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Courtesy Dr. Adam S. Faye

Dr. Adam S. Faye of Columbia University and coauthors found postdischarge thromboembolism was most likely within 60 days in IBD patients.

Older IBD patients are most at risk of postdischarge VTE

BY STEVE CIMINO
MDedge News

Hospitalized patients with inflammatory bowel diseases (IBD) are most likely to be readmitted for venous thromboembolism (VTE) within 60 days of discharge, according to a new study that analyzed 5 years of U.S. readmissions data.

"Given increased thrombotic risk postdischarge, as well as overall safety of VTE prophylaxis, extending prophylaxis for those at highest risk may have significant benefits," wrote Adam S. Faye, MD, of Columbia University, New York, and coauthors. The study was published in Clinical Gastroenterology and Hepatology.

To determine which IBD patients would be most in need of postdischarge VTE prophylaxis, as well as when to administer it, the researchers analyzed 2010-2014 data from the Nationwide Readmissions Database (NRD). They found a total of 872,122 index admissions for IBD patients; 4% of those patients had a prior VTE. Of the index

See **VTE** · *page 36*

Gene expression in Crohn's linked to treatment resistance

Associated with anti-TNF failure

BY BIANCA NOGRADY
MDedge News

Single-cell sequencing of tissues from patients with Crohn's disease has revealed a new pathogenic cellular module associated with failure of anti–tumor necrosis factor (TNF) therapy.

A paper published in the Aug. 29 online edition of Cell presented the results of a study that mapped the transcriptome – the RNA activity that reveals the patterns of gene expression for a cell – of lamina propria cells taken from biopsies of uninflamed and inflamed ileal tissues from 11 patients with ileal Crohn's disease.

Jérôme C. Martin, PharmD, PhD, from the Precision Immunology Institute at the Icahn School of Medicine at Mount Sinai, New York, and coauthors wrote that, while genomewide association studies, tissue analyses, and animal models have revealed much about the immune and inflammatory processes that contribute to inflammatory bowel disease, there still remain unanswered questions about why some patients don't respond to immune biotherapies.

"Current approaches restricted to well-estab-

See **Crohn's** · *page 36*

What is the future of celiac disease management?

BY ERIK GREB
MDedge News

CHICAGO – Several new drugs for the treatment of celiac disease are in development, and existing treatments for other indications are being studied as treatments for celiac disease as well, according to a lecture delivered at the James W. Freston Conference 2019: Food at the Intersection of Gut Health and Disease.

Home testing services and portable gluten-detection devices enable patients to diagnose and manage themselves with-

See **Celiac** · *page 37*

INSIDE

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LETTER FROM THE EDITOR:
Food as therapy and toxin

I return to write the Editor's comments after missing last month because I joined over 700,000 Americans who, this year, will undergo knee replacement surgery.

This month, we feature a couple articles from the 2019 James W. Freston Conference (an annual AGA event that highlights cutting-edge science). Jim was the 89th AGA President (1995) and this conference is a fitting legacy. This year's topic was "Food at the intersection of gut health and disease." As usual, the Freston Conference attracted international experts and interested clinicians who want to understand how current research will alter our clinical care in the near future.

Our front-page articles are fascinating. One highlights new advances in the management of celiac disease. Although the only current treatment that reverses intestinal immunological damage is adoption of a gluten-free diet, there is demand for alternative treatments including medical therapies targeting specific steps in the celiac damage pathway. While none are ready for widespread adoption, research will continue. Patient self-management with gluten-detection devices were also discussed.

Advances in the genetics of Crohn's disease are being published at an accelerating rate. This month we highlight an article about how gene expression analysis can predict response to a Crohn's flare. Evidence-based therapy for inflammatory bowel disease is complex, so clinicians need to stay current. Each year, the premier IBD educational venue is co-produced by the AGA and the Crohn's & Colitis Foundation. The 2020 Crohn's and Colitis Congress will be held in Austin, Tex. Jan. 23-25. Learn more at https://www.crohnscolitiscongress.org.


Dr. Allen

Finally, I want to highlight an article about the risk of venous thromboembolism (VTE) during and after an IBD flare. This risk is underappreciated by many treating physicians but it is real and can be life-threatening. Gastroenterologists must be knowledgeable about current guidelines for VTE in IBD patients (see Gastroenterology. 2014;146:835-48).

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

DDSEP 9
Digestive Diseases Self-Education Program

Quick quiz

Q1. A 73-year-old man with coronary artery disease requiring coronary artery bypass grafting and daily low-dose plain aspirin is hospitalized with acute anemia and melena. His aspirin is withheld, and he is placed empirically on intravenous proton pump inhibitors with continuous infusion. He undergoes upper endoscopy, which reveals a single 8-mm ulcer in the duodenal bulb with a visible vessel. After successful endoscopic therapy with epinephrine injection and the use of hemoclips, he remains stable. Prior to discharge, he is recommended to resume aspirin therapy.

Which intervention is most likely to reduce the risk of recurrent bleeding?

A. Switching to low-dose enteric coated aspirin
B. Maintenance on low-dose aspirin with the addition of daily PPI
C. Switching to low-dose buffered aspirin
D. Switching to low-dose plain aspirin

Q2. A 65-year-old man with chronic pancreatitis related to long-standing alcohol use comes to see you for a second opinion. He has been abstinent from alcohol for 20 years. He reports a 1-year history of six loose, oily stools per day, but minimal abdominal pain. He was recently found to have vitamin B_{12} deficiency by his primary care provider.

What is the likely mechanism for this patient's vitamin B_{12} deficiency?

A. Antibodies to intrinsic factor
B. Atrophy of gastric lining due to chronic alcohol use
C. Reduced breakdown of the R-protein by pancreatic proteases
D. Decreased absorption of vitamin B_{12} in the ileum due to chronic diarrhea
E. Loss of vitamin B_{12} in stool, due to steatorrhea

The answers are on page 32.

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Clip closure reduces postop bleeding risk after proximal polyp resection

BY WILL PASS
MDedge News

Closing mucosal defects with hemoclips after endoscopic resection of large polyps in the proximal colon may significantly reduce postoperative bleeding risk, according to investigators.

In a prospective study of almost 1,000 patients, this benefit was not influenced by polyp size, electrocautery setting, or concomitant use of antithrombotic medications, reported Heiko Pohl, MD, of Geisel School of Medicine at Dartmouth, Hanover, N.H., and colleagues.

"Endoscopic resection has replaced surgical resection as the primary treatment for large colon polyps due to a lower morbidity and less need for hospitalization," the investigators wrote in Gastroenterology. "Postprocedure bleeding is the most common severe complication, occurring in 2%-24% of patients." This risk is particularly common among patients with large polyps in the proximal colon.

Although previous trials have suggested that closing polyp resection sites with hemoclips could reduce the risk of postoperative bleeding, studies to date have been retrospective or uncontrolled, precluding definitive conclusions.

The prospective, controlled trial involved 44 endoscopists at 18 treatment centers. Enrollment included 919 patients with large, nonpedunculated colorectal polyps of at least 20 mm in diameter. Patients were randomized in an approximate 1:1 ratio into the clip group or control group and followed for at least 30 days after endoscopic polyp resection. The primary outcome was postoperative bleeding, defined as severe bleeding that required invasive intervention such as surgery or blood transfusion during follow-up. Subgroup analysis looked for associations between bleeding and polyp location, size, electrocautery setting, and medications.

Across the entire population, postoperative bleeding was significantly less common among patients who had their resection sites closed with clips, occurring at a rate of 3.5%, compared with 7.1% in the control group ($P = .015$). Serious adverse events were also less common in the clip group than the control group (4.8% vs. 9.5%; $P = .006$).

While the reduction of bleeding risk from clip closure was not influenced by polyp size, use of antithrombotic medications, or electrocautery setting, polyp location turned out to be a critical factor. The greatest reduction in risk of postoperative bleeding was seen among the 615 patients who had proximal polyps, based on a bleeding rate of 3.3% when clipped versus 9.6% among those who went without clips ($P = .001$). In contrast, clips in the distal colon were associated with a higher absolute risk of postoperative bleeding than no clips (4.0% vs. 1.4%); however, this difference was not statistically significant ($P = .178$).

"[T]his multicenter trial provides strong evidence that endoscopic clip closure of the mucosal defect after resection of large ... nonpedunculated colon polyps in the proximal colon significantly reduces the risk of postprocedure bleeding," the investigators wrote.

They suggested that their study provides greater confidence in findings than similar trials previously conducted, enough to recommend that endoscopic techniques be altered accordingly. "[O]ur trial was methodologically rigorous, adequately powered, and all polyps were removed by endoscopic mucosal resection, which is considered the standard technique for large colon polyps in Western countries," they wrote. "The results of the study are therefore broadly applicable to current practice. Furthermore, conduct of the study at different centers with multiple endoscopists strengthens generalizability of the findings."

The investigators also speculated about why postoperative bleeding risk was increased when clips were used in the distal colon. "Potential explanations include a poorer quality of clipping, a shorter clip retention time, possibly related to a thicker colon wall in the distal compared to the proximal colon," they wrote, adding that "these considerations are worthy of further study."

While the reduction of bleeding risk from clip closure was not influenced by polyp size, use of antithrombotic medications, or electrocautery setting, polyp location turned out to be a critical factor. The greatest reduction in risk of postoperative bleeding was seen among the 615 patients who had proximal polyps.

