patients, anti-TNF therapy was associated with lower rates of major adverse cardiovascular events (OR, 0.68; 95% CI, 0.55-0.85) and hip fracture (OR, 0.5; 95% CI, 0.34-0.83), which were statistically significant. The use of anti-TNF therapy also reduced the risk of stroke in Crohn's disease patients (OR, 0.72; 95% CI, 0.51-1.03), but there was also an increase in the risk of cancer (OR, 0.27; 95% CI, 0.98-1.65). Both of these findings nearly reached statistical significance.

In the model that censored for any of the secondary outcomes, the lower mortality risk was attenuated and very close to a null result (OR, 0.97; 95% CI 0.63-1.47).

Dr. Lewis also pointed out that in some of their models, the magnitude of benefit with anti-TNF therapy appears to be greatest in the patients with the most comorbidities.

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Dr. Lewis has disclosed financial relationships with Takeda, Pfizer, Lilly, Gilead, Johnson and Johnson, Samsung Bioepis, AbbVie, and Dark Canyon Laboratories.

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Twice-daily tofacitinib induces UC remission

BY HEIDI SPLETE
Frontline Medical News

A 10-mg dose of tofacitinib twice daily was significantly more effective than placebo for inducing remission in ulcerative colitis (UC) patients, based on data from a group of three randomized trials totaling approximately 1,500 adults. The findings were published online in the New England Journal of Medicine (2017;376:1723-36).

The series of OCTAVE studies (Oral Clinical Trials for Tofacitinib in Ulcerative Colitis) included adults with moderately to severely active UC. Patients were randomized to 10 mg of tofacitinib, 5 mg tofacitinib, or placebo. The studies were conducted over a 4-year period, at 144 sites for OCTAVE 1, 169 sites for OCTAVE 2, and 297 sites for OCTAVE Sustain.

The primary endpoints of the OCTAVE 1 and OCTAVE 2 induction studies were remission at 8 weeks (defined as a Mayo score of 2 or less, with no subscore less than 1 and a rectal bleeding subscore of 0). The primary endpoint of OCTAVE Sustain was remission at 52 weeks.

In both OCTAVE 1 and OCTAVE 2, the remission rates at 8 weeks were significantly higher in the 10-mg tofacitinib groups, compared with the placebo groups (18.5% vs. 8.2%, respectively; 16.6% vs. 3.6%, respectively). The rate of remission at 52 weeks was significantly higher in the 5-mg and 10-mg tofacitinib groups (34.3% and 40.6%, respectively) than in the placebo group (11.1%) in OCTAVE Sustain.

In addition, rates of mucosal healing were greater in the tofacitinib group than in the placebo group at 8 weeks and 52 weeks.

"Pharmacokinetic results in the OCTAVE trials did not indicate a decrease in plasma tofacitinib concentrations during the course of treatment at any given dose in individual patients," noted William J. Sandborn, MD, AGAF, of the University of California, San Diego, and his colleagues.

In OCTAVE 1, serious adverse events occurred in 4.2% and 8.0% of patients in the 10-mg and placebo groups, respectively. In OCTAVE 2, they occured in 3.4% and 4.1% of the 10-mg and placebo groups, respectively. The rate of serious adverse events in OCTAVE Sustain was 5.1%, 5.6%, and 6.6% in the 10-mg, 5-mg, and placebo groups, respectively. Tofacitinib was associated with increased lipid levels and higher rates of overall infection and herpes zoster infection, compared with placebo.

The study was supported by Pfizer. Lead author Dr. Sandborn and several coauthors disclosed financial relationships with multiple companies including Pfizer.

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Indomethacin slashes post-ERCP pancreatitis risk

Drug benefits primary sclerosing cholangitis patients.

BY MICHELE G. SULLIVAN
Frontline Medical News

AT DDW 2017

CHICAGO – Rectal indomethacin reduced by 90% the risk of post-procedural pancreatitis in patients with primary sclerosing cholangitis.

The anti-inflammatory has already been shown to reduce the risk of acute pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP) in a general population, Nikhil Thiruvengadam, MD, said at the annual Digestive Disease Week®. Now, his retrospective study of almost 5,000 patients has shown the drug's benefit in patients with primary sclerosing cholangitis (PSC), who are at particularly high risk of pancreatitis after the procedure.

The study also identified some patient characteristics that further increase the risk for post-ERCP pancreatitis (PEP), said Dr. Thiruvengadam of the University of Pennsylvania, Philadelphia.

"A prior history of PEP and a difficult initial cannulation were significant risk factors for developing PEP," he said. "Indomethacin significantly reduced this risk, and our findings suggest that future prospective trials studying pharmacological prophylaxis of PEP – including rectal indomethacin – should be powered to be able detect a difference in PSC patients, and they should be included in such studies."

In 2016 Dr. Thiruvengadam and his colleagues showed that rectal indomethacin significantly reduced the risk of PEP by about 65% in a diverse group of patients, including those with malignant biliary obstruction (Gastroenterology. 2016;151:288-97). This new study used an expanded patient cohort but focused on those with PSC, who run a higher risk of PEP because they require multiple ERCPs for diagnosis, stricture removal, and cholangiocarcinoma screening.

"A prior history of PEP and a difficult initial cannulation were significant risk factors for developing PEP. Indomethacin significantly reduced this risk."

The study comprised 4,764 patients who underwent ERCP at the University of Pennsylvania from 2007 to 2015; of these, 200 had PSC. Rectal indomethacin was routinely administered to patients beginning in June 2012. The primary outcome of the study was post-ERCP pancreatitis. The secondary outcome was the severity of post-ERCP pancreatitis.

