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# GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

JOEL AUSTELL/MDEDGE NEWS

Dr. Akbar K. Waljee, of University of Michigan, presented how precision analytics can improve treatment choices in IBD.

## Predictive analytics may individualize delivery of IBD care

**BY TED BOSWORTH**
*MDedge News*

EXPERT ANALYSIS FROM 2019 AGA TECH SUMMIT

SAN FRANCISCO – Predictive analytics of large quantities of data using machine learning present a powerful tool for improving therapeutic choices, according to a summary of work performed in inflammatory bowel disease (IBD) and presented at the 2019 AGA Tech Summit, sponsored by the AGA Center for GI Innovation and Technology.

This type of work is relevant to many fields of medicine, but studies conducted in IBD have provided particularly compelling evidence that predictive analytics will improve outcomes and lead to more cost-effective delivery of care, according to Akbar K. Waljee, MD, MSc, AGAF, an associate professor in the division of gastroenterology at University of Michigan, Ann Arbor, and a staff physician and researcher at the VA Ann Arbor Healthcare system.

"We collect large amounts of clinical data every day in the delivery of health care, but we are now only just beginning to leverage [these] data to guide treatment," Dr. Waljee said. He

*See* **Analytics** · *page 19*

## Virtual reality: Now a therapeutic tool in GI

**BY TED BOSWORTH**
*MDedge News*

EXPERT ANALYSIS FROM 2019 AGA TECH SUMMIT

SAN FRANCISCO – The body of evidence to support virtual reality (VR) as a therapeutic modality will increasingly involve the GI tract, according to evidence summarized at the 2019 AGA Tech Summit, sponsored by the AGA Center for GI Innovation and Technology. Evolving from its early use in acute or chronic pain, where its function was to simply divert attention from the symptoms, VR computer-generated environments are now being applied to alter patient perceptions and behavior.

"The field of gastroenterology is a particularly promising area for treatment based on VR because of the well-established brain-gut interaction," explained Brennan Spiegel, MD, AGAF, director of health services research for Cedars-Sinai Medical Center, Los Angeles. He said this tool has been shown repeatedly to change how patients experience their symptoms in a variety of clinical contexts.

The field is not entirely new. Already by 2017, 11 randomized controlled trials of VR for therapeutic purposes were identified in a systematic review (Innov Clin Neurosci. 2017;14:14-21). These trials, dating back to 2010, have explored this technology in depression, cognitive and motor rehabilitation, and eating

*See* **Virtual reality** · *page 18*

## Studies link TMAO to microbiome, reveal new heart disease target

**BY AMY KARON**
*MDedge News*

MIAMI – Researchers are one step closer to developing "drugs for bugs" – agents that target the gut microbiome to prevent and treat cardiometabolic diseases, Stanley L. Hazen, MD, PhD, said at the 2019 Gut Microbiota for Health World Summit.

"Each person experiences a meal differently through the filter of their gut microbiome, which helps explain individual differences in susceptibility to disease," said Dr. Hazen

*See* **TMAO** · *page 23*

## INSIDE





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DDSEP 9
Digestive Diseases Self-Education Program

## Quick quiz

**Q1.** A 45-year-old man presents to the clinic with worsening right lower quadrant pain and diarrhea for the last 2 days. His past medical history is significant for hemochromatosis and he undergoes regular therapeutic phlebotomies. He admits to dining out in a newly opened restaurant in his town 4 days ago. He describes having 5 nonbloody watery stools and also has been experiencing sore throat for the last 2 days. His physical examination is unremarkable except some mild abdominal tenderness at the right lower quadrant.

There was no rebound tenderness. Laboratory data show mild leukocytosis.

What is the most likely organism causing the symptoms of diarrhea and abdominal pain?

A. *Yersinia enterocolitica*
B. *Vibrio cholerae*
C. Enterotoxigenic *Escherichia coli*
D. *Campylobacter jejuni*
E. *Shigella sonnei*

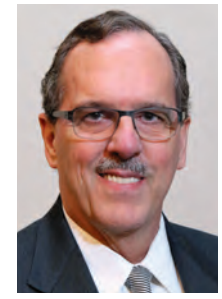
**Q2.** A 25-year-old male presents to the emergency department with severe epigastric pain and mild elevations in lipase (3 x ULN) diagnostic of acute pancreatitis. The patient describes multiple episodes of pain and associated pancreas enzyme elevations since early childhood that generally respond to brief hospitalizations and conservative treatment including intravenous fluids and IV analgesics. CT imaging reveals parenchymal calcifications seen throughout the pancreas. Further history discloses two relatives with similar pain attacks.

Which of the following gene mutations is most likely to be associated with the cause of the recurrent pancreatitis in this patient?

A. BRCA1
B. PRSS1
C. SPINK1
D. Delta F508
E. PRSS2

*The answers are on page 39.*

# LETTER FROM THE EDITOR: Spring for GI


DR. ALLEN

Spring has always been an exciting time for gastroenterologists, beginning with Colon Cancer Awareness month in March and finishing with our flagship scientific meeting in May. Gastroenterologists have led the fight against colon cancer by publishing seminal research (the National Polyp Study was published April 1, 26 years ago), building a distributed network of high-value ambulatory endoscopy centers, educating primary care physicians and the public about screening and early detection, and advocating continuously to make cancer prevention affordable for all people.

This year, AGA has sponsored two meetings where truly ground-breaking science was presented, and we have highlighted them on our front page this month. On March 23-24, the AGA worked with the European Society of Neurogastroenterology and Motility to bring you the 8th annual Gut Microbiota for Health World Summit in Miami. World leaders in microbiome research presented a breathtaking array of clinically relevant research on topics that impact your patients. Stanley L. Hazen, MD, PhD, of the Cleveland Clinic presented his work linking dietary choices to a blood marker of atherosclerotic risk (TMAO) where the key associative link is the diet-influenced microbiome.

The AGA also brought you the 10th annual AGA Tech Summit from San Francisco, April 10-12. This meeting has become the best single source to learn about new technology emerging in our field. In this issue of *GI & Hepatology News*, we highlight two presentations about managing visceral pain with virtual reality technology and how predictive analysis is being used to personalize inflammatory bowel disease therapy.

Spring wraps up with DDW® in San Diego (May 18-21). DDW begins with the AGA Postgraduate Course (May 18-19) that provides the best annual summary of both gastroenterology and hepatology combined in a single setting. The live meeting will feature key updates and new science about biosimilars, cancer prevention, celiac disease, endoscopy, the microbiome, hepatology, IBD, nutrition, and care delivery.

As usual, *GIHN* will feature key presentations from DDW, including those from the Presidential Plenary session (Monday morning May 20).

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

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FROM THE AGA JOURNALS

# No biopsy for 21% of adults with celiac disease

BY AMY KARON
*MDedge News*

Patients with celiac disease often do not receive a biopsy or nutritional recommendations at diagnosis, according to the findings of a large survey study.

Strikingly, 21% of respondents did not have a confirmatory duodenal biopsy, reported Andrew M. Joelson, MD, of Columbia University Medical Center, New York, and his associates. Gastroenterologists diagnosed 66% of biopsied patients but only 31% of nonbiopsied patients (*P* less than .001). "Patients require more education about management of celiac disease and referral to gastroenterologists for duodenal biopsy confirmation," the researchers wrote in the May issue of Clinical Gastroenterology and Hepatology.

Classic small-bowel findings in celiac disease (intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy) are not pathognomonic, making serology important for diagnosis. European guidelines discuss forgoing biopsy in children whose antitissue transglutaminase antibody titers are at least 10-fold above the upper limit of normal. However, the American College of Gastroenterology and the American Gastroenterological Association continue to recommend combining serology with confirmatory small-bowel biopsy. The extent to which physicians follow this advice is unclear, the researchers noted.

Therefore, they analyzed data from a questionnaire posted on the Celiac Disease Foundation website during a 7-month period in 2016. Among 982 adults with self-reported celiac disease, 780 said their diagnosis included both serology and biopsy and 202 said they received serology only. Only 40% of these nonbiopsied respondents said they sought nutritional counseling at diagnosis, compared with 59% of biopsied patients (*P* less than .001). Patients diagnosed by serology alone also were more likely to report using dietary supplements to aid gluten digestion (20% vs. 9% of biopsied respondents; *P* less than .001).

These associations remained statistically significant after adjustment for age and sex, said the researchers. Nonbiopsied patients had a significantly lower odds of having been diagnosed by a gastroenterologist (odds ratio, 0.16; 95% confidence interval, 0.07-0.37) and seeking nutritional counseling (OR, 0.45; 95% CI, 0.33-0.63) and were significantly more likely to use digestive supplements (OR, 2.61; 95%, CI 1.62-4.19).

Fully 87% of respondents always followed a strict gluten-free diet, but symptoms persisted in 65% of those who were not biopsied, compared with only 51% of those who were biopsied. However, they cautioned that none of the associations in this study were necessarily causal, diagnoses were not independently validated, and the reliability of self-reported celiac diagnosis remains unclear.

Survey respondents also were self-selected – for example, 91% self-identified as white and 60% reported having a bachelor's degree, compared with only about 77% and one-third of adults captured by U.S. Census Bureau data from 2017.

"Although these characteristics may limit the generalizability of our findings, this study nevertheless reflects a population of celiac disease that is not typically studied, such as those not attending large academic celiac disease centers, and those diagnosed without the involvement of a gastroenterologist," the researchers wrote.

The iCureCeliac Patient Powered Research Network is supported by the Patient-Centered Outcomes Research Institute. The investigators reported having no relevant conflicts of interest.

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**SOURCE:** Joelson AM et al. Clin Gastroenterol Hepatol. 2018 Sep 10. doi: 10.1016/j.cgh.2018.09.006.

Self-reported celiac disease diagnosis is not validated and perhaps more inaccurate now with the rise of other gluten-related disorders. Although misdiagnosis is possible, the finding in this study by Joelson et al. that 21% of self-reported celiac adults said they never had a confirmatory biopsy is remarkable. Another important observation is the low-quality celiac care among nonbiopsed adults, with less formal nutritional counseling and high use of gluten digestive supplements and persistent symptoms.

DR. RUBIO-TAPIA

Unfortunately, the reason why confirmatory biopsy was missed is unknown. The approach to confirm a diagnosis of celiac disease is changing. A few decades ago, celiac disease diagnosis required three sequential duodenal biopsies (baseline, on gluten-free diet, and after gluten challenge). More recently, the availability of more specific serology made multiple sequential biopsies unnecessary. However, a confirmatory biopsy was mandatory.

Now, biopsy confirmation may not be necessary for all. There is strong evidence for nonbiopsy diagnosis in selected symptomatic children with high titers of tissue transglutaminase antibodies (more than 10 times the upper limit of normal) and a positive endomysial antibody in a second sample. Whether the nonbiopsy approach could be applicable also in adults remains controversial. Current guidelines recommend biopsy confirmation in all adults. However, emerging evidence favors celiac disease diagnosis without use of biopsy in selected adults.

Although the debate regarding pros and cons of nonbiopsy diagnosis is far from an end, this approach is here to stay. In the future, regardless of the method selected to confirm celiac disease diagnosis, the overall quality of celiac care should be ensured.

*Alberto Rubio-Tapia, MD, is an assistant professor of medicine at the Mayo Clinic, Rochester, Minn. He has no conflicts of interest.*

# Look for functional esophageal disorders if patients fail PPIs

BY AMY KARON
*MDedge News*

In a small, first-in-kind study, functional heartburn or reflux hypersensitivity affected fully 75% of patients whose gastroesophageal reflux disease symptoms had not improved with once-daily proton pump inhibitor therapy.

At the same time, proton pump inhibitor (PPI) responders and nonresponders had similar impedance and pH parameters, reported Jason Abdallah, MD, of Case Western Reserve University, Cleveland, and his associates. The findings show "the important role of esophageal hypersensitivity in this patient population." For these patients, the investigators suggested adding a neuromodulator and possibly psychotherapy, such as cognitive-behavioral therapy, hypnotherapy, relaxation techniques, mindfulness, and biofeedback.

Symptoms in up to 45% of patients with gastroesophageal reflux disease (GERD) persist despite once-daily PPI therapy, Dr. Abdallah and his associates wrote in Clinical Gastroenterology and Hepatology. For the study, they compared reflux characteristics and patterns between 13 patients whose GERD symptoms had fully resolved on standard once-daily PPIs and 16 patients who reported at least twice-weekly heartburn, regurgitation, or both for at least 3 months, despite treatment. Patients in both groups continued PPIs and underwent upper endoscopy and combined esophageal impedance–pH monitoring.

The average age of patients in this study was 54.5 years, with a standard deviation of 14.5 years. Demographic and clinical characteristics were similar between groups, and patients in both groups were receiving omeprazole, esomeprazole, or pantoprazole. Four (31%) PPI responders had abnormal pH test results, as did four (25%) nonresponders. Responders and nonresponders had similar numbers of reflux events; proportions of events that were

*Continued on page 8*

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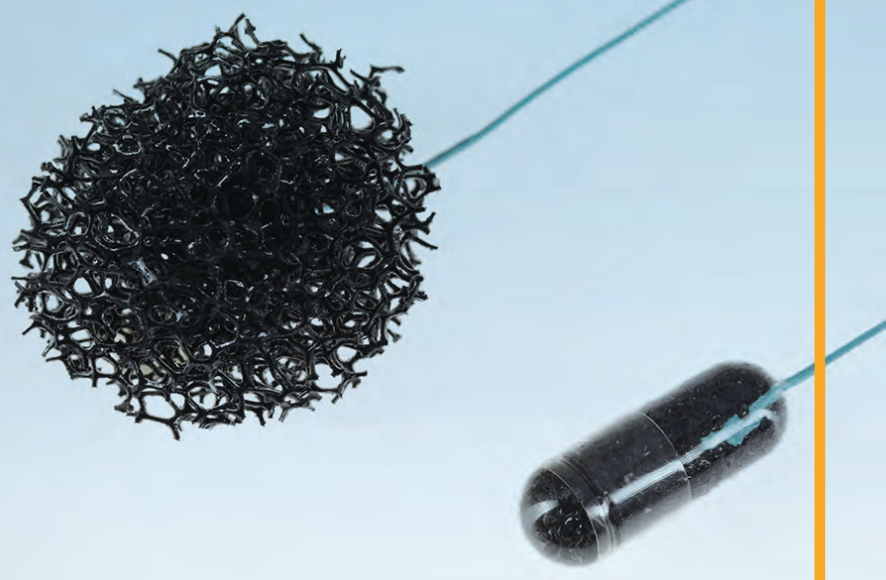

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FROM THE AGA JOURNALS

# Mucosal impedance contour rapidly distinguishes GERD, non-GERD, and eosinophilic esophagitis

BY AMY KARON
*MDedge News*

A balloon catheter system that measures mucosal impedance contour immediately distinguished gastroesophageal reflux disease (GERD), eosinophilic esophagitis, and non-GERD (normal findings), according to the findings of a prospective study of 69 adults.