Indeed, more work remains to be done. "A formal cost-effectiveness analysis is needed to better understand the value of clip closure," they wrote. "Such analysis can then also examine possible thresholds, for instance regarding the minimum proportion of polyp resections, for which complete closure should be achieved, or the maximum number of clips to close a defect."

The study was funded by Boston Scientific. The investigators reported additional relationships with U.S. Endoscopy, Olympus, Medtronic, and others.

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SOURCE: Pohl H et al. Gastroenterology. 2019 Mar 15. doi: 10.1053/j.gastro.2019.03.019.

Pelvic floor muscle training outperforms attention-control massage for fecal incontinence

BY WILL PASS
MDedge News

For first-line treatment of patients with fecal incontinence, pelvic floor muscle training (PFMT) is superior to attention-control massage, according to investigators.

In a study involving 98 patients, those who combined PFMT with biofeedback and conservative therapy were five times as likely to report improved symptoms than those who used attention-control massage and conservative therapy, reported Anja Ussing, MD, of Copenhagen University Hospital in Hvidovre, Denmark, and colleagues. Patients in the PFMT group also had significantly greater reductions in severity of incontinence, based on Vaizey incontinence score.

At 16 weeks, the difference in self-reported symptoms was dramatic, with 74.5% of patients in the PFMT group reporting improvement, compared with 35.5% in the control group.

"Evidence from randomized controlled trials regarding the effect of PFMT for fecal incontinence is lacking," the investigators wrote in Clinical Gastroenterology and Hepatology. Although previous trials have evaluated PFMT, none controlled for the effect of interactions with care providers. "To evaluate the effect of PFMT, there is a need for a trial that uses a comparator to control for this nonspecific trial effect associated with the attention given by the health care professional."

To perform such a trial, the investigators recruited 98 patients with a history of fecal incontinence for at least 6 months. Patients were excluded if they had severe neurologic conditions, pregnancy, diarrhea, rectal prolapse,

Continued on page 8

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Continued from page 6

previous radiotherapy or cancer surgery in the lower abdomen, cognitive impairment, inadequate fluency in Danish, or a history of at least two PFMT training sessions within the past year. Enrolled patients were randomized in a 1:1 ratio to receive PFMT with biofeedback and conservative treatment, or attention-control massage training and conservative therapy. The primary outcome was symptom improvement, determined by the Patient Global Impression of Improvement scale at 16 weeks. Secondary outcome measures included the Fecal Incontinence

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Severity Index, Vaizey score, and Fecal Incontinence Quality of Life Scale.

Patients were predominantly female, with just three men in the PFMT group and six in the attention-control massage group. The PFMT group also had a slightly higher median age, at 65 years, compared with 58 years in the control group.

At 16 weeks, the difference in self-reported symptoms was dramatic, with 74.5% of patients in the PFMT group reporting improvement, compared with 35.5% in the control group, which translated to an unadjusted odds ratio of 5.16 (P = .0002). When symptom improvements were confined to those who reported being "very much better" or "much better," the disparity between groups still remained strong, with an unadjusted OR of 2.98 (P = .025). Among the three secondary outcomes, only the Vaizey score showed a significant difference between groups. Patients treated with PFMT had a mean difference in Vaizey score change of –1.83 points, using a scale from 0 to 24, with 24 representing complete incontinence (P = .04).

"We were not able to show any differences between groups in the number of fecal incontinence episodes," the investigators wrote. "We had much missing data in the bowel diaries and we can only guess what the result would have been if the data had been more complete. Electronic assessment of incontinence episodes could be a way to reduce the amount of missing data in future trials."

'Our results may be highly relevant in a primary setting because there is an unmet need for treatment of fecal incontinence in primary health care, and the interventions do not necessarily need to be conducted at specialized centers.'

Still, the investigators concluded that PFMT was the superior therapy. "Based on the results, PFMT in combination with conservative treatment should be offered as first-line treatment for adults with fecal incontinence."

They also highlighted the broad applicability of their findings, regardless of facility type.

"In the current trial, more than one-third of patients had sphincter injuries confirmed at endoanal ultrasound, this reflects the tertiary setting of our trial," they wrote. "However, our results may be highly relevant in a primary setting because there is an unmet need for treatment of fecal incontinence in primary health care, and the interventions do not necessarily need to be conducted at specialized centers."

The study was funded by the Danish Foundation for Research in Physiotherapy, The Lundbeck Foundation, the Research Foundation at Copenhagen University Hospital, and the Foundation of Aase and Ejnar Danielsen. The investigators reported additional relationships with Medtronic, Helsefonden, Gynzone, and others.

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SOURCE: Ussing A et al. Clin Gastroenterol Hepatol. 2018 Dec 20. doi: 10.1016/j.cgh.2018.12.015.

Type of renal dysfunction affects liver cirrhosis mortality risk

BY WILL PASS
MDedge News

For non–status 1 patients with cirrhosis who are awaiting liver transplantation, type of renal dysfunction may be a key determinant of mortality risk, based on a retrospective analysis of more than 22,000 patients.

Risk of death was greatest for patients with acute kidney injury on chronic kidney disease (AKI on CKD), followed by AKI alone, then CKD alone, reported lead author Giuseppe Cullaro, MD, of the University of California, San Francisco, and colleagues.

Although it is well known that renal dysfunction worsens outcomes among patients with liver cirrhosis, the impact of different types of kidney pathology on mortality risk has been minimally researched, the investigators wrote in Clinical Gastroenterology and Hepatology. "To date, studies evaluating the impact of renal dysfunction on prognosis in patients with cirrhosis have mostly focused on AKI."

To learn more, the investigators performed a retrospective study involving acute, chronic, and acute on chronic kidney disease among patients with cirrhosis. They included data from 22,680 non–status 1 adults who were awaiting liver transplantation between 2007 and 2014, with at least 90 days on the wait list. Information was gathered from the Organ Procurement and Transplantation Network registry.

AKI was defined by fewer than 72 days of hemodialysis, or an increase in creatinine of at least 0.3 mg/dL or at least 50% in the last 7 days. CKD was identified by more than 72 days of hemodialysis, or an estimated glomerular filtration rate less than 60 mL/min per 1.73 m^2 for 90 days with a final rate of at least 30 mL/min per 1.73 m^2. Using these criteria, the researchers put patients into four possible categories: AKI on CKD, AKI, CKD, or normal renal function. The primary outcome was wait-list mortality, which was defined as death, or removal from the wait list for illness. Follow-up started at the time of addition to the wait list and continued until transplant, removal from the wait list, or death.

Multivariate analysis, which accounted for final MELD-Na score and other confounders, showed that patients with AKI on CKD fared worst, with a 2.86-fold higher mortality risk (subhazard ratio, 2.86) than that of patients with normal renal function. The mortality risk for acute on chronic kidney disease was followed closely by patients with AKI alone (SHR, 2.42), and more distantly by patients with CKD alone (SHR, 1.56). Further analysis showed that the disparity between mortality risks of each subgroup became more pronounced with increased MELD-Na score. In addition, evaluation of receiver operating characteristic curves for 6-month wait-list mortality showed that the addition of renal function to MELD-Na score increased the accuracy of prognosis from an area under the curve of 0.71 to 0.80 (*P* less than .001).

"This suggests that incorporating the pattern of renal function could provide an opportunity to better prognosticate risk of mortality in the patients with cirrhosis who are the sickest," the investigators concluded. They also speculated about why outcomes may vary by type of kidney dysfunction.

"We suspect that those patients who experience AKI and AKI on CKD in our cohort likely had a triggering event – infection, bleeding, hypovolemia – that put these patients at greater risk for waitlist mortality," the investigators wrote. "These events inherently carry more risk than stable nonliver-related elevations in serum creatinine that are seen in patients with CKD. Because of this heterogeneity of etiology in renal dysfunction in patients with cirrhosis, it is perhaps not surprising that unique renal function patterns variably impact mortality."

The investigators noted that the findings from the study have "important implications for clinical practice," and suggested that including type of renal dysfunction would have the most significant effect on accuracy of prognoses among patients at greatest risk of mortality.