PEP was about twice as common in the PSC group as in the overall cohort (6.5% vs. 3.8%).

Moderate-severe PEP also was twice as common (4% vs. 2%).

Dr. Thiruvengadam broke down the cohort by indication for ERCP. These included PSC as well as liver transplant, choledocholithiasis, benign pancreatic disease, bile leaks, and ampullary adenoma. PSC patients had the highest risk of developing PEP – almost 3 times more than those without the disorder (odds ratio, 2.7).

Among PSC patients, age, gender, and total bilirubin were not associated with increased risk. A history of prior PEP increased the risk by 17 times, and a difficult initial cannulation that required a pre-cut sphincterotomy increased it by 15 times.

"Interestingly, dilation of a common bile duct stricture reduced the odds of developing PEP by 81%," Dr. Thiruvengadam said.

He then examined the impact of rectal indomethacin on the study subjects. Overall, PEP developed in 5% of those who didn't receive indomethacin and 2% of those who did. In the PSC group, PEP developed in 11% of those who didn't get indomethacin and less than 1% of those who did.

Indomethacin was particularly effective at preventing moderate-severe PEP, Dr. Thiruvengadam noted. In the overall cohort, moderate-severe PEP developed in 3% of unexposed patients compared to 0.6% of those who received the drug. The difference was more profound in the PSC group: None of those treated with indomethacin developed moderate-severe PEP, which occurred in 9.3% of the unexposed group.

Generally, patients who undergo a sphincterotomy are at lower risk for PEP, Dr. Thiruvengadam said, and this was reflected in the findings for the overall group: PEP developed in 3% of the untreated patients and 0.5% of the treated patients. Post-sphincterotomy patients with PSC, however, were still at an increased risk of PEP. Indomethacin significantly mitigated this – no patient who got the drug developed PEP, compared with 10.5% of those who didn't get it.

A series of regression analyses confirmed the consistency of these findings. In an unadjusted model, rectal indomethacin reduced the risk of post-ERCP PEP by 91% in patients with PSC. A model that adjusted for common bile duct brushing, type of sedation, and common bile duct dilation found a 90% risk reduction. Another model that controlled for classic risk factors for PEP (age, gender, total bilirubin, history of PEP, pancreatic duct injection and cannulation, and pre-cut sphincterotomy) found a 94% risk reduction.

"We additionally performed a propensity score matched analysis to account for potential unmeasured differences between the two cohorts, and it also confirmed the results found and demonstrated that indomethacin significantly reduced the odds of developing PEP by 89%," Dr. Thiruvengadam said.

He had no financial conflicts of interest to disclose.

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ESG is less invasive procedure

Surgery *from page 1*

LSG, and 67 to LAGB. Patient demographic characteristics, including age, sex, and diabetes, were similar among the three groups. However, patients in the LSG group had a higher average BMI than did the LAGB and ESG groups (47.3 kg/m^2, 45.7 kg/m^2, and 38.8 kg/m^2, respectively). In addition, the incidence of hypertension, and hyperlipidemia was significantly higher in each of the surgical groups than in the ESG group (*P* less than .01).

The average postprocedure hospital stay was 0.13 days for ESG patients, compared with 3.09 days for LSG patients and 1.68 days for LAGB patients. ESG also had the lowest cost of the three procedures, averaging $12,000 for the procedure, compared with $22,000 for LSG and $15,000 for LAGB, Dr. Sharaiha reported at the annual Digestive Disease Week.

After 1 year, patients in the LSG group had the greatest percentage of total body weight loss (29.3%), followed by ESG patients (17.6%) and LAGB patients (14.5%). Rates of leaks, pulmonary embolism events, and 90-day readmission were not significantly different among the groups.

The study results do not imply that ESG will replace either LAGB or LSG for weight loss, Dr. Sharaiha noted, but the results suggest that ESG is a viable option for some patients.

The study results do not imply that ESG will replace either LAGB or LSG for weight loss, but the results suggest that ESG is a viable option for some patients.

Dr. Sharaiha had no relevant financial conflicts to disclose.

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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

Misoprostol effective for aspirin-induced GI bleeding

BY ROXANNE NELSON
Frontline Medical News

AT DDW 2017

CHICAGO – Misoprostol could be a treatment option for healing intestinal bleeding that is associated with regular aspirin use, a small study showed.

Compared with placebo, it was superior in healing small bowel ulcers. A total of 12 patients who received misoprostol had complete healing at 8 weeks, compared with 4 in the placebo group ($P = .017$).

"Among patients with overt bleeding or anemia from small bowel lesions who receive continuous aspirin therapy, misoprostol is superior to placebo in achieving complete mucosal healing," said lead author Francis Chan, MD, professor of gastroenterology and hepatology at the Chinese University of Hong Kong, who presented the findings at the annual Digestive Disease Week®.

Millions of individuals use low-dose aspirin daily to lower their risk of stroke and cardiovascular events, but they face a risk of gastrointestinal bleeding. In fact, Dr. Chan pointed out, continuous aspirin use has been associated with a threefold risk of a lower GI bleed.

"But to date, there is no effective pharmacological treatment for small bowel ulcers that are associated with use of low-dose aspirin," he said.

Misoprostol is a synthetic prostaglandin E1 analog that is indicated for reducing the risk of nonsteroidal anti-inflammatory drug–induced gastric ulcers in individuals who are at high risk of complications from gastric ulcers. In their study, Dr. Chan and his colleagues assessed the efficacy of misoprostol for healing small bowel ulcers in patients with GI bleeding who were using continuous aspirin therapy.