Each group showed a significantly different (*P* less than .01) pattern of mucosal impedance (MI), or disruption of mucosal integrity, along the esophageal axis, wrote Dhyanesh A. Patel, MD, of Vanderbilt University Medical Center in Nashville, Tenn., and his associates. Patients without GERD had higher MI values along all esophageal segments, while GERD was characterized by below-normal values in the distal esophagus only, and eosinophilic esophagitis led to low values throughout the esophagus.

The findings were validated in a separate patient cohort, and the only reported adverse event was an episode of mild chest pain. "This contour heatmap could easily be employed to establish a diagnosis during endoscopy, independent of biopsy or pH monitoring," the investigators wrote in Gastroenterology. They cautioned that the balloon catheter cannot be safely used in patients with severe fibrostenotic disease.

Current definitive diagnostics for GERD leave much to be desired. Transnasal probes are imprecise and uncomfortable, and they can be insensitive if discomfort causes patients to vary normal activity or skip meals. Wireless ambulatory pH monitoring is more tolerable but unreliable and measures acidity of refluxed material only at a single point along the esophagus. These tests also "fail to account for day-to-day variability of reflux, as they only provide a 24- to 48-hour snapshot of a disease process that is chronic in nature," the researchers wrote. Eosinophilic esophagitis is becoming more common and usually requires proximal and distal biopsies for diagnosis.

Mucosal impedance contour pattern testing is based on the fact that both GERD and eosinophilic esophagitis involve increased distance between esophageal epithelial cells. The amount of intercellular dilatation correlates inversely with MI values. In proof-of-concept studies, individuals with GERD, non-GERD, eosinophilic esophagitis, and achalasia had distinct MI patterns. However, these studies tested a single-channel catheter system that took only point measurements and was subject to interoperator variability. To improve on this concept, Dr. Patel and his associates mounted radial and axial sensors on a balloon catheter to measure MI at 180-degree intervals along a 10-cm esophageal segment.

They tested the new device prospectively in 69 patients undergoing esophagogastroduodenoscopy with or without pH monitoring (which was used as the standard). In all, 24 patients had GERD, 21 had eosinophilic esophagitis, and 24 had normal findings. By using the intercept and slope of the

*Continued on following page*

Evaluating esophageal disorders such as GERD or eosinophilic esophagitis can be time consuming for patients in clinical practice and requires multiple visits to complete testing and obtain results. Other than visualizing complications of reflux such as erosive esophagitis or Barrett's esophagus, there has been no immediate option to diagnose GERD in standard practice during routine endoscopy. Furthermore, the decision to pursue long-term medication or surgery for GERD relies on a brief pH assessment to be truly representative of a patient's everyday symptoms. Follow-up of eosinophilic esophagitis requires repeated upper endoscopies with biopsies after every incremental change in medication or diet, which unsurprisingly, can reduce compliance with ongoing management for what is often a readily treatable condition.

Both GERD and eosinophilic esophagitis can be characterized by changes in esophageal mucosal impedance. Rather than directly measuring the pH or eosinophil counts, Dr. Patel and associates prospectively validated the diagnostic test performance of an add-on endoscopic mucosal impedance device that might enable the gastroenterologist to rule out GERD or rule in eosinophilic esophagitis during the index endoscopy with reasonable accuracy (AUC above 0.8 to rule out GERD or rule in eosinophilic esophagitis) while adding 2-3 minutes of procedure time. One patient was admitted for chest pain after use of the device but was discharged without complication, and the authors caution against use in severe fibrostenotic disease.


DR. SHAH

While work to refine a clinical prediction model with this technology is ongoing, the promise of diagnosing and following common esophageal conditions of GERD and eosinophilic esophagitis during endoscopy would have clear value in expediting care and enhancing compliance with treatment.

*Eric D. Shah, MD, MBA, is assistant professor of medicine, director of gastrointestinal motility, esophageal, and swallowing disorders center, Geisel School of Medicine, Dartmouth College, Hanover, N.H. He has no disclosures.*



*Continued from page 6*

acidic, weakly acidic, or alkaline; and mean total time with pH less than 4.0.

Additionally, most patients in both groups had normal endoscopic findings. One PPI responder had Los Angeles grade A erosive esophagitis, and two PPI responders had short-segment Barrett's esophagus. Three PPI responders and two PPI nonresponders had nonobstructive Schatzki rings, and one PPI nonresponder had an esophageal stricture. Finally, five PPI responders (38%) and three nonresponders (19%) had hiatal hernias (*P* = .41).

In patients with GERD, "PPI failure" does not reflect a unique pattern of reflux events, acid exposure, or nonacidic reflux parameters, Dr. Abdallah and his associates concluded. The fact that most PPI nonresponders had a concurrent functional esophageal disorder – either reflux hypersensitivity or functional heartburn – "support[s] the hypothesis that PPI failure is primarily driven by esophageal hypersensitivity."

This was a small study – recruitment "was hampered by the invasive nature of some of the procedures," they wrote. "In addition, it is our experience that many patients who have responded to PPI [therapy] are reluctant to undergo invasive testing as part of a study protocol. Therefore, we believe that these types of prospective, invasive studies are rather difficult to perform but, at the same time, provide essential insight into the understanding of refractory GERD."

No external funding sources were acknowledged. The senior author reported ties to Ironwood Pharmaceuticals, Mederi Therapeutics, Ethicon, AstraZeneca, and Takeda. The other researchers reported no conflicts of interest.

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**SOURCE:** Abdallah J et al. Clin Gastroenterol Hepatol. 2018 Jun 15. doi: 10.1016/j.cgh.2018.09.006.

FROM THE AGA JOURNALS

# Study eyes biomarkers of regorafenib response in hepatocellular carcinoma

BY AMY KARON
*MDedge News*

Protein and microRNA expression patterns correlated with improved survival on regorafenib among patients with sorafenib-pretreated hepatocellular carcinoma, researchers reported.

"In the absence of established or predefined biomarkers for regorafenib, we performed broad exploratory biomarker analyses at the DNA, RNA, and protein level that represents a much more comprehensive approach than previous studies of regorafenib or sorafenib," wrote Michael Teufel, PhD, of Bayer Healthcare Pharmaceuticals in Whippany, N.J., and his associates. The preplanned, retrospective analysis of data from the phase 3 RESOURCE trial was reported in the May issue of Gastroenterology.

The randomized trial included 567 patients whose hepatocellular carcinoma had progressed on sorafenib. Regorafenib significantly outperformed placebo with regard to overall survival (OS). Dr. Teufel and his associates performed next-generation sequencing on 17 archived tumor samples containing sufficient tissue (all from regorafenib recipients). They also performed immune profiling on 46 tumor samples (32 from regorafenib recipients and 14 from placebo recipients), protein analysis on 499 plasma samples (332 from regorafenib recipients and 167 from placebo recipients), and microRNA analysis on 343 plasma samples (234 regorafenib recipients and 109 placebo recipients).

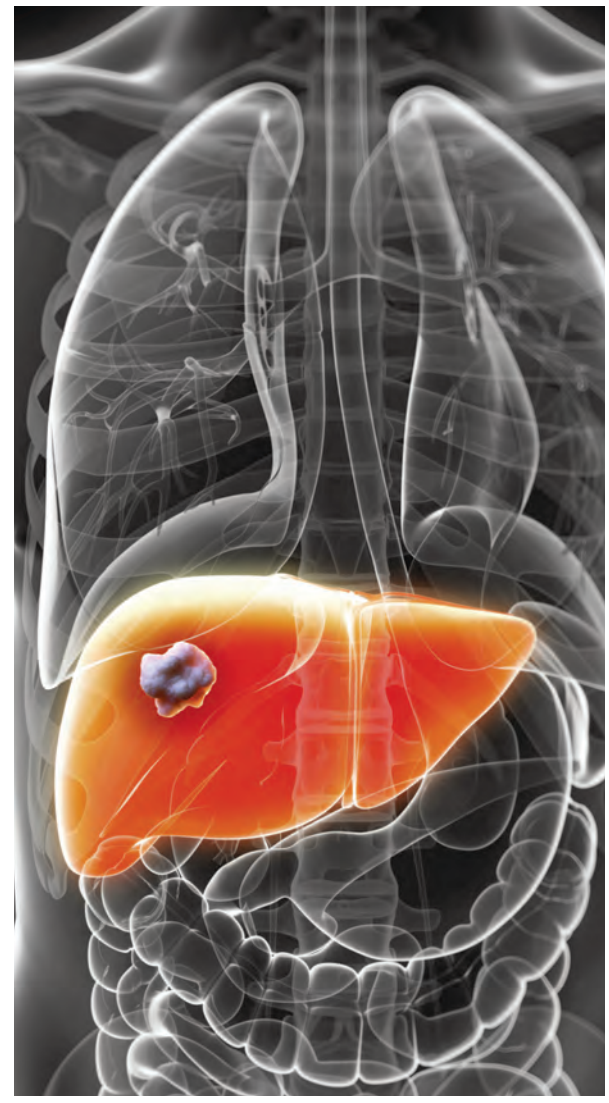
Among 266 proteins tested, decreased levels of 5 proteins correlated with significantly longer OS on regorafenib therapy. These proteins are involved in inflammation or hepatocellular carcinogenesis, the researchers noted. Importantly, none were associated with survival independent of treatment. These five proteins included angiopoietin 1 (hazard ratio for OS, 0.53; 95% confidence interval, 0.38-0.73), cystatin B (hazard ratio, 0.47; 95% CI, 0.34-0.64); the latency-associated peptide of transforming growth factor beta (HR, 0.46; 95% CI, 0.33-0.64), oxidized low-density lipoprotein receptor 1 (HR, 0.54; 95% CI, 0.41-0.72), and C-C motif chemokine ligand 3 (HR, 0.54; 95% CI, 0.39-0.74).

Additionally, baseline concentrations of 47 of the 266 proteins correlated with a time to progression benefit on regorafenib therapy (adjusted *P* less than or equal to .05 for each). The 47 proteins included all 5 that predicted an OS benefit. All but two proteins (calbindin and gelsolin) showed the same directional effect as for OS (that is, low expression predicted response).

Nine plasma microRNA's levels correlated with improved OS on regorafenib (adjusted *P* less than or equal to .05): MIR30A, MIR122, MIR125B, MIR200A, MIR374B, MIR15B, MIR107, MIR320, and MIR645. Notably, expression was linked to longer OS specifically among patients with the Hoshida S3 subtype of hepatocellular carcinoma. Next-generation sequencing of tumor samples also identified 49 variants in 27 oncogenes or tumor-suppressor genes. Mutations in CTNNB1 were found in 3 of 10 patients who progressed on regorafenib, and VEGFA amplification was found in 1 of 7 regorafenib responders.

**Among 266 proteins tested, decreased levels of 5 proteins correlated with significantly longer overall survival on regorafenib therapy. These proteins are involved in inflammation or hepatocellular carcinogenesis, the researchers noted.**

"Thus far, rational biomarker selection has been unsuccessful in identifying predictive markers for regorafenib in colorectal cancer and gastrointestinal stromal tumors," the researchers commented. "The broader approach used in this study is not only biologically warranted considering the heterogeneity of hepatocellular carcinoma tumors, but is also needed due to the multiple targets and pathways affected by MKIs such as regorafenib. Levels of these circulating biomarkers and genetic features of tumors might be used to identify patients with hepatocellular carcinoma most likely to respond to regorafenib."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Bayer funded the study, provided the study drug, and was involved in all aspects of the study. Dr. Teufel and three coinvestigators are Bayer employees. Dr. Teufel and two coinvestigators own stock in Bayer. Three other coinvestigators disclosed ties to Bayer and other pharmaceutical companies.

ginews@gastro.org

**SOURCE:** Teufel M et al. Gastroenterology. 2019 Jan 30. doi: 10.1053/j.gastro.2019.01.261.

*Continued from previous page*

balloon MI measurements, the researchers detected GERD with an area under the receiver operating characteristic curve (AUC) of 0.67, eosinophilic esophagitis with an AUC of 0.84, and non-GERD with an AUC of 0.83.

These findings held up in a separate validation cohort of 36 patients (28 with GERD and 8 with eosinophilic esophagitis) from three tertiary care centers. The probability of eosinophilic esophagitis was highest in patients with low distal MI values (that is, a low intercept) and a low slope (showing that MI values remained low proximally). A low distal MI intercept with a steeper positive slope suggested GERD, while a higher distal MI intercept with a steep slope signified non-GERD.

The system "potentially obviates the need for 24- to 48-hour ambulatory wireless pH monitoring or esophageal biopsies for histopathology," the researchers concluded. "This can help reduce diagnostic and treatment latency and might allow for monitoring disease activity over time."

The National Institutes of Health funded the external validation analysis. Diversatek Healthcare, which patented the device together with Vanderbilt University, gave research funding to four coinvestigators, including the senior author. Dr. Patel and the other five coinvestigators reported having no conflicts of interest.

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**SOURCE:** Patel DA et al. Gastroenterology. 2019 Jan 31. doi: 10.1053/j.gastro.2019.01.253.

FROM THE AGA JOURNALS

# MicroRNA-375 may be key to fibrolamellar carcinoma

BY WILL PASS
*MDedge News*

Up-regulation of microRNA-375 may be a future therapeutic strategy for patients with fibrolamellar carcinoma (FLC), according to investigators.

Analysis of primary FLC tumors showed that microRNA-375 was the most abnormal microRNA, down-regulated 27-fold, reported lead author Timothy A. Dinh, MD, of the University of North Carolina at Chapel Hill and his colleagues. Overexpression of microRNA-375 in an FLC cell line suppressed cell migration and proliferation, hinting at therapeutic potential.

"Overall, our results show that miR-375 [microRNA-375] functions as a tumor suppressor in FLC and points toward future therapies based on miR-375 mimics that may provide a viable option for patients," the investigators wrote in Cellular and Molecular Gastroenterology and Hepatology.

FLC is an uncommon liver cancer in adolescents and young adults. Currently, surgery is the only effective treatment; unfortunately, many patients have metastatic disease at the time of diagnosis, disallowing surgical cure.

"The lack of knowledge of underlying disease mechanisms has hindered our understanding of this cancer and the development of novel therapeutics for FLC patients," the investigators wrote.