The study was funded by a Paul B. Beeson Career Development Award and the National Institute of Diabetes and Digestive and Kidney Diseases. One author disclosed relationships with Salix, Merck, and Gilead.

ginews@gastro.org

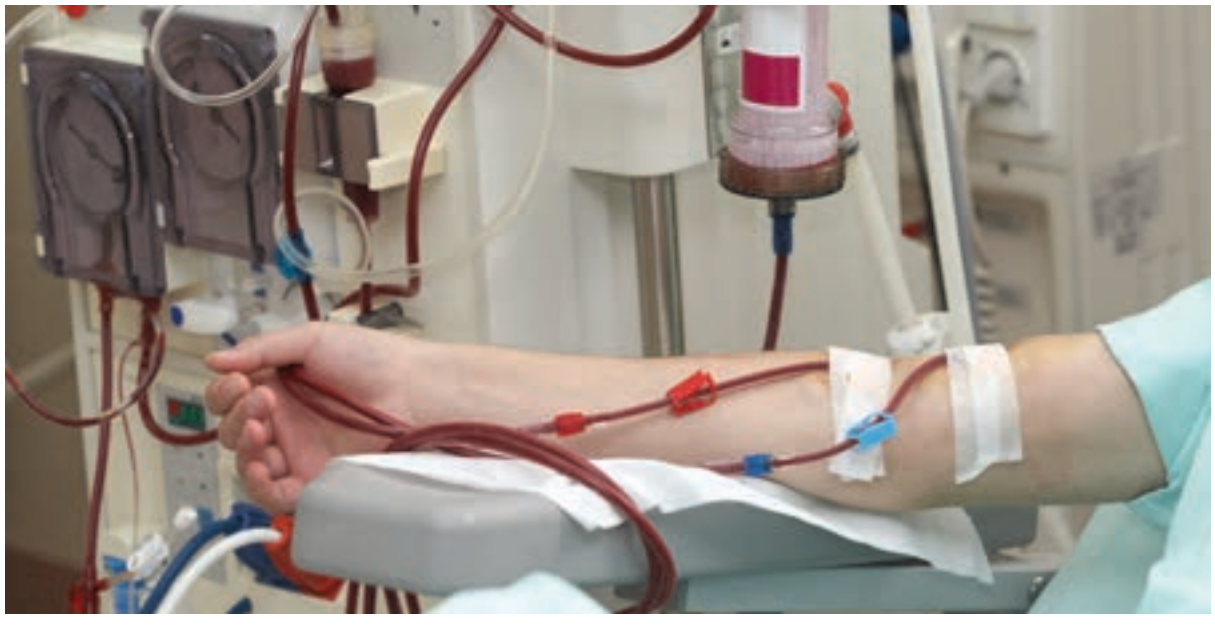
SOURCE: Cullaro G et al. Clin Gastroenterol Hepatol. 2019 Feb 1. doi: 10.1016/j.cgh.2019.01.043.

Cirrhotic patients with renal failure have a sevenfold increase in mortality compared with those without renal failure. AKI is common in cirrhosis; increasingly, cirrhotic patients awaiting liver transplantation have or are also at risk for CKD. They are sicker, older, and have more comorbidities such as obesity and diabetes. In this study, the cumulative incidence of death on the wait-list was much more pronounced for any form of AKI, with those with AKI on CKD having the highest cumulative incidence of wait list mortality compared with those with normal renal function.


Dr. Asrani

The study notably raises several important issues. First, AKI exerts a greater influence in risk of mortality on CKD than it does on those with normal renal function. This is relevant given the increasing prevalence of CKD in this population. Second, it emphasizes the need to effectively measure renal function. All serum creatinine-based equations overestimate glomerular filtration rate in the presence of renal dysfunction. Finally, the study highlights the importance of extrahepatic factors in determining mortality on the wait list. While in all-comers, a mathematical model such as the MELDNa score may be able to predict mortality, for a specific patient the presence of comorbid conditions, malnutrition and sarcopenia, infections, critical illness, and now pattern of renal dysfunction, may all play a role. The study raises questions ripe for further study: Should we incorporate pattern of renal injury into prognostic models and allocation? Investigation should focus on identifying and validating biomarkers that represent the many phenotypes/mechanisms of AKI/CKD as there may be differential effects on morbidity and mortality in cirrhotic patients.

Sumeet K. Asrani, MD, MSc, is a hepatologist affiliated with Baylor University Medical Center, Dallas. He has no conflicts of interest.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Patients with viral hepatitis are living longer, increasing risk of extrahepatic mortality

BY WILL PASS
MDedge News

Patients with viral hepatitis may live longer after treatment with direct-acting antiviral agents (DAAs), but their risk of extrahepatic causes of death may rise as a result, according to a report by investigators in Gastroenterology.

Importantly, this increasing rate of extrahepatic mortality shouldn't be seen as a causal link with DAA use, cautioned lead author Donghee Kim, MD, PhD, of Stanford (Calif.) University, and colleagues. Instead, the upward trend is more likely be-

These findings suggest assessment and identification of risk and risk factors for extrahepatic cancer, cardiovascular disease, and diabetes in individuals who have been successfully cured of HCV infection.

cause of successful treatment with DAAs, which can increase lifespan, and with it, time for susceptibility to extrahepatic conditions.

This was just one finding from a retrospective study that used U.S. Census and National Center for Health Statistics mortality records to evaluate almost 28 million deaths that occurred between 2007 and 2017. The investigators looked for mortality trends among patients with common chronic liver diseases, including viral hepatitis, alcoholic liver disease (ALD), and nonalcoholic fatty liver disease (NAFLD), noting that each of these conditions is associated with extrahepatic complications. The study included deaths due to extrahepatic cancer, cardiovascular disease, and diabetes.

While the efficacy of therapy for viral hepatitis has improved markedly since 2014, treatments for ALD and NAFLD have remained static, the investigators noted.

"Unfortunately, there have been no significant breakthroughs in the treatment of [ALD] over the last 2 decades, resulting in an increase in estimated global mortality to 3.8%," the investigators wrote in Gastroenterology.

"[NAFLD] is the most common chronic liver disease in the world," they added. "The leading cause of death in individuals with NAFLD is cardiovascular disease, followed by extrahepatic malignancies, and then liver-related mortality. However, recent trends in ALD and NAFLD-related extrahepatic complications in comparison to viral hepatitis have not been studied."

The results of the current study supported the positive impact of DAAs, which began to see widespread use in 2014. Age-standardized mortality among patients with hepatitis C virus (HCV) rose until 2014 (2.2% per year) and dropped thereafter (–6.5% per year). Mortality among those with hepatitis B virus steadily decreased over the study period (–1.2% per year).

Of note, while deaths because of HCV-related liver disease dropped from 2014 to 2017, extrahepatic causes of death didn't follow suit. Age-standardized mortality for cardiovascular disease and diabetes increased at average annual rates of 1.9% and 3.3%, respectively, while the rate of extrahepatic cancer–related deaths held steady.

"The widespread use, higher efficacy and durable response to DAA agents in individuals with HCV infection may have resulted in a paradigm shift in the clinical progression of coexisting disease entities following response to DAA agents in the virus-free environment," the investigators wrote. "These findings suggest assessment and identification of risk and risk factors for extrahepatic cancer, cardiovascular disease, and diabetes in individuals who have been successfully treated and cured of HCV infection."

In sharp contrast with the viral hepatitis findings, mortality rates among patients with ALD and NAFLD increased at an accelerating rate over the 11-year study period.

Among patients with ALD, all-cause mortality increased by an average of 3.4% per year, at a higher rate in the second half of the study than the first (4.6% vs 2.1%). Liver disease–related mortality rose at a similar, accelerating rate. In the same group, deaths due to cardiovascular disease increased at an average annual rate of 2.1%, which was accelerating, while extrahepatic cancer–related deaths increased at a more constant rate of 3.6%.

For patients with NAFLD, all-cause mortality increased by 8.1% per year, accelerating from 6.1% in the first half of the study to 11.2% in the second. Deaths from liver disease increased at an average rate of 12.6% per year, while extrahepatic deaths increased significantly for all three included types: cardiovascular disease (2.0%), extrahepatic cancer (15.1%), and diabetes (9.7%).

Concerning the worsening rates of mortality among patients with ALD and NAFLD, the investigators cited a lack of progress in treatments, and suggested that "the quest for newer therapies must remain the cornerstone in our efforts."

The investigators reported no external funding or conflicts of interest.

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SOURCE: Kim D et al. Gastroenterology. 2019 Jun 25. doi: 10.1053/j.gastro.2019.06.026.

Chronic liver disease is one of the leading causes of death in the United States. Whereas mortality from other causes (e.g., heart disease and cancer) has declined, age-adjusted mortality from chronic liver disease has continued to increase. There have been a few major advances in the treatment of several chronic liver diseases in recent years. These include nucleos(t)ide analogues for hepatitis B virus (HBV) and direct-acting antiviral agents for the treatment of hepatitis C virus infection. Many studies show that these treatments are highly effective in improving patient outcomes, including patient survival. However, whether these individual-level benefits have translated into population-level improvements remains unclear.


Dr. Kanwal

This study used the U.S. Census and the National Center for Health Statistics mortality records from over an 11-year period to examine population-level changes in overall mortality, including mortality from liver- and nonliver (extrahepatic) complications of viral hepatitis, alcoholic liver disease, and nonalcoholic liver disease in the United States.

Overall, the results were mixed; they were encouraging for viral hepatitis but concerning for alcoholic and nonalcoholic liver disease. Specifically, all-cause mortality from HCV was on an upward trajectory in the first 7 years (from 2007 to 2014) but the trend shifted from 2014 onward. Importantly, this inflection point coincided with the timing of the new HCV treatments. Most of this positive shift post 2014 was related to a strong downward trend in liver-related mortality. In contrast, upward trends in mortality related to extrahepatic causes (such as cardiovascular mortality) continued unabated. The authors found similar results for HBV. The story, however, was different for alcohol and nonalcohol-related liver disease – both conditions lacking effective treatments; liver related mortality for both continued to increase during the study period.

Although we cannot make causal inferences from this study, overall, the results are good news. They suggest that HBV and HCV treatments have reached enough infected people to result in tangible improvements in the burden of chronic liver disease. We may now need to shift the focus of secondary prevention efforts from liver to nonliver (extrahepatic) morbidity in the newer cohorts of patients with treated HCV and HBV.