"Among patients with overt bleeding or anemia from small bowel lesions who receive continuous aspirin therapy, misoprostol is superior to placebo in achieving complete mucosal healing."

The primary endpoint was complete mucosal healing in 8 weeks, and secondary endpoints included changes in the number of GI erosions.

The double-blind, randomized, placebo-controlled trial included 35 patients assigned to misoprostol and 37 to placebo. All patients were on regular aspirin (at least 160 mg/day) for established cardiothrombotic diseases and had either overt bleeding of the small bowel or anemia. They had a score of 3 (more than four erosions) or 4 (large erosion or ulcer) that was confirmed by capsule endoscopy.

Those randomized to the active therapy arm received 200 mg misoprostol four times daily, and all patients continued aspirin 80 mg/day for the duration of the trial. During the study period, concomitant NSAIDs, proton pump inhibitors, sucralfate, rebamipide, antibiotics, corticosteroids, or iron supplement was prohibited.

A follow-up capsule endoscopy was performed at 8 weeks to assess mucosal healing, and all images were evaluated by a blinded panel.

The intention-to-treat population included all patients who took at least one dose of the study drug and returned for follow-up capsule endoscopy (n = 72).

In this population, 33% of patients in the misoprostol group and 10.5% on placebo had complete mucosal healing at 8 weeks.

"For the secondary endpoint of changes in small bowel erosions, there was a significant difference between the misoprostol group and placebo group with a P value of .025," said Dr. Chan.

The study was supported by a competitive grant from the Research Grant Council of Hong Kong. Dr. Chan reported relationships with AstraZeneca, Eisai, Pfizer, and Takeda.

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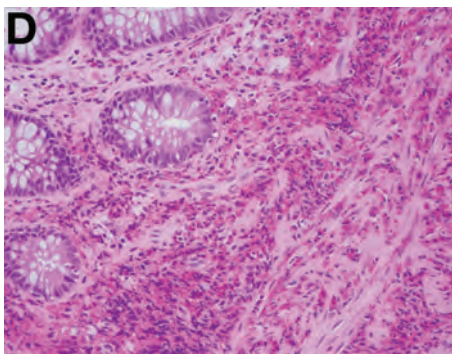
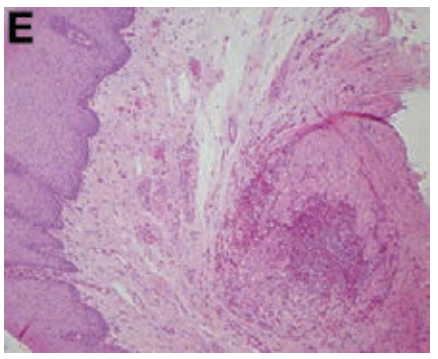
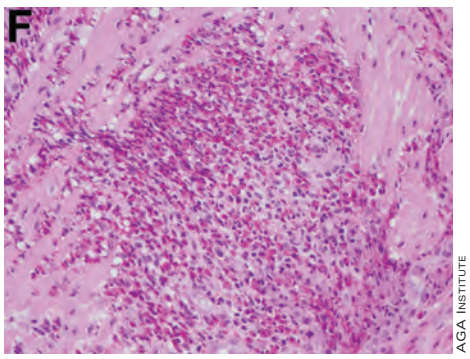
CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What's your diagnosis?" on page 2: Eosinophilic gastroenteritis







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Colonic (Figure D) and esophageal (Figures E and F) mucosal biopsies were obtained, which showed dense eosinophilic infiltrate of the esophageal and rectal submucosa and the rectal deep mucosa. These findings were consistent with eosinophilic gastroenteritis (EGE), mural type. She was empirically treated with 2 doses of ivermectin given the concern for possible underlying parasitic infection given her country of origin, and she was started on oral prednisone 40 mg/d. Eosinophilia and symptoms improved rapidly with this regimen. One month after discharge, her parasitic serology was notable for antifilarial immunoglobulin (Ig) G and IgG4 being positive. At 2-month follow-up, she felt well and denied any abdominal pain or distention with resolution of her peripheral eosinophilia.

The diagnosis of EGE is usually made by endoscopic biopsy showing proliferation of eosinophils in areas of the gastrointestinal tract where eosinophils are uncommon (e.g., esophagus, small bowel).[1] It is associated with allergy or atopy, and eosinophil-predominate ascites is a rare presentation of EGE.[2] Eosinophilic ascites in the context of postpartum EGE has been described at least twice in case reports.[3] It should be noted that eosinophilic infiltration of the gastrointestinal tract may be present in certain conditions, including IgE-mediated food allergies and inflammatory bowel disease. Although certain dietary restrictions can rarely lead to resolution of EGE, systemic steroids are most often used and lead to improved symptomatic response.

Our patient's positive filarial serology, although not associated with EGE in the literature, is the first known documented association between likely filariasis and EGE. She is presently being further evaluated for active filarial parasitemia and consideration of diethylcarbamazine therapy.

Acknowledgments
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HCV incidence in young women doubled 2006-2014

BY BIANCA NOGRADY
Frontline Medical News

The incidence of hepatitis C virus infection in reproductive-age women has doubled between 2006 and 2014 while the number of acute cases increased more than threefold, according to data published in the Annals of Internal Medicine.