Previous research has shown that possibly almost all patients with FLC have a heterozygous deletion mutation on chromosome 19. However, it is not a loss of genetic information that incites neoplasia; instead, the deletion causes a fusion of two genes DNAJB1 and PRKACA, the latter encoding cyclic adenosine monophosphate (cAMP)–dependent protein kinase A (PKA). This fusion is capable of triggering liver tumors, a phenomenon confirmed through mouse models. The present study built on these findings, along with recent awareness that several microRNAs are dysregulated in FLC, compared with normal liver tissue.

First, the investigators performed small RNA sequencing in six primary FLC tumors from The Cancer Genome Atlas (TCGA). They found that 30 microRNAs were up-regulated and 46 microRNAs were down-regulated. Among these, microRNA 375 was the most significantly down-regulated, at 27-fold ($P$ = .009). For confirmation of these findings, the same process was repeated in 18 independent samples, with the same result.

The investigators explained that, in addition to magnitude of down-regulation, microRNA-375 deserved attention for at least three other reasons: It is down-regulated in numerous cancer types, it directly targets known oncogenes, and it is suppressed by the PKA signaling axis, which is overactive in FLC.

Further testing confirmed that microRNA-375 was consistently more down-regulated in samples of FLC, by up to 20-fold, than it was in nonmalignant liver tissue. As confirmation that loss of microRNA-375 expression occurred in FLC tumor cells instead of other cell types, such as stromal cells, a patient-derived xenograft of FLC was compared with liver lineage cells, including adult hepatocytes, hepatoblasts, hepatic stem cells, and biliary tree stem cells. Again, microRNA-375 was down-regulated most in the FLC cells. Additional comparisons within the TCGA showed that microRNA-375 was more down-regulated in FLC than 21 out of 22 other tumor types (second only to melanoma).

"Taken together with our findings from primary tumor tissue, our results strongly suggest that miR-375 may function as a tumor suppressor in FLC," the investigators wrote.

Having confirmed the ubiquity of microRNA-375 down-regulation in FLC, the investigators turned to the relationship between the DNAJB1-PRKACA fusion and microRNA-375. Using two methods – genomic deletion with CRISPR/Cas9 and transposon injection – the investigators found that creating the DNAJB1-PRKACA fusion in liver cells of mice was sufficient to suppress microRNA-375 expression, which supports a downstream relationship.

**'Taken together with our findings from primary tumor tissue, our results strongly suggest that miR-375 may function as a tumor suppressor' in fibrolamellar carcinoma.**

Finally, the investigators showed that treating an FLC cell line with an microRNA-375 mimic suppressed the Hippo signaling pathway, including connective tissue growth factor (CTGF) and yes-associated protein 1 (YAP1). These events translated to reduced cellular activity, which suggests that up-regulating microRNA-375 could, indeed, control FLC.

"Importantly, introduction of a miR-375 mimic significantly reduced colony formation, EdU incorporation, and migration, indicative of reduced survival, proliferation, and metastatic potential, respectively," the investigators wrote.

"With RNA-based therapies showing increasing promise, miR-375–based therapies merit future consideration for FLC therapeutics," they concluded.

The study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Alcohol Abuse and Alcoholism, and the Fibrolamellar Cancer Foundation. The investigators declared no conflicts of interest.

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**SOURCE:** Dinh TA et al. Cell Mol Gastroenterol Hepatol. 2019 Feb 11. doi: 10.1016/j.jcmgh.2019.01.008.



For several decades, fibrolamellar carcinoma was the enigmatic liver cancer. Neither etiology nor molecular causes were known. The breakthrough came when tumor sequencing identified a hitherto undescribed fusion gene in 15 out of 15 patients analyzed: A small portion of the heat shock protein DNAJB1 was fused to the catalytic subunit of protein kinase A (PKA, or PRKACA), which retained full kinase activity. Underscoring the significance of this finding, the DNAJB1-PRKACA fusion gene was shown to be sufficient to elicit tumors similar to human fibrolamellar carcinoma when engineered in mice. The absence of conspicuous codriver genes makes DNAJB1-PRKACA a primary candidate for therapeutic target. However, PKA inhibitors would be problematic in the clinic because of the vital physiological functions of PKA.


DR. FRÖDIN

Consequently, the hunt is on to decipher the oncogenic signaling pathways emanating from DNAJB1-PRKACA with the hope to identify alternative targets among its downstream mediators. In this work, the Sethupathy lab performed a thorough study on abnormally regulated microRNAs in fibrolamellar carcinoma tumors. Intriguingly, they identified several microRNAs controlled by DNAJB1-PRKACA that have oncogenic or tumor suppressor function in other cancers. In particular, the tumor suppressor microRNA-375 was massively down-regulated by DNAJB1-PRKACA. Furthermore, introducing a microRNA-375 mimic in fibrolamellar cancer cells suppressed proliferation and motility. Important studies like this open up new avenues aiming to manipulate cancer microRNAs as alternative or complementary approaches for targeting DNAJB1-PRKACA signaling in the highly fatal fibrolamellar carcinoma.

*Morten Frödin, MSc, PhD, is an associate professor and group leader of the Biotech Research and Innovation Centre, University of Copenhagen. He has no conflicts of interest.*

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**References: 1.** NuLYTELY [package insert]. Braintree, MA: Braintree Laboratories, Inc; 2013. **2.** GoLYTELY [package insert]. Braintree, MA: Braintree Laboratories, Inc; 2013. **3.** SUPREP Bowel Prep Kit [package insert]. Braintree, MA: Braintree Laboratories, Inc; 2017. **4.** IQVIA. National Prescription Audit Report. August 2018.

*This product has been discontinued.

# Meet a rising star in fecal incontinence research

The AGA Research Foundation offers its flagship grant, the AGA Research Scholar Award, to the most promising early career investigators. Kyle Staller, MD, MPH, an assistant professor of medicine at Harvard Medical School in Boston, is no exception. We're thrilled to highlight Dr. Staller, a 2016 AGA Research Scholar Award winner.

The Staller lab's AGA-funded project is specifically focused on the risk factors for fecal incontinence, which have not been well studied. One in 10 women over age 80 suffer from this debilitating condition. Dr. Staller looked at the lifestyles and dietary factors of female study participants in research databases to determine whether they were predisposed to developing fecal incontinence beyond the usual risk factors such as childbirth, which can cause injury to the pelvic floor, and diabetes. Dr. Staller believes that understanding and modifying risk factors could decrease the chance of, or even prevent, women from developing this condition.

With his AGA Research Foundation grant, Dr. Staller found that consuming dietary fiber in higher quantities, and increasing moderate exercise up to a point, lowered the risk of developing fecal incontinence. "This tells us that not only is fiber healthy but also preventative to fecal incontinence," he said.

DR. STALLER

Dr. Staller says that he became interested in this area of study after patients, who were getting excited about their impending retirement or enjoying their retirement years, developed this life-altering condition. His compassion for his patients inspired him to study the factors leading to fecal incontinence, which will likely become more prevalent as the U.S. population ages.

Dr. Staller is using the baseline data from his AGA Research Foundation grant to support his application for a 5-year National Institutes of Health grant designed to help young investigators learn new research skills to further their careers.

Read more about Dr. Staller and other AGA Research Foundation awardees by visiting www.gastro.org/foundation.

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Help AGA build a community of investigators through the AGA Research Foundation.

Your donation to the AGA Research Foundation can fund future success stories by keeping young scientists working to advance our understanding of digestive diseases. Donate today at www.gastro.org/donateonline.

# Recap of the 2019 Gut Microbiota for Health World Summit

On March 23 and 24, AGA and the European Society of Neurogastroenterology and Motility (ESNM) gathered 350+ international clinicians and researchers to network and discuss the latest evidence on the interaction between diet, nutrition and the gut microbiome at the 2019 Gut Microbiota for Health World Summit.

Twenty-three novel abstracts were presented as posters at the meeting. The abstracts covered topics ranging from probiotics to diet to potential microbiome-driven treatments for GI disorders.

Below are some key takeaways (as shared on Twitter) from the meeting. Stay tuned for more news and resources from the 2019 Gut Microbiota for Health World Summit, including an official meeting report in Gastroenterology, on-demand presentation recordings, video clips and more.

"Excess zinc supplementation can change the gut #microbiota and increase risk AND severity of #cdiff infection, says @joeyzacks #GMFH2019 @cdiffFoundation" — Dr. Caterina Oneto (@caterina_oneto)

"You need a #dietitian for low #FODMAP diet education to ensure the patient consumes a nutritionally adequate diet. @MagnusSimren #GMFH2019" — Kate Scarlata, RDN (@KateScarlata_RD)

"Patients with cirrhosis have increased bacteremia, blood LPS levels and intestinal permeability. This background has led to study the role of gut microbiota in liver disease #GMFH2019" — GutMicrobiota Health (@GMFHx)

"Much anticipated talk on #probiotics happening now at #GMFH2019 led by AGA's probiotics experts @KashyapPurna & Geoffrey Preidis. This work will culminate in a new AGA guideline on using probiotics in clinical practice. Additional data will be presented at #DDW19" — AGA (@AmerGastroAssn)

"Eric Martens: while a low fibre diet may not drive inflammation in the short term, it may increase disease risk in the long term, due to changes in microbiota & mucus degrading bacteria! #GMFH2019" — Andrea Hardy RD (@AndreaHardyRD)

View additional Twitter coverage of the meeting: #GMFH2019.

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# AGA president advocates for increased access to care for digestive disease patients

AGA President David Lieberman, MD, AGAF, was on Capitol Hill advocating for legislation to ensure that digestive disease patients have timely access to lifesaving treatments and touted the importance of increasing access to colorectal cancer screenings. Specifically, Dr. Lieberman sought support for H.R. 1570/S. 668, the Removing Barriers to Colorectal Cancer Screening Act, legislation that would fix the current Medicare screening colonoscopy coinsurance problem. Currently, when a Medicare beneficiary has a screening colonoscopy that turns therapeutic, the procedure is no longer considered a screening and the patient is on the hook for the "surprise" bill. This bipartisan, bicameral legislation would fix this problem for beneficiaries.

Dr. Lieberman also participated in a congressional briefing sponsored by AGA, ACG, and ASGE on the importance of colorectal cancer (CRC) screening and spoke of the geographic, ethnic, and socioeconomic barriers to CRC screening and how it impacts the rates of screening. Rep. James P. McGovern, D-MA, chair of the House Rules Committee, also spoke about the importance of CRC screenings and the number of lives that can be saved with screening. He also stressed that we have made strides in screening because of the research that is funded through the National Institutes of Health, which Congress needs to continue to support.

Protection for patients who are subject to step-therapy protocols was another area that Dr. Lieberman emphasized during his meetings with congressional staff. Step therapy is a utilization management tool where insurers force patients to fail one or more therapies before they will cover the initial therapy recommended by their physician. This policy is more and more common especially for patients with inflammatory bowel disease (IBD) who rely on biologics for treatment. Dr. Lieberman stressed that forcing a patient to fail a medication that they know will be ineffective is in violation of the Hippocratic oath. Restoring the Patient's Voice Act, legislation soon to be reintroduced by Reps. Raul Ruiz, D-CA, and Brad Wenstrup, R-OH, would provide an expeditated appeals process and provide some common sense exceptions for patients when subjected to step therapy.

Dr. Lieberman stressed the importance of funding the NIH and requested Congress increase their budget by $2 billion in fiscal year 2020. Dr. Lieberman described the NIH as our country's crown jewel since it invests in biomedical research that will ultimately find cures for countless conditions, increase our country's economic competitiveness, and spur industries and invests in our country's best and brightest scientists. We are hopeful that Congress will reject the Trump Administration's recommendation of a 12% cut for NIH and instead continue to provide the necessary increases the agency needs to remain competitive.

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# Are you ready to celebrate 50 years of DDW®?

With 2019 being the 50th anniversary of Digestive Disease Week® (DDW), this year's meeting is one you won't want to miss. AGA looks forward to seeing members May 18 to 21, 2019, in San Diego, California. Register and view additional information on the DDW website: www.ddw.org. You can learn more about AGA programming and events at DDW by visiting www.gastro.org/DDW.

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# 'Put your own oxygen mask on first'

Takeaways from the leadership conference stress the importance of self-care, emotional intelligence, and remaining optimistic.

"Leadership 101: put your own oxygen mask on first @DarwinConwell #AGAleads #AGAForward @AmerGastroAssn"— Dr Michelle T. Long (@DrMTLong)

The inaugural Leadership Development Conference combined participants from three AGA programs for a weekend of networking, mentorship, and mapping out goals and initiatives.

Attendees included the 2020 class of AGA Future Leaders and mentors, Women's Leadership Conference participants, and mentors and scholars of the new AGA FORWARD Program, an NIH-funded initiative that supports underrepresented minority physicians and scientists.

"Got to meet one of my tweeps heroes today! She's even more awesome in real life!! #AGALeads #WomenInMedicine #WomenInGI @drfolamay @AmerGastroAssn" — Dr Aline Charabaty (@DCharabaty)

"Dr. Boland (Lynch syndrome) discussing career success in an ever changing scientific environment #AGALeads #AGAForward" — Eric J. Vargas M.D. (@EricJVargasMD)

*Continued on page 17*

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# GI & HEPATOLOGY NEWS

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# Top AGA Community patient cases

Physicians with difficult patient scenarios regularly bring their questions to the AGA Community (https://community.gastro.org/discussions) to seek advice from colleagues about therapy and disease management options, best practices, and diagnoses.

In case you missed it, here are the most popular clinical discussions shared in the forum recently:

**1. Biologic blood levels for pediatric IBD patient (http://ow.ly/4G2M30okWyk)**
An 11-year-old was experiencing right lower quadrant pain, a low-grade fever, painful red nodules in his legs, joint pain, moderate anemia, a perianal abscess and high fecal calprotectin. An MRI revealed signs of lower small bowel disease and moderate narrowing of the ileum. He was treated and showing no symptoms at about 20 weeks. The community discussed if the patient would benefit from adding adalimumab blood levels to his maintenance.

**2. False positives in new DNA-based colon cancer tests (http://ow.ly/S8bJ30okWuO)**
A discussion around some noninvasive colon cancer tests, such as Cologuard and liquid biopsy tests like Epi proColon, revealed community frustrations with false positives and dealing with an increased number of anxious patients awaiting colonoscopies.

**3. Olmesartan-induced enteropathy (http://ow.ly/NeAD30ol0lb)**
A female patient switched blood pressure medications and developed diarrhea, abdominal discomfort, and weight loss. She tested positive for celiac-type enteropathy and was placed on a gluten free diet, with symptoms resolving a couple weeks later. She switched back to her original medication, and her GI had questions for the community regarding potential for a long-term condition, as well as celiac serology follow-up.