Fasiha Kanwal, MD, MSHS, AGAF, is an investigator in the clinical epidemiology and comparative effectiveness program for the Center for Innovations in Quality, Effectiveness, and Safety in collaboration with the Michael E DeBakey VA Medical Center, as well as an associate professor of medicine in gastroenterology and hepatology at Baylor College of Medicine in Houston. She has no conflicts of interest.

8 new insights about diet and gut health

Three experts share their takeaways from the 2019 James W. Freston Conference: Food at the Intersection of Gut Health and Disease.

During your 4 years of medical school, you likely received only 4 hours of nutrition training. Yet we know diet is integral to the care of GI patients. That's why AGA focused the 2019 James W. Freston Conference on the topic of food.

Our course directors William Chey, MD, AGAF, Sheila E. Crowe, MD, AGAF, and Gerard E. Mullin, MD, AGAF, share eight points from the meeting that stuck with them and can help all practicing GIs as they consider dietary treatments for their patients.

1. Personalized nutrition is important. Genetic differences lead to differences in health outcomes. One size or recommendation does not fit all. This is why certain diets work only on certain people. There is no one diet for all and for all disease states. Genetic tests can be helpful, but they rely on reporting that isn't readily available yet.

2. Dietary therapy is key to managing eosinophilic esophagitis (EoE). EoE is becoming more and more prevalent. Genes can't change that fast, but epigenetic factors can, and the evidence seems to be in food. EoE is not an IgE-mediated disease and therefore most allergy tests will not prove useful; however, food is often the trigger – most common, dairy. Dietary therapy is likely the best way to manage. You want to reduce the number of eliminated foods by way of a reintroduction protocol. The six-food elimination diet is standard, though some are moving to a four-food elimination diet (dairy, wheat, egg, and soy).

3. There has been a reported increase in those with food allergies, sensitivities, celiac disease, and other adverse reactions to food. Many of the food allergy tests available are not helpful. In addition, many afflicted patients are conducting self-imposed diets rather than working with a GI, allergist, or dietitian. This needs to change.

4. There is currently insufficient evidence to support a gluten-free diet for irritable bowel syndrome (IBS). It is possible that fructans, more than gluten, are causing the GI issues. Typically, the low-FODMAP diet is beneficial to IBS patients if done correctly with the guidance of a dietitian; however, not everyone with IBS improves on it. All the steps are important though, including reintroduction and maintenance.

5. When working with patients on the low-FODMAP or other restrictive diets, it is important to know their food and eating history. Avoidance/Restrictive Food Intake Disorder (ARFID) is something we need to be aware of when it comes to patients with a history or likelihood to develop disordered eating/eating disorders. The patient team may need to include an eating disorder therapist.

6. The general U.S. population has increased the adoption of a gluten-free diet although the number of cases of celiac disease has not increased. Many have self-reported gluten sensitivities. Those that have removed gluten following trends are more at risk of bowel irregularity (low fiber), weight gain, and disordered eating. Celiac disease is not a do-it-yourself disease; patients will be best served working with a dietitian and GI.

7. Food can induce symptoms in patients with inflammatory bowel disease (IBD). It can also trigger gut inflammation resulting in incident or relapse. There is experimental plausibility for some factors of the relationship to be causal and we may be able to modify the diet to prevent and manage IBD.

8. The focus on nutrition education must continue! Nutrition should be a required part of continuing medical education for physicians. And physicians should work with dietitians to improve the care of GI patients.

For resources to help your patients understand how diet and nutrition can affect their digestive health, visit the AGA GI Patient Center, gastro.org/patient. Each disease-based resource provides tips from leading experts on the role of diet in managing GI health.

The 2019 James W. Freston Single Topic Conference took place Aug. 9 and 10 in Chicago. The Freston conference is the only conference organized by the AGA Institute Council in which the agenda is determined through an open call for proposals from AGA membership. The purpose of the conference is to focus on scientific dialogue, present opportunities for scientific collaboration, and explore new ideas that may lead to enhanced patient therapies or potential opportunities for cures of digestive diseases. The 2019 conference was sponsored by the AGA Institute Council Obesity, Metabolism & Nutrition Section. Vice chair of the section, Dr. Gerard Mullin, served as co-course director.

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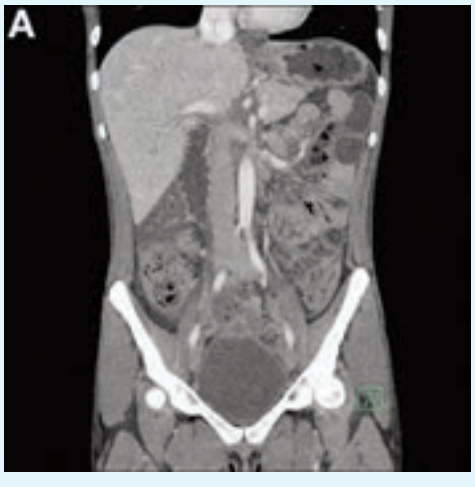
CLINICAL CHALLENGES AND IMAGES

What is your diagnosis?

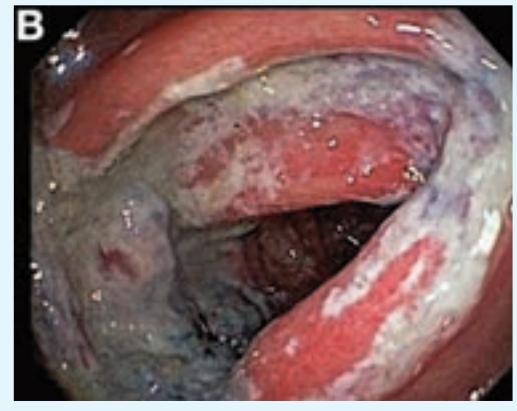
By Robert S. Robinson III, MD, Rohan M. Modi, MD, and Somashekar G. Krishna, MD, MPH. Published previously in Gastroenterology (2018;154[6]:1582-630).

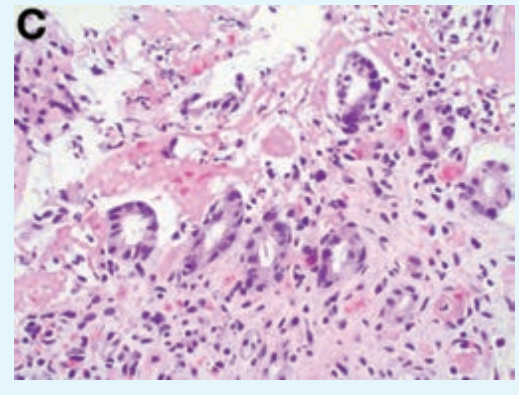
A 28-year-old woman with a history of mild iron-deficiency anemia presented with acute onset of lower abdominal pain and bloody bowel movements. The patient reported actively training for a marathon and on the day of presentation she ran approximately 20 miles before developing acute sharp, crampy lower abdominal pain. This discomfort forced her to stop her run early and she subsequently had several loose bowel movements streaked with bright red blood that prompted evaluation.



In the emergency department, she was afebrile and hemodynamically stable with physical examination revealing slight tenderness to palpation in the left upper quadrant of her abdomen. Laboratory results were significant for mild leukocytosis (white blood cell count, 16.1 × 10^3/microL), anemia (hemoglobin, 10.3 g/dL), and iron deficiency (ferritin, 14 ng/mL; iron, 11 microg/dL; and iron saturation, 2%). Of note, lactate, erythrocyte sedimentation rate, and C-reactive protein levels were all within normal limits. A computed tomography scan of her abdomen and pelvis demonstrated diffuse inflammation involving her colon and terminal ileum (Figure A). The patient underwent a colonoscopy that revealed congested and dusky mucosa in the distal descending colon and throughout the transverse colon (Figure B). Biopsies of the affected areas were performed (Figure C).

The diagnosis is on page 16.





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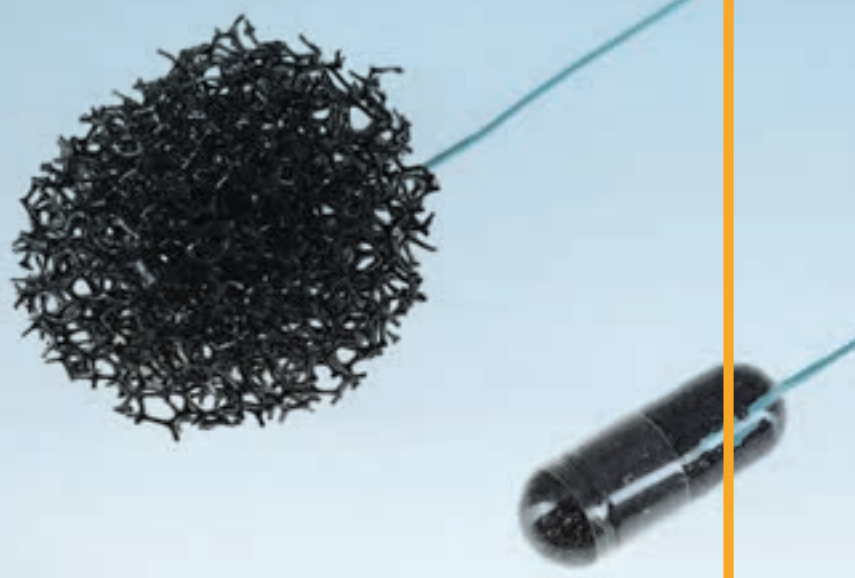
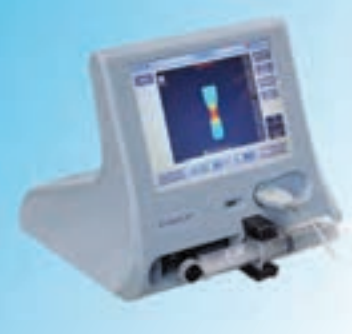


Evaluate motility function
Endoflip™ impedance planimetry system



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Update on duodenoscope reprocessing and infection control

Infection transmission from duodenoscopes is a serious and complex issue for our patients and our practices.