Researchers analyzed data from the National Notifiable Diseases Surveillance System (NNDSS) from 2006 to 2014 and the Quest Diagnostics Health Trends national database from 2011 to 2014, finding 425,322 women with confirmed HCV infection, 40.4% of whom were aged 15-44 years.

The incidence of acute and past or present infection in reproductive-aged women doubled, from 15,550 in 2006 to 31,039 in 2014, and the number of acute cases increased from 249 in 2006 to 848 in 2014.

Around half of all acute infections were in non-Hispanic white women, and of the 2,069 women with available risk information, 63% acknowledged injection drug use (Ann Intern Med. 2017 May 8. doi: 10.7326/M16-2350).

The analysis also found 1,859 cases of hepatitis C infection in children aged 2-13 years.

According to the Quest data, the proportion of children with current hepatitis C infection was 3.2-fold higher in children aged 2-3 years than in those aged 12-13 years.

Commenting on this age difference, Kathleen N. Ly, MPH, from the Centers for Disease Control and Prevention, and her coauthors noted that it may have been the result of decreased testing over time in children already known to have chronic hepatitis C infection, or could be caused by spontaneous remission of infection, which is more common in infants and children than in adults.

The rate of infection among pregnant women tested for hepatitis C virus between 2011 and 2014 was 0.73%, which the authors calculated would mean that overall, 29,000 women with hepatitis C virus infection gave birth during that period across the United States. Based on data from a recent systematic review and meta-analysis, which found a likely mother-to-child transmission rate of 5.8/100 live births, they estimated that 1,700 infants were born with hepatitis C infection during that period.

"In contrast, only about 200 childhood cases per year are reported to the NNDSS, which may suggest a need for wider screening for HCV in pregnant women and their infants, as is recommended for HIV and hepatitis B virus," the authors wrote. "However, recommendations for screening in pregnant women and clearer testing guidelines for infants born to HCV-infected mothers do not exist at this time."

The study was supported by the CDC. One author was an employee of Quest Diagnostics, but no other conflicts of interest were declared.

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AGA Resource

The AGA HCV Clinical Service Line provides tools to help you become more efficient, understand quality standards and improve the process of care for patients. Learn more at http://www.gastro.org/patient-care/conditions-diseases/hepatitis-c.

PERSPECTIVE

HCV strategies needed for reproductive-age women

Recognizing hepatitis C infection in pregnant women and neonates is possible, and clinical trials of antiviral therapy may show safety and efficacy in pregnant women and in children. Rather than silence, HCV infection calls out for public health action directed at all aspects of the epidemic, including consideration of screening pregnant women. At the very least, screening of pregnant women for HCV infection risk factors, as well as risk-based testing, requires more emphasis. Another issue in need of attention is the lack of authoritative, consensus-based recommendations for the identification, testing, and case management of newborns of infected mothers.

Much work lies ahead to eradicate HCV, starting with resources for public health surveillance to monitor incidence and prevalence and to fully characterize the infection in the population. Strategies to effectively prevent or cure infection in reproductive-age women and their sexual and needle-sharing partners are critical.

Alfred DeMaria Jr., MD, is from the Massachusetts Department of Public Health. These comments are taken from an accompanying editorial (Ann Intern Med. 2017 May 8. doi: 10.7326/M17-0927). No conflicts of interest were declared.

Norfloxacin improves short-term advanced cirrhosis survival

BY SARA FREEMAN
Frontline Medical News

AMSTERDAM – Prolonged oral treatment with norfloxacin improved the survival of patients with Child-Pugh class C liver disease versus no antibiotic prophylaxis in a randomized, double-blind, placebo-controlled, phase III multicenter trial.

Fewer patients (15.3% vs. 24.5%) treated with norfloxacin for 6 months died by the 6-month mortality primary endpoint than did those treated with placebo, with a hazard ratio of 0.59 (95% confidence interval, 0.35-0.99; *P* = .047) favoring prolonged antibiotic treatment. Adjustments for the concomitant use of nonselective beta-blockers and corticosteroids did not greatly alter the significance of the findings (adjusted HR, 0.58; 95% CI, 0.34-0.98; *P* = .042).

The survival benefit was lost by 1 year of follow-up, however, suggesting that perhaps treatment needs to continue beyond 12 months, according to author Richard Moreau, MD, of Hôpital Beaujon, Clichy, France, who reported the results at a meeting sponsored by the European Association for the Study of the Liver.


DR. MOREAU

"The results of this study provide evidence that 6 months of norfloxacin therapy reduces the risk of death in the short term, but not in the long term," he observed in an official EASL press release.

The occurrence of infections at 6 months and 12 months were secondary outcomes of the study and showed that fewer infections overall (23.9% vs. 35.0%, *P* = .04) had occurred in the norfloxacin group versus the placebo group at 6 months, which was sustained at 12 months, suggesting an overhanging effect of the antibiotic treatment.

There was no difference between the groups in the incidence of other secondary endpoints including septic shock, systolic blood pressure, liver transplantation, kidney dysfunction, encephalopathy, and variceal bleeding at 6 months, Dr. Moreau reported on behalf of the NORFLOCIR study group.

Norfloxacin is a fluoroquinolone antibiotic and earlier data (Gastroenterology. 2007;133:818-24) had suggested that its prolonged use could improve survival in patients with advanced cirrhosis significantly at 3 months and non-significantly at 12 months. This was a small study, however, and although several other small-sized trials followed, the long-term use of fluoroquinolone therapy to improve outcomes in patients cirrhosis remained debated," Dr. Moreau said during his presentation of the study's findings.