**4. Inactive UC (http://ow.ly/hng930okiA3)**
A 49-year-old woman with a history of pancolitis hasn't required therapy for over 10 years. Recent biopsies showed architectural distortion and atrophy consistent with inactive colitis, without any active colitis in the rectum, but the descending colon presented a polyp mucosa with chronic colitis, erosion, and regenerative hyperplasia. Given her history, the physician solicited advice on therapy and rescoping consistency going forward.

More clinical cases and discussions are at https://community.gastro.org/discussions.

*Continued from page 13*

"7 AGA Presidents, moderated by Dr. Anandasabapathy on Pathways to Leadership and Overcoming Challenges of the Era Presidential Panel @AmerGastroAssn Leadership conference program @SeragHashem @BCMDeptMedicine @KanwalFasiha @Aketwaroo @richashukla84" — Ruben Hernaez (@ruben_hernaez)

The event coincided with International Women's Day, giving Women's Leadership Conference attendees the chance to celebrate their journeys and grow into leadership roles with other #WomenInGI.

"#AGALeads #womenleadershipconference #womeninGI #InternationWomensDay with some amazing ladies in GI!! @AmerGastroAssn @AlisonGoldinMD @ibddocmaria @joanwchen" — ReezwanaCMD (@reezwanc)

"#AGAleads #WomeninGI women negotiating in a group are perceived favorably – Ellen Zimmerman, MD"
— Fazia Mir-Shaffi,MD (@Faiziya) March 9, 2019
"What I learned at @AmerGastroAssn #womeninGI Leadership course (after waiting a bit to see what stuck w me)
1. If you say yes to a request, you're saying yes to doing it well.
2. Knowing your limitations will serve you better than being great at everything" — Laura Targownik (@UofM_GI_Head)

Aline Charabaty Pishvaian, MD, shared some takeaways in the AGA Community forum (community.gastro.org) about challenges women in GI face — a breakout discussion from the Women's Leadership Conference.

View more insight and takeaways from participants on Twitter using #AGALeads.

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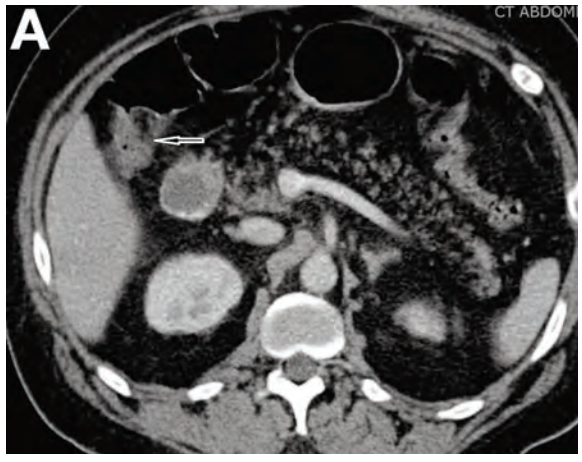
## CLINICAL CHALLENGES AND IMAGES

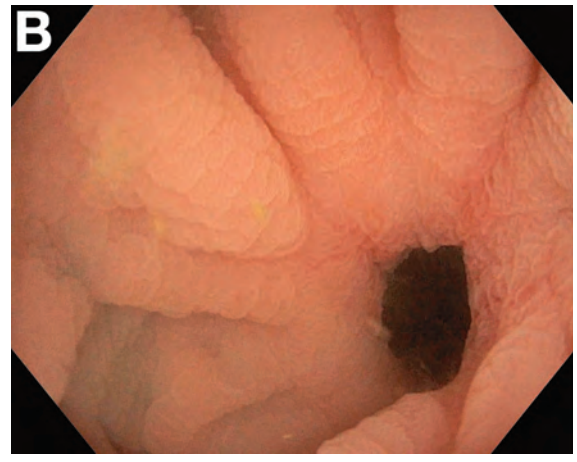
### What is your diagnosis?

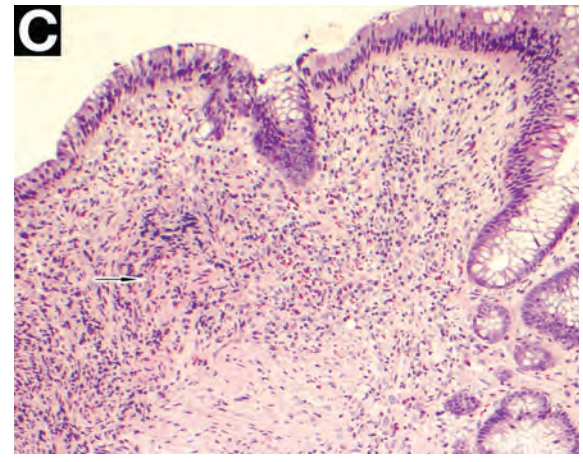
*By Vu Q. Nguyen, MD, Douglas J. Grider, MD, and Paul Yeaton, MD. Published previously in Gastroenterology (2017;152[3]:490-1).*

A 57-year-old man presented to our hospital with a week of generalized weakness and abdominal pain. Relevant medications included diclofenac 75 mg twice daily, aspirin 81 mg, and clopidogrel 75 mg/d. Vital signs were normal. Physical examination showed mild diffuse abdominal tenderness. Admission blood work revealed a hemoglobin of 8.8 g/dL, decreased from a baseline hemoglobin of 12 g/dL. The patient did not have overt gastrointestinal bleeding, but tested positive for fecal occult blood. A computed tomography scan demonstrated luminal narrowing at the hepatic flexure without bowel wall thickening or obstruction (Figure A). Esophagogastroduodenoscopy was normal. Colonoscopy revealed a circumferential stricture in the right colon with an estimated diameter of 8 mm (Figure B). Biopsies of the stricture showed significant lamina propria fibrosis, eosinophilic infiltration, and mild crypt distortion (Figure C).

*The diagnosis is on page 34.*



# Changes in brain function

**Virtual reality** *from page 1*

disorders. Most showed significant benefit. In eating disorders for example, response at 1 year was 44% in those receiving VR as an adjunct to cognitive-behavioral therapy versus 10% in the controls.

"VR may not just alter perception. In studies being conducted with functional MRI imaging, changes in brain function similar to those observed in patients taking opioids have been observed," said Dr. Spiegel, outlining objective evidence that VR has physiological effects.

VR already has an established role as a training tool for physicians in GI and other areas of medicine, but Dr. Spiegel focused on the evidence of its applications in treatment. Earlier this year, an expert panel in which he participated published a methodology for VR clinical trials to help move the field forward by defining how to establish evidence of benefit (JMIR Ment Health. 2019;6:e11973). With a growing body of data suggesting VR has measurable clinical benefits, the field is poised to grow quickly.

In gastroenterology specifically, Dr. Spiegel envisions applications in functional diseases, such as irritable bowel syndrome (IBS), in which there is already strong evidence of a mind-gut component to symptom flares. He said, "VR can help patients to engage with their body differently, changing how they react to symptoms and leading to better coping mechanisms."

Implementation of VR as a therapeutic tool is not without obstacles. For example, patients susceptible to motion sickness can react poorly to the 3-D environment created by VR, according to Dr. Spiegel. Many patients have expressed reluctance to try VR for any number of reasons, including skepticism. However, there are many potential advantages. In the management of pain, for example, VR circumvents a long list of adverse events related to opioids or other analgesics.

**'We have good evidence that VR is a powerful tool to manage mood disorders and pain perception. Although there is so far a fairly limited amount of research specific to GI conditions, this is coming,' Dr. Spiegel said.**

This technology is being used only in a few centers, but there is enough evidence of clinical benefit that Dr. Siegel expects it to be more broadly adopted as indications expand. With more controlled trials being performed to measure and establish benefits, he envisions an evidence-based VR pharmacy that will allow clinicians to prescribe specific VR software suitable not only for the target condition but matched to patient preferences for VR environments.

"We have good evidence that VR is a powerful tool to manage mood disorders and pain perception. Although there is so far a fairly limited amount of research specific to GI conditions, this is coming," Dr. Spiegel said.

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# Algorithms to predict response

**Analytics** *from page 1*

has now published several papers on the role of precision analytics of big data to improve treatment choices in IBD, as well as other diseases. These analyses are relevant for determining both who to treat with a certain drug and who to not treat with it.

In one example, data from 1,080 IBD patients taking thiopurines were used to develop a machine learning algorithm that analyzed multiple readily available variables, such as a complete blood count with differential and a chemistry panel, to predict whether someone was or was not in remission. This was then used to compare the mean yearly clinical event rates (new steroids prescriptions, hospitalizations, and abdominal surgeries) between the two groups (1.08 vs. 3.95 events) to show the associated clinical benefit of using this algorithm.

**'If machine learning predicts effective choices, there will be an opportunity to accelerate the time to disease control, as well as save costs by avoiding therapies not likely to be effective,' Dr. Waljee explained.**

"The heterogeneity of response to therapies for IBD is well established. If machine learning predicts effective choices, there will be an opportunity to accelerate the time to disease control, as well as save costs by avoiding therapies not likely to be effective," Dr. Waljee explained.

In another example, an algorithm was developed to predict the likelihood of achieving a corticosteroid-free biologic remission at 1 year in Crohn's disease patients when patients were evaluated 6 weeks after initiating the gut-selective biologic vedolizumab. Again, it was based on an analysis of numerous variables, including laboratory data, sex, and race. Based on the model drawn from the analysis of 472 patients, 35.8% of the patients predicted to be in corticosteroid-free biologic remission at 1 year achieved this endpoint, whereas only 6.7% of the patients predicted to fail achieved the endpoint.

"This suggests that we can use an algorithm relatively early in the course of this biologic to predict who is going to respond," reported Dr. Waljee. Again, patients with a low likelihood of response at 6 weeks can be started on an alternative treatment, which could potentially accelerate the time to disease control and avoid the costs of an ineffective and expensive treatment.

IBD is a particularly attractive focus of precision analytics with big data. IBD has a relatively unpredictable relapsing/remitting course and a heterogeneous response to available therapies. Algorithms predictive of response circumvent the inherent delays from evaluating disease control over an extended period.

"With ever-increasing concern about costs of care and access to care, these treatment algorithms promise to use resources more efficiently," Dr. Waljee said.

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In Focus
Brought To You By The New Gastroenterologist

# Exploring multidisciplinary treatments in the traumatizing aspects of chronic abdominal pain

BY EMILY WEAVER, LCSW, AND EVA SZIGETHY, MD, PHD

**Ms. Weaver** is a UPMC Total Care–IBD program senior social worker; **Dr. Szigethy** is professor of psychiatry and medicine, codirector, IBD Total Care Medical Home, University of Pittsburgh Medical Center, departments of medicine and psychiatry.

## Introduction

Abdominal pain is a complex phenomenon that involves unpleasant sensory and emotional experiences caused by actual or potential visceral tissue damage. As pain becomes chronic, there is a functional reorganization of the brain involved in emotional and cognitive processing leading to amplification of pain perception and associated pain suffering.[1,2] With the rising recognition of the complexity of pain management in the 1960s, the treatment of pain became a recognized field of study, leading to the formation of interdisciplinary teams to treat pain. However, although efficacious, this model lacked adequate reimbursement structures and eventually subsided as opioids (which at the time were widely believed to be nonaddictive) become more prevalent.[3] Not only is there a lack of empirical evidence for opioids in the management of chronic abdominal pain, there is a growing list of adverse consequences of prolonged opioid use for both the brain and gastrointestinal tract.[4]

Recently, there has been more clinical focus on behavioral interventions that can modulate gut pain signals and associated behaviors by reversing maladaptive emotional and cognitive brain processes.[5] One such psychological process that has received little attention is the traumatizing nature of chronic abdominal pain. Chronic pain, particularly when it feels uncontrollable to patients, activates the brain's fear circuitry and drives hyperarousal, emotional numbing, and consolidation of painful somatic memories, which become habitual and further amplify negative visceral signals.[6,7] These processes are identical to the symptom manifestations of posttraumatic stress disorder (PTSD) such as intrusiveness, avoidance, negative mood and cognitions, and hyperarousal from life events. In fact, individuals with a history of other traumatizing exposures have an even higher risk of developing chronic pain disorders.[8] This review has two objectives: to provide a theoretical framework for understanding chronic pain as a traumatizing experience with posttraumatic manifestations and to discuss behavioral interventions and adjunctive nonopioid pharmacotherapy embedded in multidisciplinary care models essential to reversing this negative brain-gut cycle and reducing pain-related suffering.

## Trauma and chronic abdominal pain

Trauma is defined as an individual's response to a threat to safety. Traumatized patients or those with PTSD are at higher risk for chronic abdominal pain.[9] Given the strong neurobiological connection between the brain and gut that has been phylogenetically preserved, emotional (e.g., fear, terror) or physical (e.g., pain) signals represent danger, and with chronicity, there can be a kindling-related consolidation of these maladaptive neurobiological pathways leading to suffering (e.g., hopelessness, sense of failure) and disability (Figure 1).

The interrelationship between chronic pain and trauma is multifaceted and is further complicated by the traumatizing nature of chronic pain itself, when pain is interpreted as a signal that the body is sick or even dangerously ill. Patients with chronic abdominal pain may seek multiple medical opinions and often undergo extensive, unnecessary, and sometimes harmful interventions to find the cause of their pain, with fear of disability and even death driving this search for answers.

The degree to which an individual with long-lasting pain interprets their discomfort as a risk to their well-being is related to the degree of trauma they experience because of their pain.[10] Indeed, many of the negative symptoms associated with posttraumatic stress are also found in those with chronic abdominal pain. Trauma impacts the fear circuitry centers of the brain, leading to altered activation of the hypothalamic-pituitary-adrenal axis and the amygdala, as well as chronic activation of the sympathetic nervous system and stress-released hormones, all of which are potential pathways that dysregulate the brain-gut relationship.[11-13] Worries for safety, which are reactivated by physiological cues (e.g., GI symptoms, pain), as well as avoidance of potential triggers of GI symptoms (e.g., food, exercise, medications, and situations such as travel or scheduled events, and fear of being trapped without bathroom access), are common. Traumatized individuals can experience a foreshortened sense of the future, which may lead to decreased investment in long-term determinants of health (e.g., balanced diet, exercise, social support) and have higher rates of functional impairment and higher health care utilization.[14] Negative mood, including irritability, anxiety, depression, insomnia, and impaired concentration are common in those with trauma and chronic pain and can be accompanied by internalized blame (e.g., depression, substance abuse, suicidality) or externalized blame (e.g., negative relationships with health care providers, rejection from their support or faith system). These can be worsened by an impaired sense of trust, which impacts the patient-provider relationship and other sources of social support leading to lack of behavioral activation, anhedonia, and isolation.