As previously shared with our members late last year, the U.S. Food and Drug Administration (FDA) reported on preliminary data from manufacturer testing of duodenoscopes following reprocessing (cleaning). The report showed that, in about 5% of cases, samples tested positive for "high concern" bacteria after the scopes had been reprocessed as recommended. According to FDA, these are bacteria that are more often associated with disease. The final results and more granular detail are expected later this year.

This is a serious and complex issue for our patients and our practices. Duodenoscopes are necessary for performing endoscopic retrograde cholangiopancreatography (ERCP). This minimally invasive procedure is typically performed in patients with diseases of the liver, pancreas, and gallbladder and obviates the necessity for more morbid surgical and radiologic procedures.

A recent article in The New York Times reviewing this issue largely understated the value of duodenoscopes and the procedure for which they are used. This is a potentially life-saving procedure for nearly 700,000 patients each year in the United States. When a doctor recommends ERCP, it often is because the patient is seriously ill, and the benefits of the procedure far outweigh the risks. ERCPs also spare patients more invasive alternatives, including surgery. Withdrawal of these instruments from the marketplace is simply not feasible and would be a major step backward in our ability to treat common and complex disease in the most beneficial manner.

We do agree and support the identification and development of safe and effective solutions that eliminate risk of infection transmission as a top priority. This cannot happen overnight: We cannot adopt new technologies, such as disposable duodenoscopes, without first understanding the new and unintentional risks we may be introducing to our patients such as an increased risk of procedural failure, perforation, or pancreatitis.

The GI societies have been working closely with FDA and industry to identify and properly vet potential solutions. FDA has already reviewed and cleared new reprocessing and sterilization technologies and revised designs for some duodenoscopes; all are intended to enhance ease of cleaning and reprocessing, thereby improving safety from transmitted infection. Other redesigns and new technologies for endoscope reprocessing, as well as single-use instruments, are in the pipeline. All of these options, and others, will likely enter the marketplace in the coming months and years after FDA vetting and approval and with postmarketing studies to ensure the efficacy of the technology and patient safety.

AGA is currently seeking feedback from AGA members to provide to FDA for consideration as they make upcoming review and approval decisions. If you are concerned about losing access to ERCP, a valuable procedure, please share your comments in the AGA Community. We will be sharing these comments with FDA to ensure their decisions reflect the needs of our members.

Since it was discovered several years ago that cases of infection transmission associated with duodenoscopes had been experienced by hospitals in the United States and Europe, health care organizations across the board recognized the need to escalate infection control efforts and to swiftly identify and disseminate best practices. FDA, the Centers for Disease Control and Prevention, state and local health departments, scope manufacturers, and medical societies have collaborated continuously to determine best practices for identifying and reporting sources of infection and effectively cleaning equipment.

Since this problem was identified, vigilance has been raised and infection rates have improved. As with all medical procedures, physicians should discuss the risks and benefits with their patients who require ERCP.

This article was developed in collaboration with American Society for Gastrointestinal Endoscopy (ASGE) and the Society of Gastroenterology Nurses and Associates (SGNA).

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AGA urges Medicare to fix CRC screening coinsurance issue

AGA and our sister societies met with Medicare staff in Washington to voice our opposition to its proposal that would require physicians to inform patients about potential colorectal cancer (CRC) screening costs. Under the proposal, physicians who plan to perform a CRC screening for a Medicare beneficiary must tell the beneficiary in advance that they may have to pay coinsurance under the Medicare program if the screening finds polyps that are removed as part of the screening procedure and document the conversation in the beneficiary's medical record starting Jan. 1, 2020.

Under the Affordable Care Act, Medicare beneficiaries do not need to pay for screenings that receive an A or B from the U.S. Preventive Services Task Force (USPSTF), such as screening colonoscopy. However, because of Medicare's interpretation of the coding rules, when a polyp is found and removed during a screening colonoscopy, it is considered a diagnostic procedure and the patient is required to pay the coinsurance. Medicare's new proposal does not solve the underlying problem – fixing the coinsurance issue for Medicare beneficiaries; instead, it shifts responsibility to notify Medicare beneficiaries to the physician.

The gastroenterology community, together with patient advocates, has been asking CMS since 2011 to use its authority to fix the Medicare screening colonoscopy coinsurance problem. It was never the intention of Congress for polypectomy resulting from the initial screening to be excluded from the screening benefit. The Obama administration provided guidance for commercial plans on this screening benefit and stated that plans should not impose coinsurance since "removal of polyp is integral to the screening" and thus most private insurers recognize the benefit of waiving the coinsurance.

In our meeting with Medicare, we told them that beneficiaries should not be penalized because of the agency's misinterpretation of Congress' legislation. We also urged Medicare not to add to physician burden, to take responsibility for notifying patients of its own coverage and payment policies, and to focus on ways to help patients avoid unfair financial penalties resulting from its misinterpretation of Congress's mandate for free CRC screening.

Medicare needs to hear from you today. Sign our letter on gastro.org/advocacy to let your voice be heard.

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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) 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. **Indefinite metaplasia Barrett's esophagus (http://ow.ly/vdnr30pt869)** – The GI community considers whether a 47-year-old Barrett's esophagus patient with a history of smoking is a candidate for radiofrequency ablation.
2. **Anastomotic pouch inflammation (http://ow.ly/rFBq30pt88c)** – A colleague asks: Have you managed a patient with signs of pouchitis or diversion colitis at the ileocolonic anastomosis pouch-like area?
3. **Incidental Crohn's disease (http://ow.ly/ffpF30pt8aA)** – A colonoscopy performed on an asymptomatic 35-year-old male revealed superficial ulcers in the distal TI. An AGA member solicits suggestions for treatment options and next steps.

Access these clinical cases and more discussions at https://community.gastro.org/discussions.

Frequent heartburn affects

UP TO **75%** of sufferers at night[1]

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*Use as directed. Take 1 pill in the morning for 14 days. May take 1 to 4 days for full effect.

†Based on a post hoc analysis of 2-week data from 2 previously published identical phase IV, multicenter, randomized, double-blind, placebo-controlled trials that demonstrated efficacy and safety of esomeprazole 20 mg once daily in the morning in subjects with sleep disturbances due to reflux and frequent nighttime heartburn.

‡Complete resolution of heartburn was defined as 7 consecutive days without heartburn.

§First resolution defined as a study day when patients recorded "NO" sleep disturbances due to frequent heartburn on daily diary card.

References: 1. National Sleep Foundation. Ease heartburn at bedtime. https://sleep.org/articles/ease-heartburn-bedtime/. Accessed August 6, 2018. **2.** Johnson DA, Le Moigne A, Hugo V, Nagy P. Rapid resolution of sleep disturbances related to frequent reflux: effect of esomeprazole 20 mg in two randomized, double-blind, controlled trials. *Curr Med Res Opin.* 2015;31(2):243-250.

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Include the AGA Research Foundation in your estate plan

Gifts to charitable organizations, such as the AGA Research Foundation, in your future plans ensure your support for our mission continues even after your lifetime. Review these goals to turn financial aspiration into charitable action to achieve your philanthropic vision.

Goal: Take care of those you love

Use your will or living trust to clearly communicate your intentions for how you would like to provide for your loved ones and favorite causes, including the AGA Research Foundation. You can feel secure knowing you will maintain control of your assets until after your lifetime and that your gifts are revocable so you can change your mind at any time.

Goal: Eliminate capital gains tax on stocks

When you donate appreciated securities – that is, stocks you've owned for more than 1 year that are now worth more than you originally paid for them – you can benefit yourself and the AGA Research Foundation. You can reduce or even eliminate federal capital gains taxes on the stock transfer, and you may be entitled to a federal income tax charitable deduction.

Tip: There are a number of ways to give appreciated securities, such as outright giving or funding a charitable gift annuity or a charitable remainder trust.

Goal: Conserve today's finances

Save critical funds now by naming the AGA Research Foundation as the beneficiary of all or a percentage (1%-100%) of your IRA. Leaving all or part of your IRA to charity after your lifetime dramatically lowers future taxes for your beneficiaries. Naming a charity, like the AGA Research Foundation, as a beneficiary can eliminate federal income taxes that could consume a substantial portion of your account.

Want to learn more about including a gift to the AGA Research Foundation in your future plans? Visit our website at https://gastro.planmylegacy.org or contact Harmony Excellent at 301-272-1602 or hexcellent@gastro.org.

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Tell your patients these four things about prebiotics

Stephen R. Lindemann, PhD, assistant professor of food science and nutrition science, Purdue University, West Lafayette, Indiana, shares four talking points to use when your patients ask about prebiotics.