There was also the concern that such prolonged antibiotic use might up the risk for infection with gram-positive bacteria, he observed, but the current study's finding showed that this was not the case. The cumulative incidence of gram-positive (3.4% vs. 8.1%, *P* = .08) infections was numerically although not significantly lower in the antibiotic-treated patients at 6 months while the cumulative incidence of gram-negative infections was significantly lowered (3.2% vs. 13.0%, *P* less than .005).

The study does have its limitations, Dr. Moreau conceded.

Continued on following page

Long-term albumin shows survival benefit in cirrhosis

BY SARA FREEMAN
Frontline Medical News

AMSTERDAM – Long-term treatment with human albumin improved the overall survival of patients with decompensated liver cirrhosis, compared with standard medical care, in a randomized, controlled trial presented at the International Liver Congress.

The final results of the ANSWER study showed that a 38% reduction in the risk of death could be achieved at 18 months' follow-up by giving patients human albumin, with an overall survival of 78% vs. 66% in the two groups, respectively (hazard ratio, 0.62; 95% confidence interval, 0.40-0.95; *P* = .028).

"Long-term albumin administration to patients with decompensated cirrhosis may be seen as a disease-modifying treatment," said the presenting study author, Mauro Bernardi, MD, professor in the department of medical and surgical sciences at the University of Bologna (Italy).

Not only was the overall survival improved, but there was improvement in the management of ascites, a reduction in the incidence of severe complications (such as spontaneous bacterial peritonitis, renal dysfunction, and hepatic encephalopathy), a reduction in the number of hospitalizations and duration of in-hospital treatment, and a signal for improved quality of life, he said.

"We know that it is good to give albumin as an infusion in many, many circumstances," Frank Tacke, MD, PhD, who was not involved in the study, said at a press briefing at the meeting, sponsored by the European Association for the Study of the Liver.

"What we did not know before was if there was a role for giving albumin – which is unfortunately quite expensive – for a longer period of time in patients with liver cirrhosis," said Dr. Tacke, EASL

Continued on following page

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Fewer patients were recruited than anticipated, 291 rather than a planned sample size of 392 patients, which was caused by a combination of factors – slow recruitment, termination of funding, and time expiry of the trial drug. Nevertheless, the study findings are strengthened by the fact it was conducted in 18 centers throughout France and that liver transplantation was taken into account as a potential competing risk.

During the trial, 144 patients with Child-Pugh class C cirrhosis were randomized to receive oral norfloxacin at a dose of 400 mg/day and 147 were randomized to a matching placebo daily for 6 months. Patients were followed for 6 additional months.

Just 3% of patients were lost to follow-up by the time of the primary endpoint assessment at 6 months, with just over half (55%) modifying their consent and almost half (46%) discontinuing the study because of death (15%), liver transplant (9%), elevated systolic blood pressure (9%), or patient decision (12%).

Patients included in the study were mostly middle-aged (55 years or older), male (more than 65%), and had alcoholic cirrhosis (greater than 74%) or alcoholic hepatitis (39%), with around 88% having ascites.

Dr. Moreau had nothing to disclose. The study was sponsored by the French government.

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Continued from previous page

vice-secretary and professor of medicine in the department of gastroenterology, metabolic diseases and intensive care medicine at University Hospital Aachen (Germany).

Although long-term treatment with human albumin is relatively expensive, particularly because it requires weekly infusion, Dr. Bernardi noted that the cost of treatment could be offset by the reduction in paracentesis, duration of hospitalization, and reduced need for treating patients with complications, compared with standard medical care.

"The idea of supplying albumin to patients with advanced cirrhosis is quite an old one, and there is long debate. The point is that a reliable study that could resolve this was simply lacking up to now," Dr. Bernard said at the briefing.

The results could mean that patients with decompensated cirrhosis now have a much-needed therapeutic option. These patients have "a very poor prognosis," Dr. Bernardi said. The 1-year probability of survival is about 20%, and the only curative therapy at present is liver transplantation.

A total of 440 patients, most of whom were male, average age 61 years, with cirrhosis and uncomplicated ascites were randomized at 33 Italian centers to standard medical treatment alone (n = 213) or with human albumin (n = 218) given at an infused dose of 40 g twice a week for the first 2 weeks, then 40 g every week. The albumin was provided by five pharmaceutical companies and sent to a central location for generic relabeling and distribution out to the participating trial centers.

Significantly fewer patients who were given human albumin than those who were not (66% vs. 38%, *P* less than .001) needed at least one paracentesis. The incidence rate for the removal of peritoneal fluid in the standard medical treatment arm was 3.5/person per year. There was a 54% reduction in this rate by the addition of human albumin (hazard ratio, 0.46; 95% confidence interval, 0.40-0.53; *P* less than .0001). There was a significant 46% reduction in the incidence of refractory ascites (48% vs. 25%, *P* less than .0001).

"The idea of supplying albumin to patients with advanced cirrhosis is quite an old one, and there is long debate. The point is that a reliable study that could resolve this was simply lacking up to now."

Patients who received standard medical treatment plus albumin needed fewer hospitalizations and fewer days of in-hospital care per person per year than did those in the standard care–only arm. The use of human albumin reduced the number of hospital stays by 35% (HR, 0.65; 95% CI, 0.55-0.77; *P* less than .0001) and the duration of days in hospital by 45% (HR, 0.55; 95% CI, 0.52-0.58; *P* less than .0001).

Although not statistically significant, a trend for greater improvements and fewer decreases in quality of life, measured via the EQ-5D visual assessment scale, at 3, 6, and 12 months, was seen with the use of human albumin.