Another commonality is hypervigilance, as those with chronic abdominal pain are often hyperaware of physical symptoms and always "on alert" for a signal indicative of a pain flare. Anxiety and depression frequently co-occur in populations with trauma and chronic pain; these diagnoses are associated with higher rates of catastrophizing and learned helplessness, which may be exacerbated by lack of a "cure" for functional gastrointestinal disorders (FGIDs) and chronic pain.[15] These factors could potentially lead to lack of engagement with treatment or, alternatively, risky or destructive attempts to cure pain including dan-

Management of chronic abdominal pain remains one of the most challenging tasks that clinicians face. While many of these patients are treated solely with pharmacotherapy, it's also important to acknowledge that the treatment of chronic abdominal pain may benefit from a multidisciplinary approach that utilizes behavioral therapies. In this quarter's In Focus article, brought to you by *The New Gastroenterologist*, Emily Weaver and Eva Szigethy (University of Pittsburgh) provide a fantastic overview of how to better understand chronic abdominal pain as well as nonopioid pharmacotherapy and behavioral therapy options that can be utilized in its treatment. Given the dire need for effective nonopioid management of chronic abdominal pain, this article will no doubt be important to all practicing in the field of gastroenterology.

***Bryson W. Katona, MD, PhD***
***Editor in Chief, The New Gastroenterologist***

gerous complementary alternative treatments or substance abuse to numb sensations. Another feature of trauma in chronic pain is the sense of dissociation from and lack of control over the body, sometimes induced by negative medical experiences (e.g., unwanted physical examinations, medication side effects, traumatic procedures, or hospitalizations).[16,17]

## The importance of treating trauma in the management of chronic pain

Behavioral treatment is increasingly being recognized as an essential component in the management of any chronic pain syndrome.[18] The most studied psychosocial interventions for chronic abdominal pain are cognitive-behavioral therapy (CBT) and gut-focused hypnosis. CBT is usually a problem-focused, short-term intervention that can be delivered individually in the office, via group therapy, or through virtual platforms. CBT is most effective when cognitive distortions and ineffective behaviors create emotional distress, and the therapy targets patient's stress reactivity, visceral anxiety, catastrophizing, and inflexible coping styles.[5] Gut-focused hypnosis is the second most–studied behavioral treatment for chronic abdominal pain and utilizes the trance state to make positive suggestions leading to broad and lasting physiological and psychological improvement.[19] In addition to pain management, both CBT and hypnosis are efficacious treatments for PTSD.[20,21]

Utilizing a multidisciplinary medical team including integrated behavioral experts, such as in a patient-centered medical home, is considered the standard of care for treatment of chronic pain. The patient-provider relationship is essential, as is consistent follow-up to ensure effective symptom management and improvements in quality of life. Additionally, patient education, including a positive (i.e., clear) diagnosis and information on the brain-gut relationship, is associated with symptom improvement. In our subspecialty medical home for inflammatory bowel disease (IBD), we found that, in our patients who were on opioids for their chronic pain, engagement with our embedded behavioral and pain specialists resulted in significant reduction in opioid use and depression as well as improved self-reported quality of life.[22] Gastroenterologists and advanced-practice providers operating without embedded behavioral therapists can consider referring patients to behavioral treatment (e.g., licensed clinical social workers, licensed professional counselors, marriage and family therapists, psychologists, and psychiatrists; the latter often specialize in medication management and may not offer behavioral therapy) for trauma if patients have undergone a traumatic event (e.g., exposure to any potentially life-threatening event, serious injury, or violence) at any point in their lifetime and are experiencing intrusive symptoms (e.g., memories, dreams, or flashbacks to trauma), avoidance of trauma reminders, and negative mood or hyperarousal related to traumatic events (Table 1).[23]

With the traumatization component of chronic abdominal pain, which can further drive maladaptive coping cycles, incorporation of trauma-informed treatment into gastroenterology clinics is an avenue toward more effective treatment. The core principles of trauma-informed care include safety, choice, collaboration, trustworthiness, and empowerment,[24] and are easily aligned with patient-centered models of care such as the interdisciplinary medical home model. Incorporation of screening techniques, interdisciplinary training of clinicians, and use of behavioral providers with experience in evidenced-based treatments of trauma enhance a clinic's ability to effectively identify and treat individuals who have trauma because of their abdominal pain.[25] Additionally, the most common behavioral interventions for functional gastrointestinal disorders (FGIDs) are also efficacious in the treatment of trauma. CBT is a well-validated treatment for PTSD that utilizes exposure therapy to help individuals restructure nega-

*Continued on following page*

**Table 1: Effective interventions for posttraumatic stress disorder** [21,29-33]

| Intervention | Description | Session number and format |
|---|---|---|
| Cognitive-behavioral therapy (CBT), including cognitive processing therapy, cognitive therapy, and prolonged exposure | Teaches coping skills to target and change maladaptive thoughts, feelings, and behaviors related to unhealthy interpretations of trauma to improve overall functioning. Prolonged exposure can be used independently or in conjunction with other CBTs and teaches individuals to gradually face their trauma memories/triggers to reduce avoidance behaviors; also utilizes relaxation skill training. | 12-16 sessions over 3-month period, individual or group (prolonged exposure generally individual) |
| Brief eclectic psychotherapy | Utilizes CBT and psychodynamic therapy along with positive patient-provider rapport to reduce guilt and shame related to trauma | 16 weekly sessions, individual |
| Eye movement desensitization and reprocessing therapy | While focusing on trauma memory, uses bilateral stimulation (usually eye movements) to reduce strength of trauma memory on emotions | 6-12 sessions delivered once or twice weekly, individual |
| Trauma-focused hypnosis | Utilizes induction of trance state and resulting openness to therapist's suggestions to change relationship between emotions, thoughts, behaviors, and perceptions to enhance trauma healing | 4-6 weekly sessions over at least 6 weeks |
| Narrative exposure therapy | Helps individuals create an account of traumatic experiences with the goal to empower and increase self-respect | 4-10 sessions, usually group |
| Interpersonal psychotherapy (IPT) | Focuses on the impact of trauma on interpersonal relationships; combination of psychoeducation, problem solving, interpersonal skill training in the areas of grief, role disputes, or role transitions | 12-16 weekly sessions, individual or group |
| Medications | Sertraline, paroxetine, fluoxetine, and venlafaxine (only sertraline and paroxetine are FDA approved) | Titrate over 1-2 months to maintenance dose |

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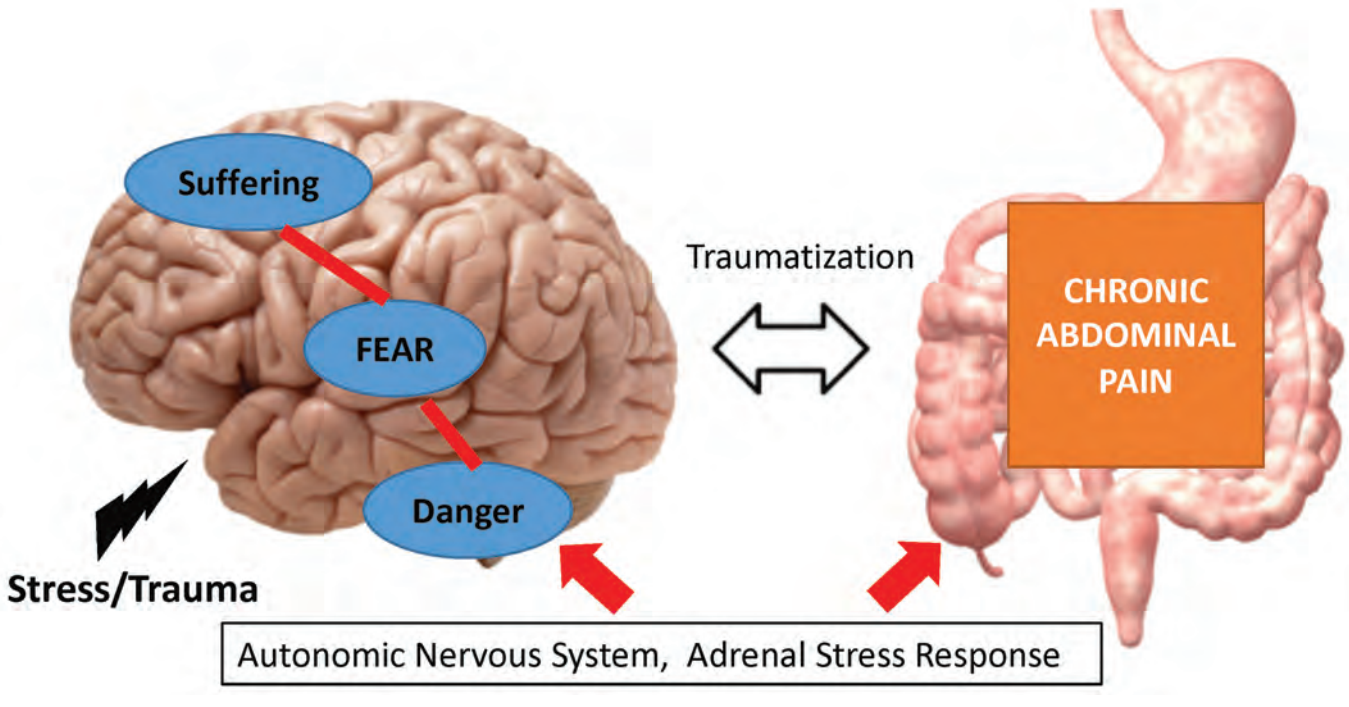
*Figure 1*

## Trauma and the Brain-Gut Interaction with Chronic Abdominal Pain

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tive beliefs shaped by their negative experience and develop relaxation skills. Hypnosis is also validated in the treatment of trauma, with the possible mechanism of action being the replacement of the negative or dissociated traumatic trance with a healthy, adaptive trance facilitated by the hypnotherapist.[21]

### Adjunctive nonopioid medications for chronic abdominal pain

While there are few randomized controlled trials establishing efficacy of pharmacotherapy for sustained improvement of abdominal pain or related suffering, several small trials and consensus clinical expert opinion suggest partial improvement in these domains.[26,27] Central neuromodulators that can attenuate chronic visceral pain include antidepressants, antipsychotics, and other central nervous system–targeted medications.[26] Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, imipramine, desipramine) are often first-line treatment for FGIDs.[28] Serotonin noradrenergic reuptake inhibitors (e.g., duloxetine, venlafaxine, desvenlafaxine, milnacipran) are also effective in pain management. Selective serotonin reuptake inhibitors (e.g., paroxetine, fluoxetine, sertraline, citalopram, escitalopram) can be used, especially when comorbid depression, anxiety, and phobic disorders are present.

**Use of behavioral providers with experience in evidenced-based treatments of trauma enhance a clinic's ability to effectively identify and treat individuals who have trauma because of their abdominal pain.**

Tetracyclic antidepressants (e.g., mirtazapine, mianserin, trazodone) are effective treatments for early satiety, nausea/vomiting, insomnia, and low weight. Augmenting agents are utilized when single agents do not provide maximum benefit, including quetiapine (disturbed sleep), bupropion (fatigue), aripiprazole, buspirone, and tandospirone (dyspeptic features and anxiety). Delta ligands including gabapentin and pregabalin are helpful for abdominal wall pain or fibromyalgia. Ketamine is a newer but promising pathway for treatment of pain and depression and is increasingly being utilized in outpatient settings. Additionally, partial opioid-receptor agonists including methadone and suboxone have been reported to decrease pain in addition to their efficacy in addiction recovery. Medical marijuana is another area of growing interest, and while research has yet to show a clear effect in pain management, it does appear helpful in nausea and appetite stimulation. Obtaining a therapeutic response is the first treatment goal, after which a patient should be monitored in at least 6-month intervals to ensure sustained benefits and tolerability, and if these are not met, enhancement of treatment or a slow taper is indicated. As in all treatments, a positive patient-provider relationship predicts improved treatment adherence and outcomes.[26] However, while these pharmacological interventions can reduce symptom severity, there is little evidence that they reduce traumatization without adjunctive psychotherapy.[29]

### Summary

Both behavioral and pharmacological treatment options are available for chronic abdominal pain and most useful if traumatic manifestations are assessed and included as treatment targets. A multidisciplinary approach to the treatment of chronic abdominal pain with increased screening and treatment of trauma is a promising pathway to improved care and management for patients with chronic pain. If trauma is left untreated, the benefits of otherwise effective treatments are likely to be significantly limited.

***See references at www.mdedge.com/gihepnews/new-gastroenterologist***


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# Hyperglycemia drives leaky gut syndrome, inflammation

**BY AMY KARON**
*MDEdge News*

MIAMI – Hyperglycemia increases intestinal permeability, which facilitates enteric infections and systemic inflammation, reported Christoph Thaiss, PhD.

The findings upend the old idea that intestinal barrier dysfunction leads to diabetes, Dr. Thaiss said during a plenary session at the annual Gut Microbiota for Health World Summit. Multiple mouse models link hyperglycemia to intestinal barrier dysfunction, and hemoglobin $A_{1c}$ levels in humans "highly correlate with the influx of microbial molecules into the intestinal epithelium."

Researchers often struggle to decide if apparent causes are really confounders or even downstream results (reverse causation). In the metabolic syndrome, patients are known to have increased intestinal permeability – so-called leaky gut – and microbes crossing the gastrointestinal epithelium have been found to cause both gut mucosal infections and chronic systemic inflammation. But because these mechanisms were poorly understood, some experts posited that intestinal barrier dysfunction induced pancreatic beta-cell inflammation, insulin resistance, and diabetes.


DR. THAISS

To take a deeper dive, Dr. Thaiss and his associates at the University of Pennsylvania, Philadelphia, started with a mouse model of morbid obesity. The mice had multiple systemic sites with microbial pattern recognition ligands, signifying microbial influx from the gut. They also had genetic signatures indicating a marked disruption of junctions between epithelial cells, compared with healthy controls.

The obese mice also were much more susceptible to enteric infections with *Citrobacter rodentium* (a *Salmonella* analog), but obesity itself did not drive this risk, Dr. Thaiss explained. In fact, two different murine models of nonobese type 1 diabetes mellitus showed "leaky" intestinal epithelial adherence junctions, heightened susceptibility to *C. rodentium* infection, and showed systemic pathogen spread. Ribosomal DNA sequencing showed that these hyperglycemic (diabetic) mice had shifts in their gut microbiomes; however, translocating the altered microbiota to normal mice did not make them more susceptible to enteric infections or systemic inflammation.