Explaining prebiotics:

1. Prebiotics serve as food for specific microbes in the gut but their health benefits are likely due to broader changes in the function of communities of microbes.
2. Prebiotics can lead to a durable change in overall function of a gut microbial community with potential for long-term health benefit while probiotics are live microorganisms that when administered in adequate amounts can confer a health benefit even in the short term.
3. Prebiotics ferment to short-chain fatty acids known to positively influence human metabolism and immunity. Commercial prebiotics may be beneficial in some individuals but intolerable in others.
4. Further research is needed to determine the specificity of prebiotics in terms of their biological effects. Other dietary fibers/proteins may have similar health benefits that have not yet been determined.

These tips are from "Prebiotics 101," the first of a four-part CME series in AGA University, agau.gastro.org, titled, "The Microbiome and Digestive Health: A Look at Prebiotics." Part two, "Diet vs. Prebiotics" is also available.

Looking for more information on prebiotics?

AGA has educational materials for patients on probiotics (also available in Spanish) at gastro.org/patient.

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CLINICAL CHALLENGES AND IMAGES

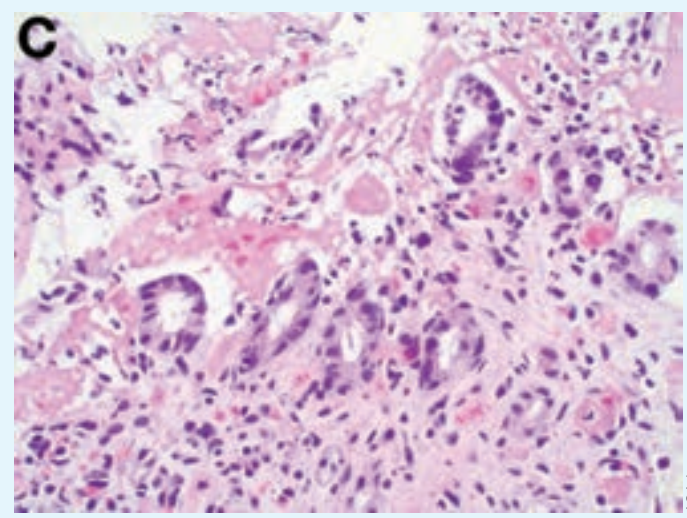
The diagnosis

Answer to "What is your diagnosis?" on page 12: Exercise-induced acute ischemic colitis or "runner's colitis"

Biopsies of the abnormal mucosa noted on colonoscopy revealed mucosal necrosis with stromal hyalinization, crypt atrophy, and acute inflammation (Figure C), consistent with a diagnosis of exercise-induced acute ischemic colitis. Exercise-induced ischemic colitis, sometimes referred to colloquially as "runner's colitis," is a rare but well-documented complication of long-distance running.[1]

A number of physiologic changes occur in the human body during prolonged exercise, including redirection of blood flow from the gut to exercising muscles. Although this process usually serves to better manage available oxygen and nutrients during times of stress, it can occasionally result in unfavorable outcomes as depicted herein. During exercise, the increased sympathetic tone influences rerouting blood with some studies demonstrating up to 80% reduction in splanchnic blood flow with prolonged exercise.[2] In addition, the transient hypovolemia many runners experience if they do not remain adequately hydrated can impair mesenteric perfusion. The splenic flexure of the colon and the rectosigmoid junction are particularly prone to ischemic injury in these settings, given the "watershed" nature of their blood supply.

An extensive review of published cases revealed the reversible nature of this ailment, as all but one subject, who required subtotal colectomy for colonic perforation, had resolution of ischemia on repeat evaluation.[3] The patient had a follow-up computed tomography angiogram 2 months after discharge that revealed unremarkable mesenteric vasculature and resolution of the previously seen colonic wall thickening and pericolonic fat stranding.



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Biliary stents reduced risk of recurrent strictures in CP

BY MICHELE G. SULLIVAN
MDedge News

Most patients with chronic pancreatitis (CP, 77.4%) who received an indwelling stent were still stricture free at 5 years, Sundeep Lakhtakia, MD, and colleagues reported in Gastrointestinal Endoscopy.

Patients with severe disease at baseline were more than twice as likely to develop a postprocedural stricture (odds ratio, 2.4). Longer baseline stricture length was less predictive, but it was still significantly associated with increased risk (OR, 1.2), according to Dr. Lakhtakia of the Asian Institute of Gastroenterology, Hyderabad, India, and coauthors.

'In patients with chronic [symptomatic] pancreatitis ... associated with benign biliary strictures, the single placement of a fully covered self-expanding metal stent for an intended indwell of 10-12 months allows more than 60% to remain free of symptoms up to 5 years.'

The results indicate that indwelling biliary stenting is a reasonable and beneficial procedure for many of these patients, wrote Dr. Lakhtakia and coauthors.

"The major message to be taken from this study is that in patients with chronic [symptomatic] pancreatitis ... associated with benign biliary strictures, the single placement of a fully covered self-expanding metal stent for an intended indwell of 10-12 months allows more than 60% to remain free of symptoms up to 5 years later without additional intervention."

The prospective nonrandomized study comprised 118 patients with chronic symptomatic pancreatitis and benign biliary strictures. All received a stent with removal scheduled for 10-12 months later. Patients were followed for 5 years. The primary endpoints were stricture resolution and freedom from recurrence at the end of follow-up.

Patients were a mean of 52 years old; most (83%) were male. At baseline, the mean total bilirubin was 1.4 mg/dL, and the mean alkaline phosphate level was 338.7 IU/L. Mean stricture length was 23.7 mm, but varied from 7.2 to 40 mm. Severe disease was present in 70%.

Among the cohort, five cases (4.2%) were considered treatment failures, with four lost to follow-up and one treated surgically for chronic pancreatitis progression. Another five experienced a spontaneous complete distal stent migration. The rest of the cohort (108) had their scheduled stent removal. At that time, 95 of the 118 expe-

Continued on following page

Statins hamper HCC in viral hepatitis patients

BY HEIDI SPLETE
MDedge News

Lipophilic statin therapy significantly reduced the incidence and mortality of hepatocellular carcinoma in adults with viral hepatitis, based on data from 16,668 patients.

The mortality rates for hepatocellular carcinoma in the United States and Europe have been on the rise for decades, and the risk may persist in severe cases despite the use of hepatitis B virus suppression or hepatitis C virus eradication, wrote Tracey G. Simon, MD, of Harvard Medical School, Boston, and colleagues. Previous studies suggest that statins might reduce HCC risk in viral hepatitis patients, but evidence supporting one type of statin over another for HCC prevention is limited, they said.

In a study published in the Annals of Internal Medicine, the researchers reviewed data from a national registry of hepatitis patients in Sweden to assess the effect of lipophilic or hydrophilic statin use on HCC incidence and mortality.

They found a significant reduction in 10-year HCC risk for lipophilic statin users, compared with nonusers (8.1% vs. 3.3%). However, the difference was not significant for hydrophilic statin users vs. nonusers (8.0% vs. 6.8%). The effect of lipophilic statin use was dose dependent; the largest effect on reduction in HCC risk occurred with 600 or more lipophilic statin cumulative daily doses in users, compared with nonusers (8.4% vs. 2.5%).

'Of note, our findings were robust across several sensitivity analyses and were similar in all predefined subgroups, including among men and women and persons with and without cirrhosis or antiviral therapy use.'

The study population included 6,554 lipophilic statin users and 1,780 hydrophilic statin users, matched with 8,334 nonusers. Patient demographics were similar between both types of statin user and nonuser groups.

In addition, 10-year mortality was significantly lower for lipophilic statin users compared with nonusers (15.2% vs. 7.3%) and also for hydrophilic statin users, compared with nonusers (16.0% vs. 11.5%).

In a small number of patients with liver disease (462), liver-specific mortality was significantly reduced in lipophilic statin users, compared with nonusers (adjusted hazard ratio, 0.76 vs. 0.98).

"Of note, our findings were robust across several sensitivity analyses and were similar in all predefined subgroups, including among men and women and persons with and without cirrhosis or antiviral therapy use," the researchers noted.

The study findings were limited by several factors including the potential confounding from variables such as smoking, hepatitis B viral DNA, hepatitis C virus eradication, stage of fibrosis, and HCC screening, as well as a lack of laboratory data to assess cholesterol levels' impact on statin use, the researchers said. In addition, the study did not compare lipophilic and hydrophilic statins.

However, the results suggest potential distinct benefits of lipophilic statins to reduce HCC risk and support the need for further research, the researchers concluded.

Dr. Simon had no financial conflicts to disclose, but disclosed support from a North American Training Grant from the American College of Gastroenterology. Several coauthors disclosed relationships with multiple companies including AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and Merck Sharp & Dohme. The study was supported in part by the American College of Gastroenterology, the American Association for the Study of Liver Diseases, the Boston Nutrition Obesity Research Center, the National Institutes of Health, Nyckelfonden, Region Orebro (Sweden) County, and the Karolinska Institutet.

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SOURCE: Simon TG et al. Ann Intern Med. 2019 Aug 19. doi: 10.7326/M18-2753.

Continued from previous page

rienced successful stent removal, without serious adverse events or the need for immediate replacement.