Four patients had adverse drug reactions: two were mild allergic reactions, and two were potentially life-threatening septic shock that needed intensive care treatment. One of the latter cases might have been caused by pneumonia, and the other required study interruption. But in all cases the patients recovered.

The Italian Drug Agency funded the study. Dr. Bernardi had acted as a speaker for and consultant to CLS Behring and Baxter Healthcare, and as a speaker to the Plasma Protein Therapeutics Association's Europe division, Grifols, Gilead Sciences, and AbbVie Italia. Dr. Tacke had nothing to disclose.

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Persistent diarrhea:
are there faster diagnostic pathways?*

Persistent diarrhea is a common condition associated with multiple etiologies, which can make it challenging to diagnose the underlying cause.[1,2] A new advancement that streamlines the diagnostic pathway could help healthcare providers consider condition-specific treatment early for their patients.

Current challenges

The differential diagnosis for persistent diarrhea is extensive.[1] It is also not uncommon for patients to have more than 1 potentially causative factor.[3] The etiology of persistent diarrhea can include numerous infectious causes, including parasites (eg, *Giardia* and *Cryptosporidium*) and bacteria (eg, *Escherichia coli*, *Shigella*, and *Campylobacter*), and viruses (eg, norovirus).[4] There are also multiple noninfectious causes, including inflammatory bowel disease (IBD), celiac disease, irritable bowel syndrome (IBS), and bile acid malabsorption (BAM), which may be more prevalent than previously believed.[4,5]

As a result, diagnosis of persistent diarrhea can be a slow process,[1,4] and some patients may suffer longer than necessary. Having to order multiple tests may also be inconvenient for both healthcare providers and patients.

Convenient all-in-one testing is now available

Now there is a stool and serum test that may help healthcare providers diagnose many common causes of persistent diarrhea all at 1 time for added convenience. The PROMETHEUS® IBcause™ Diagnostic Test helps physicians diagnose common causes of persistent diarrhea—including intestinal inflammation, celiac disease, IBS, multiple pathogens, and BAM.[1,4,6-9,**] IBcause can also help clinicians determine if a multifactorial gastrointestinal condition may be irritating the bowel and causing persistent diarrhea, something that could remain unrecognized with sequential testing or empiric treatment.[4]

Combines multiple stool and serum assays***

IBcause evaluates a unique combination of 20 stool and serum measures all at 1 time, which may help clinicians get to a diagnosis faster and a specific treatment plan sooner (compared to sequential testing and empiric treatment). It quickly helps identify both infectious and noninfectious causes of persistent diarrhea in 1 easy-to-order test that is convenient for both clinicians and their patients.

Addition of BAM assay provides a more complete view*

Bile acid diarrhea is common in patients who have ileal-specific Crohn's disease or have undergone ileal resection surgery.[10] Perhaps lesser known is that BAM may affect up to 50% of patients with unexplained persistent diarrhea.[10] BAM is also a condition that is often overlooked or is misdiagnosed as diarrhea-predominant irritable bowel syndrome (IBS-D).[5,11] Some have suggested that IBS-D patients who fail standard therapy should be evaluated for possible BAM. A challenge is that the standard test for measuring bile acid diarrhea (the selenium homocholic acid taurine test, or SeHCAT) is not readily available in the United States, thereby hindering proper diagnosis.[10]

IBcause features a proprietary assay for BAM that is not available elsewhere to test for elevated 7α-hydroxy-4-cholesten-3-one (7C4) plasma levels, which have been associated with BAM.[10]

IBcause represents an important advancement for IBS-D patients who have not had success with standard therapy and can now be evaluated for BAM.[10] In a study where serum 7C4 levels were measured in IBS-D patients (n = 26), IBS with constipation patients (IBS-C, n = 26), and healthy subjects (n = 26), the IBS-D patients had increased hepatic bile acid synthesis, and greater levels of excreted bile acid were detected in stools collected for over 2 days.[12]

Tests for 14 types of pathogens

IBcause allows clinicians to simultaneously test for multiple pathogens that may present concurrently in patients with persistent diarrhea, including 8 types of bacteria, 3 types of parasites, and 3 types of viruses. Due to advanced polymerase chain reaction (PCR)–based amplification, IBcause is faster and more sensitive than conventional culture-based stool-testing methods. Clinicians can use IBcause to rule out > 90% of acute diarrhea-causing agents, including bacterial toxins.[13-15]

Utilizing IBcause can help clinicians streamline the diagnostic pathway for patients who present with persistent diarrhea.* For more information, visit IBcause.com or call Prometheus Customer Services at **888-423-5227**, Option 1, for additional information.

A new way to streamline the diagnostic pathway for persistent diarrhea*

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*Compared to sequential testing with standard workup for persistent diarrhea.

**IBcause is recommended for patients with ongoing diarrhea (which may be referred to as persistent or chronic).

***Assays can also be ordered separately and all results should be used in combination with other clinical findings.

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PRACTICE MANAGEMENT TOOLBOX: Challenges facing independent integrated gastroenterology in 2017

BY FRED B. ROSENBERG, MD, LAWRENCE S. KIM, MD, AGAF, AND SCOTT R. KETOVER, MD, AGAF

The practice of gastroenterology is challenging for community physicians, those employed in multi-specialty clinics or large health care systems, and those in academic health centers. Unique challenges confront independent GI practices, and there are mounting regulatory, financial, and operational barriers. Election results of 2016 have thrown us into an even more confusing future. In this month's column, national GI leaders summarize the major challenges facing independent practices. Each leads (or has led) large GI practices, and each has extensive experience with the policies, politics, payers, and pitfalls that impact our specialty. They have written a clear and helpful article for all physicians trying to maintain their independence and patient-focused practices. I have worked in many settings from the VA, to small and then large, independent practices, within a health system and in two academic medical centers. There is much to treasure in every type of practice and also many challenges. Physician leaders, both old and young, need to be informed and active in shaping medical policy.