Based on these findings, the researchers

*Continued on following page*

# Red meat culprit

**TMAO** *from page 1*

of Cleveland Clinic. "In the future, our medicine cabinets will have drugs in them that not only affect us, but also target the microbial enzymes that affect levels of metabolites like TMAO."

Trimethylamine N-oxide (TMAO) is produced by gut bacteria. High levels (in one study, approximately 6.2 micromolar) significantly increase the risk of major adverse cardiovascular events even after controlling for traditional demographic and clinical risk factors. Studies indicate that TMAO alters cholesterol and bile acid metabolism, upregulates inflammatory pathways, and promotes foam cell formation, all of which worsen atherosclerosis. In addition, TMAO increases clotting risk by enhancing platelet reactivity.

"Reducing the amount of animal products in one's diet helps reduce TMAO levels," said Dr. Hazen. Certain fish – mainly those found in deep, cold water, such as cod – are high in TMAO. However, a bigger culprit in the United States is red meat, which contains two major TMAO precursors – choline and carnitine. In a recent study, Dr. Hazen and his associates gave 113 healthy volunteers three isocaloric diets in random order based on red meat, white meat, or plant-based protein. After 4 weeks, eating the daily equivalent of 8 ounces of steak or two quarter-pound beef patties nearly tripled plasma TMAO levels ($P$ less than .05) from baseline. The white meat and vegetarian diets showed no such effect.

Crucially, the effect of red meat was reversible – TMAO levels fell significantly within 4 weeks after participants stopped consuming red meat. Eating red meat low in saturated fat did not prevent TMAO levels from rising, Dr. Hazen noted at the meeting sponsored by the American Gastroenterological Association and the European Society for Neurogastroenterology and Motility.

In a second study, Dr. Hazen and his associates identified a two-step process by which gut bacteria metabolize carnitine to TMAO. The second step was greatly enhanced in individuals who eat red meat, suggesting a possible therapeutic target. In a third study, they found that high TMAO levels in mice fell significantly with a single oral dose of a second-generation inhibitor of trimethylamine lyase, the enzyme used by gut bacteria to convert choline to TMAO. The inhibitory effect was irreversible, did not reduce the viability of commensal microorganisms, and significantly lowered platelet hyperreactivity and clot formation.

Such results are exciting, but "drugs for bugs" will exhibit varying effects depending on which gut species are present at baseline, Dr. Hazen explained. Investigators will need to understand and account for these differences before therapies for the microbiome can enter the clinic. For now, a blood test for TMAO is available and can help clinicians tailor their suggestions on what to eat.

Dr. Hazen disclosed a consulting relationship with Procter & Gamble;royalties for patents from Procter & Gamble, Cleveland Heart Lab, and Quest Diagnostics; and research support from AstraZeneca, Pfizer, Roche Diagnostics, and Procter & Gamble.

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# POEM outcomes 'outstanding' in achalasia with long-term follow-up

**BY ANDREW D. BOWSER**
*MDEdge News*

PHILADELPHIA – The minimally invasive peroral endoscopic myotomy (POEM) approach has matured as a treatment for achalasia, with "outstanding" 2- to 5-year outcomes now reported, Stavros N. Stavropoulos, MD, AGAF, said at a meeting jointly provided by Rutgers and Global Academy for Medical Education.

"POEM represents a first-line treatment option for achalasia that has equivalent or superior efficacy to Heller [myotomy]," said Dr. Stavropoulos director of the program in advanced GI endoscopy at NYU Winthrop Hospital, Mineola, N.Y.

Although POEM is associated with more gastrointestinal reflux disease (GERD) than laparoscopic Heller myotomy, there is some evidence that the advantage of Heller in this respect may decrease over time, he told attendees.

"GERD after POEM is easily treatable with proton pump inhibitors (PPIs), with good patient satisfaction and no significant long-term GERD complications," Dr. Stavropoulos said in a presentation on minimally invasive approaches to esophageal disorders.

NYU Winthrop Hospital was the site of the first human POEM outside of Japan, performed in 2009 by Dr. Stavropoulos, who along with colleagues recently published what he said is the largest single-operator POEM series in the Western hemisphere.

That report in Gastrointestinal Endoscopy (2018 Apr;87[4]:972-85) was based on 318 consecutive POEMs performed through October 2016. Dr. Stavropoulos and colleagues reported that over a median follow-up of 28 months they had a 95.7% clinical success rate, defined as a Eckardt score of 3 or more and no further treatment needed.

**'The absolute difference in GERD rates between laparoscopic Heller myotomy and POEM is 20%-25% at 1 year, but may decrease with time, and may be associated with inferior dysphagia relief in LHM patients.'**

Those results suggested POEM should be a "treatment of choice" for challenging cases managed at centers who have a high level of experience with the procedure, the investigators said at the time.

Dr. Stavropoulos presented his center's updated experience including 515 patients undergoing POEM, with a median follow-up of 37 months. About 50% of the patients were previously treated, including 73 (14% who underwent Heller myotomy).

Mean Eckardt scores were 7.7 preprocedure and 0.5 post procedure, while on timed barium swallow, emptying of 50% or greater at 5 minutes was seen in 96% of patients, and 100% emptying at 5 minutes was seen in 68%, according to data Dr. Stavropoulos presented.

Andrew Bowser/MDedge News

Dr. Stavros N. Stavropolous, director of the program in advanced GI endoscopy at NYU Winthrop Hospital, recently published a large single-operator POEM series.

Disease-free probability was 99% at 1 year and 90% at 5 years, he added.

There were no deaths, leaks, aborted procedures, or need for drains in this series, according to the investigator. Three percent of patients had a hospitalization exceeding 5 days, while 1% were readmitted because of minor adverse events related to POEM, such as dehydration, Dr. Stavropoulos reported.

In 2017, the American Gastroenterological Association published a clinical practice update "legitimizing" POEM as a first-line achalasia treatment, Dr. Stavropoulos said. That update said POEM should be performed in high-volume centers by experienced physicians.

Patients who experience GERD after POEM can be effectively treated with standard, once-daily PPI therapy, according to the expert.

"The absolute difference in GERD rates between laparoscopic Heller myotomy and POEM is 20%-25% at 1 year, but may decrease with time, and may be associated with inferior dysphagia relief in LHM patients," Dr. Stavropoulos told attendees.

Dr. Stavropoulos disclosed that he is a consultant for Boston Scientific and ERBE.

Global Academy and this news organization are owned by the same company.

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*Continued from previous page*

hypothesized that hyperglycemia itself drove susceptibility to enteric infections. They confirmed this by administering insulin to the mice with type 1 diabetes, which restored intestinal epithelial adherence junctions and stopped the systemic spread of pathogens. In vitro, exposing intestinal epithelial cells to glucose-induced barrier dysfunctions that increased over time and with higher glucose concentrations. RNA sequencing demonstrated that hyperglycemia markedly changed expression of genes that encode proteins that regulate intestinal barrier function. Moreover, hyperglycemic mice lacking the bidirectional glucose transporter GLUT2 showed no intestinal barrier dysfunction and were not susceptible to *C. rodentium* infection and systemic spread.

Finally, the investigators studied more than 30 clinical measures and microbial products in the systemic circulation of 27 healthy human volunteers. "Of all the variables we measured, $HbA_{1c}$ showed the strongest correlation with the influx of microbial molecules," said Dr. Thaiss. Serum $HbA_{1c}$ correlated highly ($P$ = .008) with levels of toll-like receptor 4, an indicator of systemic pathogens, but not with body mass index ($P$ = .76).

The findings in humans confirm those in mice and indicate that hyperglycemia is a direct cause of intestinal barrier dysfunction and susceptibility to enteric infection, Dr. Thaiss said, adding that the systemic influx of microbial products might explain the wide range of otherwise unrelated inflammatory conditions seen in patients with metabolic syndrome. Future studies of therapies for enteric infection and systemic inflammation might focus on glucose as a modifier of intestinal barrier function.

These findings, reported at the meeting sponsored by the American Gastroenterological Association and the European Society for Neurogastroenterology and Motility, were also published in Science.

The work was supported by a Boehringer Ingelheim Funds PhD fellowship, the Leona M. and Harry B. Helmsley Charitable Trust, the Adelis Foundation, the Gurwin Family Fund for Scientific Research, the Crown Endowment Fund for Immunological Research, and others. Dr. Thaiss and his coinvestigators reported having no conflicts of interest.

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**SOURCE:** 2019 Gut Microbiota for Health World Summit; Thaiss C et al. Science. 2018;359(6382):1376-83.

# An HCV-infected population showed gaps in HBV testing, vaccination, and care

**BY MARK S. LESNEY**
*MDedge News*

Assessment of a large cohort of hepatitis C virus (HCV)–infected patients revealed a high prevalence of current or past hepatitis B virus infection. However, within this cohort, there were notable gaps in HBV testing, directed care, and vaccination, according to Aaron M. Harris, MD, of the Centers for Disease Control and Prevention.

Dr. Harris and his colleagues abstracted patient-level data from the Grady Health System EHR in August 2016 to create an HCV patient registry. They found that, among 4,224 HCV-infected patients, 3,629 (86%) had test results for the hepatitis B surface antigen (HBsAg), with 43 (1.2%) being HBsAg positive.

"Our results identified a gap in care as a minority of HBsAg-positive patients with HCV coinfection received HBV DNA and/or e-antigen [HBeAg] testing," the researchers stated.

Overall, only 2,342 (55.4%) patients had test results for all three HBV serologic markers. Among these, 789 (33.7%) were anti-HBc positive only, 678 (28.9%) were anti-HBc/anti-HBs positive, 190 (8.1%) were anti-HBs positive only, and 642 (27.4%) were HBV susceptible.

In addition, only 50% of the HBV-susceptible patients received at least one dose of hepatitis B vaccine, according to the report published in Vaccine.

"Strategies are needed to increase hepatitis B testing, linkage to hepatitis B–directed care of HBV/HCV-coinfected patients, and to increase uptake in hepatitis B vaccination for HCV-infected patients within the Grady Health System," the researchers concluded.

The study was funded by the CDC and the authors reported that they had no relevant financial conflicts.

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**SOURCE:** Harris AM et al. Vaccine. 2019;37:2188-93.

# Novel microbiome signature may detect NAFLD-cirrhosis

**BY CALEB RANS**
*MDedge News*

A novel fecal microbiome–derived signature could be a useful biomarker to help identify cirrhosis in patients with nonalcoholic fatty liver disease (NAFLD), according to results from a study published in Nature Communications.

"Limited data exist concerning the diagnostic accuracy of gut microbiome–derived signatures for detecting NAFLD-cirrhosis," wrote Cyrielle Caussy, MD, PhD, of the University of California, San Diego, along with her colleagues.

The researchers conducted a cross-sectional analysis of 203 patients with NAFLD. Data were collected from a twin and family cohort with a total of 98 probands that included the complete spectrum of the disease. In addition, 105 first-degree relatives of the probands were also included.

The team analyzed stool samples of participants using MRI and assessed whether the novel signature could accurately identify cirrhosis in NAFLD.

After analysis, the researchers found that, in a specific cohort of probands, the microbial biomarker showed strong diagnostic accuracy for identifying cirrhosis in patients with NAFLD (area under the ROC curve, 0.92). These findings were validated in another cohort of first-degree relatives of the proband group (AUROC, 0.87).

The authors acknowledged that a key limitation of the analysis was that it was only a single-center study. As a result, the widespread generalizability of the findings could be restricted.

**After analysis, the researchers found that, in a specific cohort of probands, the microbial biomarker showed strong diagnostic accuracy for identifying cirrhosis in patients with NAFLD.**

"This conveniently assessed microbial biomarker could present an adjunct tool to current invasive approaches to determine stage of liver disease," they concluded.

The study was supported by funding from the National Institutes of Health and Janssen. The authors reported financial affiliations with the American Gastroenterological Association, Atlantic Philanthropies, the John A. Hartford Foundation, and the Association of Specialty Professors.

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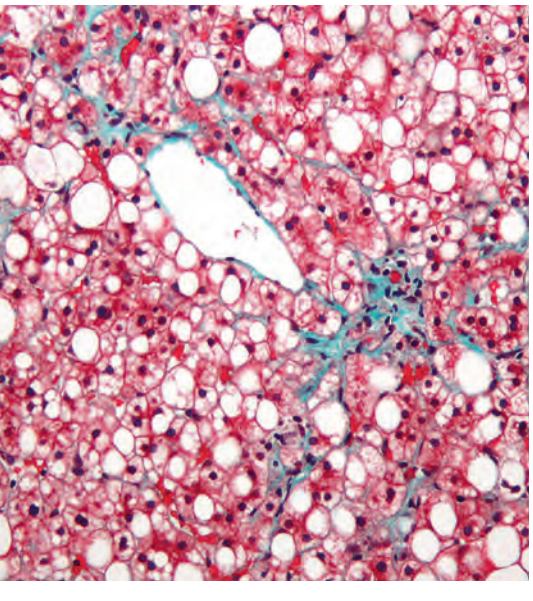
**SOURCE:** Caussy C et al. Nat Commun. 2019 Mar 29. doi: 10.1038/s41467-019-09455-9.



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# OCA reversed NASH liver fibrosis in phase 3 trial

**BY MITCHEL L. ZOLER**
*MDedge News*

VIENNA – Daily treatment of patients with nonalcoholic steatohepatitis with obeticholic acid led to a near doubling of patients who had fibrosis regression in a phase 3 trial with 931 patients, making obeticholic acid the first agent proven to improve the course of this disease.

"There is no doubt that with these data we have changed the treatment" of nonalcoholic steatohepatitis (NASH), Zobair M. Younossi, MD, of Inova Fairfax Medical Campus in Falls Church, Va., said at the International Liver Congress, sponsored by the European Association for the Study of the Liver. "We are at a watershed moment" in NASH treatment, Dr. Younossi added in a video interview.

Until now "we have had no effective treatments for NASH. This is the first success in a phase 3 trial; obeticholic acid looks very promising," commented Philip N. Newsome, PhD, professor of experimental hepatology at the University of Birmingham (England).

Obeticholic acid (OCA), an agonist of the farnesoid X receptor, already has Food and Drug Administration marketing approval for the indication of primary biliary cholangitis, a much rarer disease than NASH.

The REGENERATE (Randomized Global Phase 3 Study to Evaluate the Impact on NASH With Fibrosis of Obeticholic Acid Treatment) trial has so far enrolled 931 patients at about 350 sites in 20 countries, including the United States, and followed them during 18 months of treatment, the prespecified time for an interim analysis. The study enrolled adults with biopsy-proven NASH and generally focused on patients with either stage 2 or 3 liver fibrosis and a nonalcoholic fatty liver disease activity score of at least 4. Enrolled patients averaged about 55 years old, slightly more than half the enrolled patients had type 2 diabetes, and more than half had stage 3 fibrosis.