At 5 years, patients were reassessed, with the primary follow-up endpoint of stricture resolution. Secondary endpoints were time to stricture recurrence and/or changes in liver function tests. Overall, 79.7% (94) of the overall cohort showed stricture resolution at 5 years.

Among the 108 who had a successful removal, a longer time of stent indwell was associated with a decreased chance of recurrent placement. Among those with the longer indwell (median, 344 days), the risk reduction was 34% (OR, 0.66). Of the 94 patients with stricture resolution at stent removal, 77.4% remained stent free at 5 years.

At the end of follow-up, 56 patients had symptomatic data available. Most (53) had not experienced symptoms of biliary obstruction and/or cholestasis. The other three had been symptom free at 48 months but had incomplete or missing 5-year data.

By 5 years, 19 patients needed a new stent. Of these, 13 had symptoms of biliary obstruction.

About 23% of stented patients had a stent-related serious adverse event. These included cholangitis (9.3%), abdominal pain (5%), pancreatitis (3.4%), cholecystitis (2%), and cholestasis (1.7%).

About 80% of the 19 patients who had a stricture recurrence experienced a serious adverse event in the month before recurrent stent placement. The most common were cholangitis, cholestasis, abdominal pain, and cholelithiasis.

In a univariate analysis, recurrence risk was significantly associated with severe baseline disease and longer stricture length. The associations remained significant in the multivariate model.

"Strikingly, patients with initial stricture resolution at [stent] removal ... were very likely to have long-term stricture resolution" the authors noted.

Dr. Lakhtakia had no financial disclosures.

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SOURCE: Lakhtakia S et al. Gastrointest Endosc. 2019. doi: 10.1016/j.gie.2019.08.037.

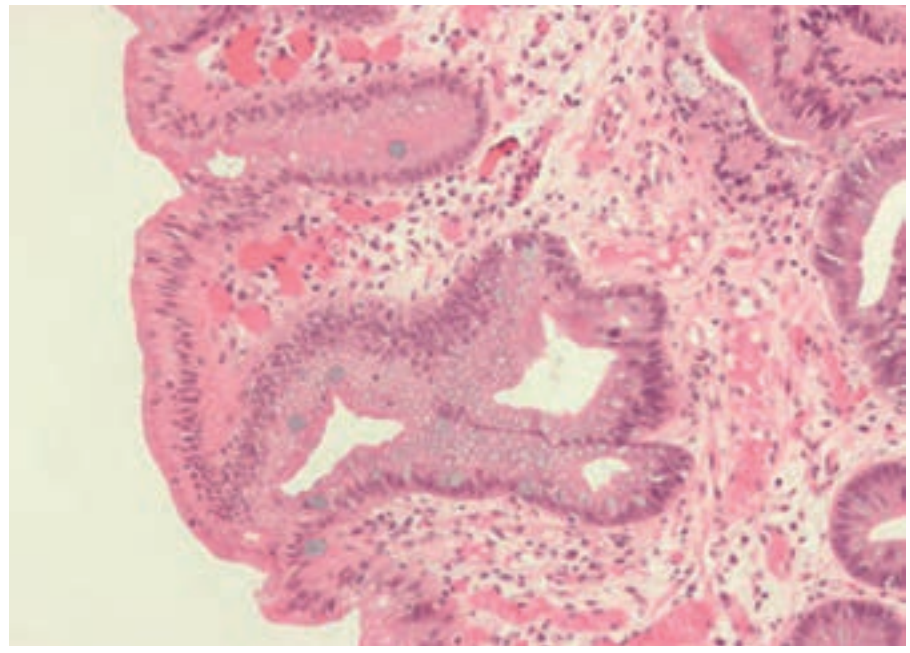
Endoscopic therapy decreases recurrence of intestinal metaplasia, dysplasia in patients with Barrett's esophagus

BY STEVE CIMINO
MDedge News

A study of patients with Barrett's esophagus found that, although intestinal metaplasia and dysplasia in the cardia were common before treatment, they were more frequently present at higher levels and successful endoscopic eradication therapy lessened the risk.

"The results of this study provide evidence to suggest that, in Barrett's esophagus patients who have achieved CEIM [complete eradication of intestinal metaplasia], it is sufficient to perform a close examination of the cardia and, in the absence of visible abnormalities, to randomly biopsy only at the level of TGF [top of gastric folds], rather than deeper into the cardia, during surveillance exams," wrote Swathi Eluri, MD, of the University of North Carolina in Chapel Hill and coauthors. The study was published in Clinical Gastroenterology and Hepatology.

To determine the prevalence of intestinal metaplasia or dysplasia in the cardia of patients with Barrett's esophagus who successfully underwent endoscopic eradication therapy (EET), along with the incidence of cardia intestinal metaplasia or dysplasia in patients undergoing EET, this single-center study examined two groups: a cross-sectional group of 116 patients who had achieved CEIM, and a longitudinal group of 42 treatment-naive patients who were receiving EET and subsequently achieved CEIM.



Nephron/Wikimedia Commons/CC BY-SA 3.0/No changes

Along with clinical biopsies, the cross-sectional group underwent standardized biopsies from four quadrants in four locations: the distal esophagus, 1 cm proximal to top of gastric folds (TGF–1); at TGF; at 1 cm into the gastric cardia (TGF+1); and at 2 cm into the cardia (TGF+2). The longitudinal group also underwent 16 biopsies in the same areas; after CEIM was achieved, they underwent standard research biopsies of the distal esophagus and cardia at 6- and 18-month follow-ups.

Within the cross-sectional group, 15% of patients (n = 17) had intestinal metaplasia or dysplasia in the cardia after CEIM. Of those 17 patients, 12 had intestinal metaplasia, 2 were indefinite for dysplasia, and 3 had low-grade dysplasia. Of the 12 patients with cardia intestinal metaplasia, 83% had it at the level of TGF; 50% at TGF+1; and 25% at TGF+2.

Within the longitudinal group, 28% of patients (n = 12) had intestinal metaplasia or dysplasia in the cardia before ablation. Of those 12 patients, 9 had dysplastic intestinal metaplasia. Cases of pretreatment dysplasia were all found at the level of TGF, with one case extended to TGF+1. All patients achieved CEIM; at 18 months post CEIM, two patients had intestinal metaplasia and none had dysplasia.

The authors shared their study's limitations, which included the lack of generalizability of a single-center study and a notable number of dropouts in the longitudinal group. They also acknowledged using multiple ablation modalities, although they added that most patients in both groups underwent radiofrequency ablation, the most commonly used treatment method and one that made "the results of the study more applicable to real-world practice."

In turn, the authors noted their study's strengths, which included the collection of data in a standardized manner and the availability of complete ablation history for all patients. Theirs was also the first study to systematically sample the cardia at multiple levels, which allows for "a more granular understanding of the location of initial and incident cardia lesions, which can guide depth of ablation during EET."

The study was funded by an American Gastroenterological Association Research Scholar Award and CSA Medical. The authors reported no conflicts of interest.

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SOURCE: Eluri S et al. Clin Gastroenterol Hepatol. 2019 May 8. doi: 10.1016/j.cgh.2019.04.065.

Early post-ACS bleeding may signal cancer

BY KARI OAKES
MDedge News

PARIS – Bleeding after acute coronary syndrome is associated with an increased risk for a new diagnosis of cancer, according to work presented at the annual congress of the European Society of Cardiology.

Of 3,644 patients discharged with dual-antiplatelet therapy after acute coronary syndrome (ACS), 1,215 (33%) had postdischarge bleeding. Taken together, patients who bled had a hazard ratio of 3.43 for a new cancer diagnosis (*P* less than .001).

Of the patients in the post-ACS cohort, 227 were newly diagnosed with cancer after discharge, making up 1% of the patients who did not bleed after discharge, and 3.9% of the patients who experienced postdischarge bleeding. Put another way, "[t]he positive predictive value for cancer diagnosis of post-discharge bleeding was 7.7%," wrote Isabel Muñoz Pousa, MD, and her colleagues in the poster accompanying the presentation.

This elevated risk for cancer diagnosis was driven primarily by the 827 incidents of spontaneous bleeding; here, the HR was 4.38 (*P* less than .001). The 389 bleeds occuring after trauma, such as bladder catheterization or a fall, did not carry an increased risk for a new cancer diagnosis.

"Spontaneous post-discharge bleeding in ACS patients is strongly associated with subsequent cancer diagnosis within the first 6 months," wrote Dr. Muñoz Pousa and her colleagues of the Hospital Universitario Alvaro Cunqueiro, Vigo, Spain. The investigators found a median time of 4.6 months from the bleeding episode to cancer diagnosis.

Of all anatomic locations, genitourinary bleeds were the most strongly associated with new cancer: 228 patients saw a HR of 8.63 for a new cancer diagnosis (*P* less than .001). Bronchopulmonary bleeds, sustained by 56 patients, carried a HR of 4.26 for new cancer diagnosis; and gastrointestinal bleeds, a HR of 3.78 (*P* = .001 and *P* less than .001, respectively). Dr. Muñoz Pousa and her coinvestigators aggregated data from patients who had bleeding at other sites and saw no significant association with new cancers in this group of patients.