John I. Allen, MD, MBA, AGAF
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DR. KIM


DR. KETOVER

Physicians practicing in independent settings report greater satisfaction with their careers compared with those employed in hospital systems. In a recent survey,[1] nearly two-thirds of independent practitioners strongly agreed with the statement, "I like being a physician," compared with approximately half of those employed by hospital systems. The rapid pace of change in care delivery is forcing all caregivers to modify how they provide care. For physicians practicing in independent settings, understanding, reacting, and adapting to these changes is especially challenging.

It is particularly difficult for physicians and practices to remain abreast and cognizant of the ever-changing rules governing how we deliver care for our patients. The Digestive Health Physicians Association was formed 2 years ago to provide an active voice specifically for independent gastroenterology (GI) practices. The mission of the Digestive Health Physicians Association is to promote and protect the high-quality and cost-efficient care provided in the integrated GI practice model.

In the past decade, meeting the goal of the Triple Aim (improving population health, improving patient experience of care, and reducing the per-capita cost of health care) has become a central tenet of our national health policy strategy, especially since the enactment of the Affordable Care Act. Achieving the goals of the Triple Aim and complying with the changes and new requirements challenges all gastroenterologists, but particularly those working in the independent practice setting, and especially those in small group practices. The Centers for Medicare & Medicaid Services (CMS) recently estimated that, under the Merit-Based Incentive Payment System, payment reductions resulting from the first year of reporting in 2017 will occur in 87% of solo practices, in 70% of groups with 2-9 physicians, and in 60% of groups with 10-24 physicians.[2]

Preparing yourself and your practice for the changes ahead will require an understanding of the rules, an assessment of your practice's readiness, and the creation of a plan for compliance to ensure success.

The care model has undergone major changes in the past decade. The development of regional hospital systems has resulted in increasing numbers of employed physicians. Independent gastroenterology practices also have made changes in how they provide care. Vertical integration by independent practices has been a major, positive, and continuing development. As practices have grown more sophisticated with greater areas of specialization, they are increasingly capable of providing services directly to their patients rather than outsourcing them to external providers. Beginning first with endoscopic procedures and now extending to anesthesia, pathology, infusion, and other critical services, increased integration of services across the entire continuum of care has led to improved efficiency and care coordination, benefitting patients with improved outcomes as well as lower costs to our health care system.

The benefits and successes of practice integration, unfortunately, also have made vertically integrated practices a target for regulators and policy makers. Attacks on the integrated delivery model in gastroenterology have at times been supported, if not directly initiated, by our own colleagues in the house of medicine. In this article, we describe some of the threats and challenges confronting independent GI practice.

Anesthesia services

In April 2016, the Florida Society of Anesthesiologists (FSA) made headlines by drawing attention to its role as the relator in a qui tam (whistle-blower) lawsuit that it had filed against more than 50 physicians, Ambulatory Surgery Centers, and anesthesia entities. This legal action — which the FSA filed in October 2013 but remained under seal until earlier this year — alleged that the defendants perpetrated Medicare and Medicaid fraud through violations of the federal Anti-Kickback Statute and the False Claims Act. In this lawsuit, the FSA specifically targeted the company model used to provide anesthesia services. Based on publicly available documents, the case currently is in its early stages, although the FSA has made it clear that it views the lawsuit as a blueprint for attacking integrated anesthesia services.

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The FSA's qui tam action in Florida is part of a broader agenda by those who seek to undermine the integrated care model that enables gastroenterologists and other physician specialists to integrate anesthesia services into lawful care models. A website describing the Florida qui tam action hailed the American Society of Anesthesiology for having "repeatedly petitioned the Office of the Inspector General, brought the issue up with Congressional leaders and executive branch regulators, and provided information and legal resources to its members."[3] These efforts to undermine integrated, coordinated care at the federal level also have extended to the state level, in which efforts have been made in front of licensing boards and state legislatures – albeit unsuccessfully – to restrict the integration of anesthesia services.

In-Office Ancillary Services Exception

The In-Office Ancillary Services Exception (IOASE) to the federal physician self-referral statute (the Stark Law) allows physician practices to provide certain services, including diagnostic imaging and anatomic pathology, in an integrated and coordinated fashion within their respective practices when strict criteria are met.

Not surprisingly, competing providers of these services have long fought for the elimination of the IOASE. In 2013, Representative Jackie Speier (D-Calif.) introduced the Promoting Integrity in Medicare Act. This bill sought to eliminate those legal protections for providing those integrated medical services under the IOASE. Vigorous support for the legislation was provided by a group called the Alliance for Integrity in Medicine, a coalition of organizations including the College of American Pathologists, the American Society for Clinical Pathology, the American Clinical Laboratory Association, and the American College of Radiology. Although that bill did not even receive a vote during the last Congress, Representative Speier has re-introduced it in this current session, and continues to lobby aggressively in support of this legislation. President Obama's budget for 2016, as the President's budget proposal had done for the past several years, also included elimination of the IOASE provision. Extensive advocacy efforts by a broad range of specialty organizations have been