DR. NEWSOME


DR. YOUNOSSI

The study design included two coprimary endpoints, and specified that a statistically significant finding for either outcome meant a positive trial result, but the design also prespecified that the benefit would need to meet a stringent definition of statistical significance, compared with placebo patients, with a *P* value of no more than .01. REGENERATE tested two different OCA dosages, 10 mg or 25 mg, once daily. The results showed a trend for benefit from the smaller dosage, but these effects did not achieve statistical significance.

For the primary endpoint of regression of liver fibrosis by at least one stage with no worsening of NASH the intention-to-treat analysis showed after 18 months a 13% rate with placebo, a 21% rate with the 10-mg dosage, and a 23% rate with the 25-mg dosage, a statistically significant improvement over placebo for the higher dosage.

The second primary endpoint was resolution of NASH without worsening liver fibrosis, which occurred in 8% of placebo patients, 11% of patients on 10 mg OCA/day and 12% of those on 25 mg/day. The differences between each of the active groups and the controls were not statistically significant for this endpoint.

Among the 931 enrolled patients 668 (72%) actually received treatment fully consistent with the study protocol, and among these per-protocol patients the benefit from 25 mg/day OCA was even more striking: a 28% rate of fibrosis regression, compared with 13% in the control patients. Regression by at least two fibrotic stages occurred in 5% of placebo patients and 13% of those on 25 mg/day OCA. Many treated patients also showed normalizations of liver enzyme levels.

Adverse events on OCA were mostly mild or moderate, with similar rates of serious adverse events in the OCA groups and in control patients. The most common adverse effect on OCA treatment was pruritus, a previously described effect, reported by 51% of patients on the 25 mg/day dosage and by 19% of control patients.

REGENERATE will continue until a goal level of endpoint events occur, and may eventually enroll as many as 2,400 patients and extend for a few more years. By then, Dr. Younossi said, he hopes that an analysis will be possible of "harder" endpoints than fibrosis, such as development of cirrhosis. He noted, however, that the FDA has designated fibrosis regression as a valid surrogate endpoint for assessing treatment efficacy for NASH.

Already on the U.S. market, a single 10-mg OCA pill currently retails for almost $230; a 25-mg formulation is not currently marketed. Dr. Younossi said that subsequent studies will assess the cost-effectiveness of OCA treatment for NASH. He also hopes that further study of patient characteristics will identify which NASH patients are most likely to respond to OCA. Eventually, OCA may be part of a multidrug strategy for treating this disease, Dr. Younossi said.

REGENERATE was sponsored by Intercept, the company that markets OCA (Ocaliva). Dr. Younossi is a consultant to and has received research funding from Intercept. He has also been a consultant to Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Novartis, Novo Nordisk, Quest, Siemens, Terns Pharmaceutical, and Viking Therapeutics. Dr. Newsome has been a consultant or speaker for Intercept as well as Boehringer Ingelheim, Dignity Sciences, Johnson & Johnson, Novo Nordisk, and Shire, and he has received research funding from Pharmaxis and Boehringer Ingelheim.

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# Research coalition issues plan for curing hepatitis B virus

**BY MITCHEL L. ZOLER**
*MDedge News*

VIENNA – An international coalition of hepatitis B virus researchers, patients, and health organizations have released a comprehensive plan for developing a cure for this infection. They hope either to have a cure or to have made substantial progress toward this goal over the next 10 years.

Treatments already are on the market that effectively inhibit hepatitis B replication in infected patients (and an effective preventive vaccine also exists). Still, these treatments are not curative, and for the vast majority of patients treatment must continue indefinitely, while their risk for liver cancer and their virally induced immune system abnormalities remain, Peter A. Revill, PhD, said during a press briefing that introduced a strategy for HBV cure development from the International Coalition to Eliminate HBV. Concurrently with the briefing session, the strategy appeared in an article published online (Lancet Gastroenterol Hepatol. 2019 Apr 10. doi: 10.1016/s2468-1253[19]30119-0).

The way forward will likely be a "two-pronged approach or restoring immune responses and targeting the virus," Dr. Revill, head of molecular virology at the Doherty Institute in Melbourne, said in a video interview.

The new strategy recognizes the huge challenge of devising a treatment that produces a total cure that includes elimination of all traces of viral DNA from patients and for the immediate future focuses on the goal of functional cure. The term functional cure means a sustained period without detectable HBV surface antigen or HBV DNA in a patient's serum, as well as suppressed virus release. Another feature of a functional cure would be a halt to progression of liver disease, replaced by liver regeneration, said Anna S. Lok, MD, AGAF, professor of medicine and director of clinical hepatology at the University of Michigan, Ann Arbor, and a member of the strategy-writing group. She and her colleagues foresee the need for drug combinations with agents that can hit multiple viral targets as well as agents that restore normal immune function.

Several novel drug classes aimed at new viral targets, such as capsid inhibitors, are in clinical development, said Fabien Zoulim, MD, head of the gastroenterology and hepatology service at the Red Cross Hospital in Lyon, France, and another member of the writing panel. "We have many drug candidates" that use novel approaches to further restrict viral growth, roughly 50 agents in phase 1 and 2 studies, he said during the press briefing, held during the ILC, sponsored by the European Association for the Study of the Liver. The other, immunologic aspect of the two-part cure strategy – restoring the "exhausted" HBV-specific T-cell population and stimulating production of neutralizing antibody to HBV – remains hypothetical right now, however.

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# Bariatric surgery may be appropriate for class 1 obesity

**BY RANDY DOTINGA**
*MDedge News*

LAS VEGAS – Once reserved for the most obese patients, bariatric surgery is on the road to becoming an option for millions of Americans who are just a step beyond overweight, even those with a body mass index as low as 30 kg/m$^2$.

In regard to patients with lower levels of obesity, "we should be intervening in this chronic disease earlier rather than later," said Stacy A. Brethauer, MD, professor of surgery at the Ohio State University, Columbus, in a presentation about new standards for bariatric surgery at the 2019 Annual Minimally Invasive Surgery Symposium by Global Academy for Medical Education.

Bariatric treatment "should be offered after nonsurgical [weight-loss] therapy has failed," he said.

As Dr. Brethauer noted, research suggests that all categories of obesity – including so-called class 1 obesity (defined as a BMI from 30.0 to 34.9 kg/m$^2$) – boost the risk of multiple diseases, including hypertension, coronary artery disease, congestive heart failure, stroke, asthma, pulmonary embolism, gallbladder disease, several types of cancer, osteoarthritis, and chronic back pain.

"Ultimately, you can conclude from all this evidence that class 1 is a chronic disease, and it deserves to be treated effectively," he said.

There are, of course, various nonsurgical treatments for obesity, including diet and exercise and pharmacotherapy. However, systematic reviews have found that people find it extremely difficult to keep the weight off after 1 year regardless of the strategy they adopt.

Beyond a year, Dr. Brethauer said, "you get poor maintenance of weight control, and you get poor control of metabolic burden. You don't have a durable efficacy."

In the past, bariatric surgery wasn't considered an option for patients with class 1 obesity. It's traditionally been reserved for patients with BMIs at or above 35 kg/m$^2$. But this standard has evolved in recent years.

In 2018, Dr. Brethauer coauthored an updated position statement by the American Society for Metabolic and Bariatric Surgery that encouraged bariatric surgery in certain mildly obese patients.

"For most people with class 1 obesity," the statement on bariatric surgery says, "it is clear that the nonsurgical group of therapies will not provide a durable solution to their disease of obesity."

The statement went on to explain that "surgical intervention should be considered after failure of nonsurgical treatments" in the class 1 population.

Bariatric surgery in the class 1 population does more than reduce obesity, Dr. Brethauer said. "Over the last 5 years or so, a large body of literature has emerged," he said, and both systematic reviews and randomized trails have shown significant postsurgery improvements in comorbidities such as diabetes.

"It's important to emphasize that these patients don't become underweight," he said.

Are weight-loss operations safe in class 1 patients? The American Society for Metabolic and Bariatric Surgery statement says that research has found "bariatric surgery is associated with modest morbidity and very low mortality in patients with class 1 obesity."

In fact, Dr. Brethauer said, the mortality rate in this population is "less than gallbladder surgery, less than hip surgery, less than hysterectomy ... – operations people are being referred for and undergoing all the time."

He added: "The case can be made very clearly based on this data that these operations are safe in this patient population. Not only are they safe, they have durable and significant impact on comorbidities."

Global Academy for Medical Education and this news organization are owned by the same parent company. Dr. Brethauer discloses relationships with Medtronic (speaker) and GI Windows (consultant).

**AGA Resource**

Review the AGA Practice guide on Obesity and Weight management, Education and Resources (POWER) white paper, which provides physicians with a comprehensive, multidisciplinary process to guide and personalize innovative obesity care for safe and effective weight management. Learn more at http://ow.ly/WV8l30oeyYv.

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## CLINICAL CHALLENGES AND IMAGES

# The diagnosis

**Answer to "What is your diagnosis?" on page 17: Nonsteroidal anti-inflammatory drug–induced diaphragm disease**

Nonsteroidal anti-inflammatory drug (NSAID)–induced diaphragm disease is a rare cause of colonic stricture. To date, only about 50 cases have been reported. Diaphragm-like strictures occur predominantly in the right colon. The most common clinical presentations are obstructive symptoms and gastrointestinal bleeding after taking traditional NSAIDs or cyclo-oxygenase-2 inhibitors for more than 1 year.[1] The thin diaphragm strictures are difficult to detect on imaging studies. They are seen during endoscopy or surgery. Concentric strictures in the right colon in the setting of chronic NSAID use are almost diagnostic of colonic diaphragm disease.[2] Histopathology demonstrates submucosal fibrosis on resection specimens. Endoscopic biopsies may show lamina propria fibrosis, increased eosinophils with relative paucity of neutrophils, and even crypt distortion. The mechanism is thought to be due to contraction of scar tissue from healing concentric ulceration resulting in diaphragm-like strictures. Discontinuation of NSAIDs is recommended. Surgery is required to relieve obstruction in 75% of reported cases. Some have reported success with endoscopic balloon dilation.[3]

Using a 15-mm balloon, we performed endoscopic through-the-scope balloon dilation under fluoroscopy (Figures D, E). After dilation, the colonoscopy was completed to the distal ileum. There were two additional proximal concentric colonic strictures that allowed passage of the colonoscope and did not require dilation (Figure F). The patient was advised to stop diclofenac. He had no further gastrointestinal symptoms at the 3-month follow-up visit.

**References**

1. Wang Y-Z et al. Gastroenterol Res Pract. 2016;2016:3679741.
2. Püspök A et al. Dis Colon Rectum. 2000;43:685-91.
3. Smith JA et al. Gastrointest Endosc. 2000;52:120-5.

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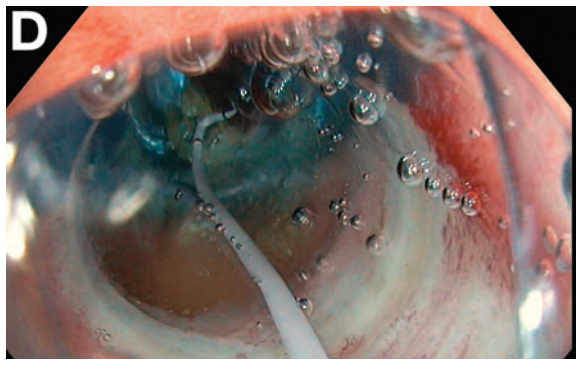


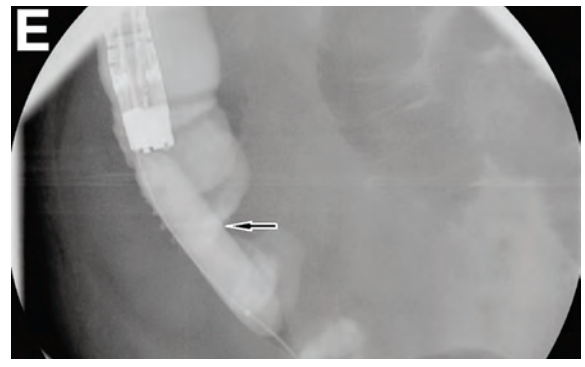


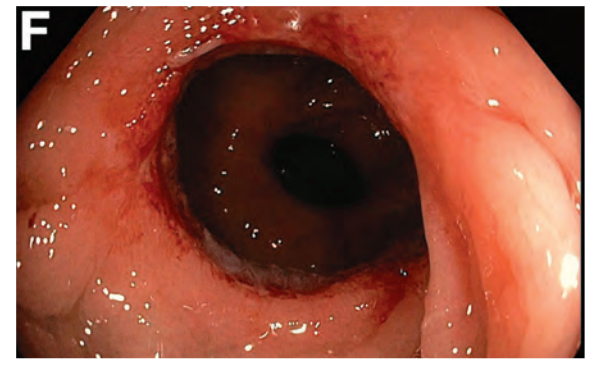

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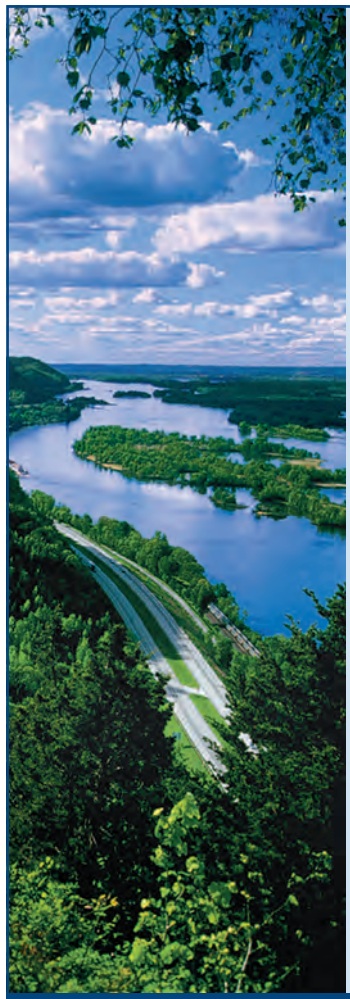

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# Preclinical findings highlight value of Lynch syndrome for cancer vaccine development

**BY SHARON WORCESTER**
*MDedge News*

ATLANTA – Lynch syndrome serves as an excellent platform for the development of immunoprevention cancer vaccines, and findings from a preclinical Lynch syndrome mouse model support ongoing research, according to Steven M. Lipkin, MD, PhD.

A novel vaccine, which included peptides encoding four intestinal cancer frameshift peptide (FSP) neoantigens derived from coding microsatellite (cMS) mutations in the genes Nacad, Maz, Xirp1, and Senp6 elicited strong antigen-specific cellular immune responses in the model, Dr. Lipkin, the Gladys and Roland Harriman Professor of Medicine and vice chair for research in the Sanford and Joan Weill Department of Medicine, Weill Cornell Medical College, New York, reported at the annual meeting of the American Association for Cancer Research.

CD4-specific T cell responses were detected for Maz, Nacad, and Senp6, and CD8-positive T cells were detected for Xirp1 and Nacad, he noted, explaining that the findings come in the wake of a recently completed clinical phase 1/2a trial that successfully demonstrated safety and immunogenicity of an FSP neoantigen-based vaccine in microsatellite unstable (MSI) colorectal cancer patients.

The current effort to further develop a cancer preventive vaccine against MSI cancers in Lynch syndrome using a preclinical mouse model involved a systematic database search to identify cMS sequences in the murine genome. Intestinal tumors obtained from Lynch syndrome mice were evaluated for mutations affecting these candidate cMS, and of 13 with a mutation frequency of 15% or higher, the 4 FSP neoantigens ultimately included in the vaccine elicited strong antigen-specific cellular immune responses.

Vaccination with peptides encoding these four intestinal cancer FSP neoantigens promoted antineoantigen immunity, reduced intestinal tumorigenicity, and prolonged overall survival, Dr. Lipkin said.

Further, based on preclinical data suggesting that naproxen in this setting might provide better risk-reducing effects, compared with aspirin (which has previously been shown to reduce colorectal cancer risk in Lynch syndrome patients), its addition to the vaccine did, indeed, improve response, he noted, explaining that naproxen worked as "sort of a super-aspirin," that improved overall survival, compared with vaccine alone or nonsteroidal anti-inflammatory agents alone.

In a video interview, Dr. Lipkin describes his research and its potential implications for the immunoprevention of Lynch syndrome and other cancers.

Vaccination with as few as four mutations that occur across Lynch syndrome tumors induced complete cures in some mice and delays in disease onset in others, he said.

"[This is] a very simple approach, very effective," he added, noting that the T cells are now being studied to better understand the biology of the effects. "The idea of immunoprevention ... is actually very exciting and ... can be expanded beyond this."

Lynch syndrome is a "great place to start," because of the high rate of mutations, which are the most immunogenic types of mutations, he said.

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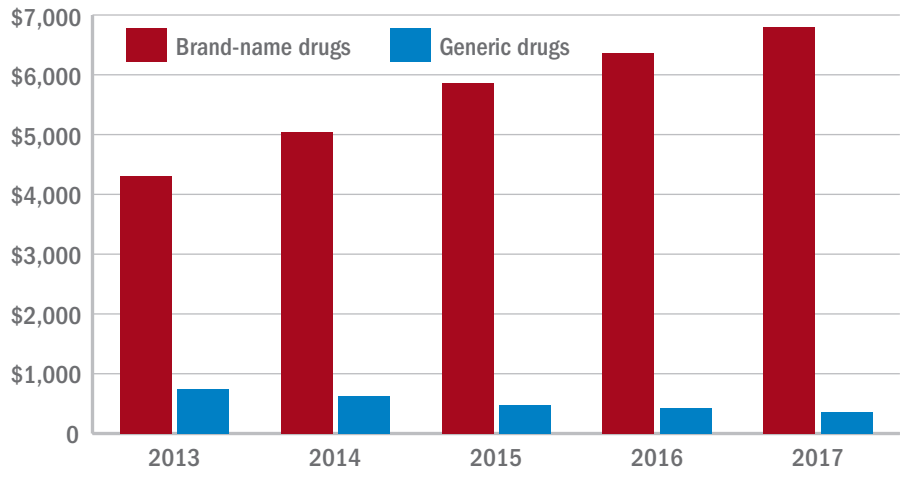
# Cost gap widens between brand-name, generic drugs

BY RICHARD FRANKI
*MDedge News*

The average cost of a brand-name drug was 18.6 times higher than its generic equivalent in 2017, and the size of that gap has more than tripled since 2013, according to a report from the AARP Public Policy Institute.

In 2017, the average retail cost of 260 generic drugs widely used by older adults for chronic conditions was $365 for a year of therapy, compared with $6,798 for brand-name drugs. In 2013, that same year of therapy with an average brand-name drug ($4,308) was only 5.7 times more expensive than the generic ($751), the AARP wrote in the report, produced in collaboration with the PRIME Institute at the University of Minnesota, Minneapolis.

**Average annual cost of therapy: Generics vs. brand-name drugs**




**Note:** Based on a market basket of 260 drugs widely used by older adults for chronic conditions
**Source:** AARP Public Policy Institute and the PRIME Institute, University of Minnesota

"Generics account for nearly 9 out of every 10 prescriptions filled in the U.S. but represent less than a quarter of the country's drug spending. These results highlight the importance of eliminating anticompetitive behavior by brand-name drug companies so that we get more lower-priced generic drugs on the market," Debra Whitman, executive vice president and chief public policy officer at AARP, said in a written statement.

The average retail cost of a larger group of 390 generic drugs used by older adults fell by 9.3% from 2016 to 2017, compared with an increase of 8.4% for a group of 267 brand-name prescription drugs. Over that same time, the general inflation rate rose by 2.1%, the AARP noted.

The AARP's annual Rx Price Watch Report is based on data from the Truven Health MarketScan research databases.

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## PRACTICE MANAGEMENT TOOLBOX:

# Coding and payment changes could hit GIs in 2021

BY BRADEN KUO, MD, AND SHIVAN MEHTA, MD, MBA, MSHP

Welcome to the new Practice Management Toolbox.

The AGA Practice Management and Economics Committee (PMEC) is pleased to host an updated Practice Management Toolbox column featuring contemporary GI practice management issues and news. As chair of the PMEC, I am excited to bring you this content on behalf of my colleagues on the committee. Each month we will highlight a timely topic relevant to gastroenterologists in practice. The AGA and PMEC strive to be at the forefront of changes to the field of gastroenterology, providing you with tools and resources to succeed. If there is an article topic you would like to suggest, please reach out to Jacob Manthey, Practice and Quality Manager at jmanthey@gastro.org.

***Anton Decker, MD, AGAF***
***Chair, AGA Practice Management and Economics Committee***

Last year, Medicare began laying groundwork for major changes to coding and payment for common evaluation and management (E/M) services and two high-volume GI endoscopy procedures beginning Jan. 1, 2021, with expected adoption by commercial payers. Learn about these potential changes now to help prepare your practice for the financial impact.

### 2021 E/M Changes: New guidelines, new payments

The Centers for Medicare & Medicaid Services (CMS), announced in its 2019 Physician Fee Schedule proposed rule that it wanted to reduce administrative burden and improve payment accuracy for office/outpatient new and established patient codes (99201-99205 and 99211-99215) by paying level 2-5 codes at a single payment rate and simplifying documentation to support only a level 2 E/M visit, except when using time for documentation (Table).

**Proposed payment for office/outpatient-based E/M visits**

| Level | Current payment* (established patient) | Proposed payment** | Level | Current payment* (new patient) | Proposed payment** |
|---|---|---|---|---|---|
| 1 | $22 | $24 | 1 | $45 | $44 |
| 2 | $45 | $93 | 2 | $76 | $135 |
| 3 | $74 | | 3 | $110 | |
| 4 | $109 | | 4 | $167 | |
| 5 | $148 | | 5 | $211 | |

MDedge News

* Then-current payment for CY2018

** Proposed payment based on the CY2019 proposed rule relative value units and the CY2018 payment rate

**Source:** Centers for Medicare & Medicaid Services

In the original proposal, those who reported mostly level 2 and 3 E/M visits would have experienced modest payment increases while those who reported mostly level 4 and 5 E/M visits would have endured payment cuts between 20% and 40%. Ultimately, the physician community, including AGA and its sister societies, opposed the proposed payment consolidation and pressured CMS not to finalize most of its proposed changes and preserve the current payment rates. The 2019 MPFS final rule made no changes to the relative values for office/outpatient new and established patient codes 99201-99205 and 99211-99215, but did outline a new plan "for paying a single rate for E/M office/outpatient visit levels 2 through 4 for established and new patients while maintaining the payment rate for E/M office/outpatient visit level 5 in order to better account for the care and needs of complex patients." CMS agreed to continue to accept input on improvements to the proposal before CMS' planned implementation in 2021.

A proposal to simplify E/M guidelines within Current Procedural Terminology (CPT) and preserve the individual levels of the new and established patient office/outpatient E/M codes, except 99201 which was proposed for deletion, was presented to the American Medical Association (AMA) CPT Editorial Panel, the body responsible for creating and maintaining CPT codes, and approved at its February 2019 meeting. The approved changes will not be publicly available until the CPT 2021 book is released in August 2020. In the meantime, the AMA Specialty Society Relative-value scale Update Committee (RUC) will make recommendations to CMS on potential new relative values for the E/M codes.

It is unclear whether CMS will accept the AMA CPT Editorial Panel's changes and potential new

*Continued on following page*

*Continued from previous page*

values or move forward with the plan for three levels of E/M for office/outpatient new and established patient codes. However, any changes to the current guidelines will undoubtedly involve a learning curve for both physicians and coders and it is unclear whether approximately 4 months from the time the 2021 CPT book is released and the time the new rates will be implemented on Jan. 1, 2021, is enough to master the changes and update internal systems. In addition, any changes to reimbursement will impact each practice's bottom line.

### 2021 potential payment changes for CPT codes 43239 and 45385

In the same proposed rule, CMS announced that an unnamed party had nominated 7 CPT codes, including esophagogastroduodenoscopy (EGD) with biopsy (CPT code 43239) and colonoscopy with snare polypectomy (CPT code 45385), as potentially overvalued and recommended reducing their reimbursement based on data from the 2017 Urban Institute report for CMS. The AGA and its sister societies pointed out to CMS major flaws in the Urban Institute study's methods that should have prevented its use as evidence that the codes were misvalued and we provided data from the GI societies' robust sample of physicians to support the current values.

In the 2019 MPFS final rule, CMS revealed Anthem, a major U.S. health insurance company, as the nominating party sparking concern that this unprecedented development may result in other payers using the flawed Urban Institute study to influence CMS to revalue other services.

Codes CMS identified as potentially misvalued in the 2019 MPFS final rule were referred to the RUC for resurvey of physician work and practice expense for consideration at the April 2019 RUC meeting. The AGA and its sister societies conducted a survey of a random sample of our memberships during February and March and presented our recommendations based on the data we collected. CMS's proposed values will be published in July 2020 in the 2021 MPFS proposed rule and finalized in the final rule that November.

### Next steps

CMS will announce changes to E/M coding and documentation guidelines and any new payment changes to CPT codes 43239 and 45385 in the 2021 MPFS proposed rule in July 2020. Be prepared to use this information to model the financial impact to your practice so you can determine what, if any changes, should be made. Contact your coding and billing staff, consultants and software providers to find out how they plan to implement any changes. Additional E/M training may be required for your providers and staff. The GI Societies remain vigilant and continue to advocate on the behalf of its members to advise and shape these policy evaluations and changes.

*Dr. Kuo is assistant professor, director of the Center for Neurointestinal Health, GI Unit, Massachusetts General Hospital, Harvard Medical School, Boston; AGA CPT Advisor; he has no conflicts of interest. Dr. Mehta is assistant professor, Perelman School of Medicine; associate chief innovation officer, Penn Medicine, Philadelphia; AGA RUC Advisor; he has no conflicts of interest.*



## INDEX OF ADVERTISERS

DDSEP 9
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# Quick Quiz Answers

**Q1.** Correct answer: A

**Rationale**

This is an example of Yersinia infection. Transmission of yersiniosis is largely foodborne.

Risk factors associated with yersiniosis include consumption of undercooked or raw pork products and exposure to untreated water. *Y. enterocolitica* infection has also been associated with iron-overload states (such as hemochromatosis) and blood transfusions, because iron likely promotes virulence of this organism. The incubation period for yersiniosis is typically 4-6 days. Clinical manifestations of acute yersiniosis include diarrhea, abdominal pain, and fever; nausea and vomiting may also occur. Localization of abdominal pain to the right lower quadrant is also a diagnostic clue. However, both Yersinia and Campylobacter can present with right lower quadrant pain that may be confused as appendicitis. Another diagnostic clue is pharyngitis, which may be an accompanying symptom. Yersinia causes diarrhea through penetration of the mucosa and proliferation in the submucosa. Pathogenic *Y. enterocolitica* pass through the stomach, adhere to gut epithelial cells, invade the gut wall, localize in lymphoid tissue within the gut wall and in regional mesenteric lymph nodes, and evade the host's cell-mediated immune response. *Vibrio cholerae* and enterotoxigenic *E. coli* (ETEC) secrete enterotoxins that stimulate secretion and/or impair absorption.

Some bacteria produce toxins in contaminated food; when ingested, the toxins cause acute symptoms, usually nausea and vomiting. Enteropathogenic *E. coli* and enterohemorrhagic *E. coli* adhere to the intestinal mucosa, where they attach and cause effacement of the microvilli. Shigella, enteroinvasive *E. coli*, and *Campylobacter jejuni* penetrate the mucosa, spread, and cause mucosal damage with erosions and ulcers.

**Reference**

1. Cover TL, Aber RC. Yersinia enterocolitica. N Engl J Med. Jul 6 1989;321(1):16-24.

**Q2.** Correct answer: B

**Rationale**

The PRSS1 mutation has been shown to be the causative genetic factor in hereditary pancreatitis. Hereditary pancreatitis is an autosomal-dominant gene mutation with 80% penetrance. Symptoms start in childhood with acute recurrent pancreatitis and progress to chronic pancreatitis, diabetes, and exocrine insufficiency. The incidence of pancreatic cancer is increased to 40% by age 70. BRCA1 mutations have been associated with familial pancreas cancer families. SPINK mutations have been associated with chronic tropical pancreatitis. Delta F508 is the most common mutation in cystic fibrosis that leads to pancreas insufficiency in childhood. The clinical scenario is classic for hereditary pancreatitis.

**Reference**

1. Shelton CA, Umapathy C, Stello K, Yadav D, Whitcomb DC. Hereditary pancreatitis in the United States: Survival and rates of pancreatic cancer. Am J Gastroenterol. 2018 Sep;113(9):1376-84.

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**References: 1.** IQVIA. National Prescription Audit Report. September 2018. **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; 2017. **4.** Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc.* 2015;81(1):31-53.

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