Continued on page 30

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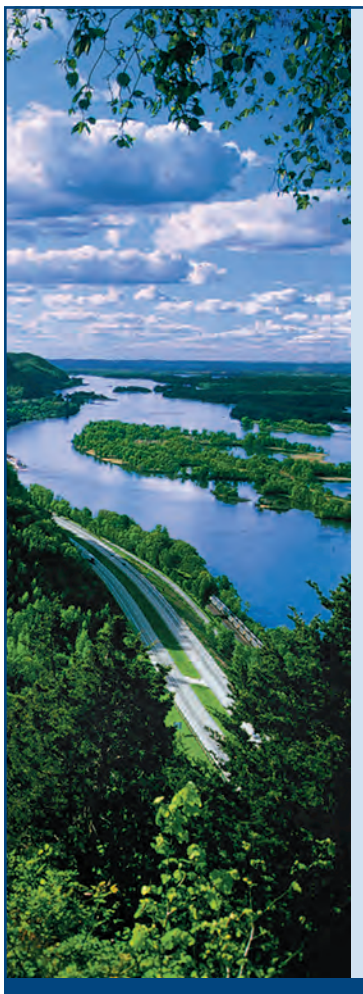

Continued from page 28

instrumental to date in defeating this proposal. A study commissioned by the Digestive Health Physicians Association,[4] using Medicare data, showed that GI-related anatomic pathology services actually increased more slowly in professional settings (physician offices and laboratories), at an annual rate of 1.2% from 2009 to 2013, compared with the outpatient hospital setting of 3.5% during that same period. Efforts to restrict practice integration similarly are being made at the state level. In California, legislation to eliminate the IOASE under the State's self-referral law was introduced in 2014. Coordinated efforts by California patient- and physician-interest groups were successful in educating legislators on the value of the integrated care mode and the bill was soundly defeated.

Medicare Part B Drug Benefit

In March 2016, a new threat to integrated care in GI surfaced when the CMS released a proposed rule that would test a new Medicare Part B payment model for infused drugs including infliximab and vedolizumab. Under the proposal, the CMS would reduce the current reimbursement of 6% above average sales price (ASP) to ASP plus 2.5%, plus a flat fee of $16.85 per infusion. CMS calculations in this proposal failed to include the mandatory 2% sequestration of Medicare payments under the Budget Control Act, which means that the actual reimbursement will be less than 1% over ASP. Because many practices are unable to negotiate discounts for these drugs, unintended consequences of this proposal may disrupt care coordination efforts, resulting in movement of infusions performed in the office setting into the more costly hospital setting. Perversely, although the stated intent of this proposal was to reduce incentives for prescribing more expensive drugs, infused biologic agents are actually treatments of last choice for many inflammatory bowel disease patients.

Vigorous advocacy by a coalition of more than 300 medical societies and patient-interest groups led to a bipartisan letter signed by over 240 members of Congress expressing concern that the proposed payment model was developed without stakeholder input and would severly harm patient access to essential medications. In December 2016, CMS announced that it was abandoning the proposed rule.

Take-away points:

1. Integration of services is critical to allow independent GI practices to improve efficiency and care coordination under value-based health care programs.
2. Examples of integrated services include endoscopy centers, anesthesia, pathology, and infusions.
3. The integrated model faces ongoing regulatory and legislative challenges, such as to the In-Office Ancillary Services Exception and Stark Law reform.
4. Gastroenterologists have successfully advocated for the benefits of the integrated model of care, but continued engagement and collaboration among GI organizations is critical.

Stark Law

The Stark Law, commonly known as the Physician Self-Referral Law, originally was passed by Congress in 1989 and was substantially amended last in 1993. The Stark Law was enacted to address concerns of potential overuse or inappropriate use of services in a fee-for-service payment system. Health care delivery has changed dramatically since the Stark Law was passed 27 years ago, but this statute has not kept pace and is incompatible with new and innovative delivery models that now mandate a shift from fee-for-service payment models to value-based care and the development of risk-sharing arrangements and bundling of services. In 2011, the CMS created a set of waivers for Accountable Care Organizations in the Medicare Shared Savings Program, but these waivers do not apply to many of the alternative payment models under development by independent physicians.

In the past year, Congress repealed the Sustainable Growth Rate formula. Both the Affordable Care Act and the Medicare Access and Children's Health Insurance Program Reauthorization Act of 2015 were designed to move our health care system away from fee for service (volume)

and toward payment for value. The current Stark Law was created to control arrangements in a fee-for-service system, but the Stark Law now obstructs the ability of physicians in independent practices to coordinate care and work as teams across specialties and with their colleagues who care for patients in other sites of service such as hospitals and academic medical centers.

Congress and CMS recently have heard from dozens of physician organizations, including all of the GI societies, about the need to modernize the Stark Law (by way of updates to the Stark statute and its corresponding regulations) to keep pace with the changes in health care delivery and to ensure successful implementation of the Medicare Access and Children's Health Insurance Program Reauthorization Act. The changes sought include modifications to the definition of the term group practice to permit coordinated care across specialties and sites of service as well as to promote value-based compensation for all physicians.

Conclusions

To maximally amplify our voices as well our ability to effect positive change, gastroenterologists and other specialists should be actively engaged with the GI societies to help influence those changes proposed. Joining together will facilitate the adaptation by practices to change as it is mandated. The American Gastroenterological Association has long advocated for independent practices promoting optimal patient care delivery. Working cooperatively and collectively with colleagues in all GI professional organizations will enhance our ability to advance the best interests of our patients and our practices.

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