Though patients were initially discharged on dual-antiplatelet therapy, many patients stopped taking the medication over the mean 56.2 months of follow-up. The risk of bleeding did not differ significantly between those who

Continued on page 24

AGA Clinical Practice Update on the utility of endoscopic submucosal dissection in T1b esophageal cancer: Expert review

BY WILL PASS
MDedge News

Endoscopic submucosal dissection (ESD) is a viable treatment option for patients with submucosal (T1b) esophageal cancer who have a low risk of lymph node metastasis, according to an expert review.

Among patients with T1b esophageal cancer, ideal candidates for ESD have small (less than 2 cm), well-differentiated tumors that do not invade beyond the superficial submucosa (SM1) and lack lymphovascular invasion, reported lead author Mohamed O. Othman, MD, of Baylor College of Medicine in Houston, and colleagues. The literature review was recently commissioned by the American Gastroenterological Association (AGA), because of high clinical relevance.

"[ESD] has been gaining momentum as an alternative to surgery in treating early gastrointestinal neoplasms," the investigators wrote in Clinical Gastroenterology and Hepatology.

Most patients who undergo surgical resection develop gastroesophageal reflux, the investigators noted, and many others develop serious complications or do not survive the procedure. "Even a high-volume center such as Mayo Clinic reported a surgical mortality of 4% for T1a esophageal cancer," the investigators wrote. "Moreover, 34% of patients developed postoperative complications such as anastomotic leaks, anastomotic strictures, cardiopulmonary complications, and feeding jejunostomy leaks. ... Therefore, a less-invasive alternative to esophagectomy would be extremely valuable in the management of early stage [esophageal cancer] if proven effective."

The investigators reviewed studies evaluating safety and efficacy of surgical and endoscopic techniques, as well as available data for chemoradiation and radiofrequency ablation combinations, which could potentially optimize outcomes of endoscopic resection.

They concluded that most patients with esophageal cancer that does not extend beyond the mucosa (T1a) can be cured with endoscopic resection, based on 5-year survival rates from several Japanese trials. For patients with T1b disease, however, ESD is best suited for those with a low risk of lymph node metastasis. Unfortunately, identifying these candidates can be challenging, according to the investigators.

'The risk of lymph node metastasis depends on the depth of invasion, histologic type, and molecular characterization of the tumor,' the investigators explained, noting that depth of invasion is the trickiest to discern.

"The risk of lymph node metastasis depends on the depth of invasion, histologic type, and molecular characterization of the tumor," the investigators explained, noting that depth of invasion is the trickiest to discern. Although endoscopic ultrasound (EUS) is still recommended for submucosal imaging, the review showed that EUS may overstage cancer in Barrett's esophagus. The investigators suggested that volume laser endoscopy with infrared light could be a more accurate alternative, but it is not yet a clinical reality.

The review also showed potential for combining ESD with other modalities. For example, a study by Hamada and colleagues involving 66 patients with submucosal (T1b) esophageal squamous cell carcinoma found that a combination of ESD with chemoradiation led to similar 3- and 5-year survival rates as radical esophagectomy. The investigators highlighted the importance of lymph node metastasis in this study, as none of the 30 patients lacking lymph node involvement had metastatic recurrence, compared with 6 of the 36 patients who exhibited lymph node metastasis. According to the investigators, promising data are also anticipated for this combination among those with adenocarcinoma. For patients with intestinal metaplasia and/or dysplasia, adding radiofrequency ablation after ESD appears to be an effective option; one recent study by Sharmila Subramaniam, BMBS, and colleagues found that this strategy led to clearance rates of 85% and 96% for metaplasia and dysplasia, respectively.

"Additional treatment should be determined by factors such as tumor grade, status of lymphovascular invasion, and depth of tumor, which have a direct influence on metastatic potential," the investigators wrote.

Looking to the future, the investigators suggested that better diagnostics are needed to characterize T1b disease, as this could streamline patient selection. "Future research should focus on novel biological and immunohistochemistry markers that can aid in the prediction of tumor behavior and [lymph node metastasis] in T1b esophageal cancer," they concluded.

The study was commissioned by the American Gastroenterological Association. The investigators disclosed additional relationships with Boston Scientific, Olympus, Lumendi, and others.

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SOURCE: Othman MO et al. CGH. 2019 Jun 4. doi: 10.1016/j.cgh.2019.05.045.

Continued from page 21

were taking DAPT and those off DAPT, wrote Dr. Muñoz Pousa and her colleagues, adding: "We found a higher incidence of cancer in the first six months after discharge regardless of whether patients were taking dual-antiplatelet therapy or not."

In their statistical analysis, Dr. Muñoz Pousa and colleagues adjusted for potential confounders, and looked at the effect of bleeding as a time-varying covariate on subsequent cancer diagnosis, using Cox regression models.

"Most of the bleeding episodes in the study were mild," noted Dr. Muñoz Pousa in a press statement. However, she said, "The bleeding events more strongly related with a new cancer diagnosis were severe hemorrhages of unknown cause requiring surgery – for example digestive bleeding needing endoscopic treatment."

Breaking bleeding severity down by Bleeding Academic Research Consortium (BARC) criteria, the investigators found that most patients had relatively mild bleeding episodes categorized as BARC 1 or 2, with about half of all bleeding falling into the BARC 1 category.

Still, the 436 patients who had BARC 2 bleeding had a hazard ratio of 4.88 for cancer diagnosis, and the 71 BARC 3A patients saw the HR climb to 7.30. The risk for cancer subsequent to bleeding peaked at BARC 3B, with a HR of 12.29 for these 46 individuals (*P* less than .001 for all). Just 37 patients experienced BARC 3C bleeds, which were associated with a nonsignificant HR of 3.17 for new cancer diagnosis.

Although it's not known why the post–ACS cancer bleeding association exists, Dr. Munoz Pousa put forward a plausible reason for the link. "A possible explanation is that there is a preexisting subclinical lesion in an organ that is triggered to become cancer by antiplatelet drugs or a stressful situation such as heart attack," she said in the press release.

Antiplatelet therapy should be taken as prescribed post ACS, and the physician threshold for further evaluation should be low when a significant spontaneous bleed is seen soon after ACS. "A prompt evaluation of bleeding could be useful for enabling an early detection of cancer in these patients," said Dr. Muñoz Pousa and her colleagues. "Our results suggest that patients should seek medical advice if they experience bleeding after discharge for a heart attack."

The authors reported no conflicts of interest.

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SOURCE: Muñoz Pousa I. et al. ESC Congress 2019, Abstract P677.

Supercooling extends donor liver viability by 27 hours

BY WILL PASS
MDedge News

A new supercooling process could extend ex vivo liver viability by more than a day, potentially expanding transplant availability, according to investigators.

Standard cooling to 4°C provides just 12 hours of organ preservation, but laboratory testing showed that supercooling to –4°C added 27 hours of viability, reported lead author Reinier J. de Vries, MD, of Harvard Medical School and Massachusetts General Hospital in Boston, and colleagues.

"The absence of technology to preserve organs for more than a few hours is one of the fundamental causes of the donor organ–shortage crisis," the investigators wrote in Nature Biotechnology.

Supercooling organs to high-subzero temperatures has been shown to prolong organ life while avoiding ice-mediated injury, but techniques that are successful for rat livers have been difficult to translate to human livers because of their larger size, the investigators explained.

Three strategies were employed to overcome this problem: minimization of air-liquid interfaces, development of a new supercooling-preservation solution, and hypothermic machine perfusion to more evenly distribute preservation solution throughout the liver tissue. For recovery of organs after supercooling, the investigators used subnormothermic machine perfusion, which has been used effectively in rat transplants.

To measure the effect of this process on organ viability, the investigators first measured adenylate energy content, both before supercooling and after recovery.

"Adenylate energy content, and, particularly, the organ's ability to recover it during (re)perfusion, is considered the most representative metric for liver viability," they wrote.

The difference between pre- and postsupercooling energy charge was less than 20%; in comparison, failed liver transplants in large animals and clinical trials have typically involved an energy-charge loss of 40% or more.

To further test organ viability, the investigators measured pre- and postsupercooling levels of bile production, oxygen uptake, and vascular resistance. All of these parameters have been shown to predict transplant success in rats, and bile production has additional precedent from human studies.

On average, bile production, portal resistance, and arterial resistance were not significantly affected by supercooling. Although portal vein resistance was 20% higher after supercooling, this compared favorably with increases of 100%-150% that have been measured in nonviable livers. Similarly, oxygen uptake increased by a mean of 17%, but this was three times lower than changes that have been observed in livers with impaired viability, at 51%.

Additional measures of hepatocellular injury, including AST and ALT, were also supportive of viability after supercooling. Histopathology confirmed these findings by showing preserved tissue architecture.

"We find that the human livers tested displayed no substantial difference in viability before and after extended subzero supercooling preservation," the investigators wrote.

To simulate transplantation, the investigators reperfused the organs with blood at normal temperature, including platelets, complement, and white blood cells, which are drivers of ischemia reperfusion injury. During this process, energy charge remained stable, which indicates preserved mitochondrial function. While energy charge held steady, lactate metabolism increased with bile and urea production, suggesting increased liver function. Bile pH and HCO_{3-} levels fell within range for viability. Although bile glucose exceeded proposed criteria, the investigators pointed out that levels still fell within parameters for research-quality livers. Lactate levels also rose within the first hour of reperfusion, but the investigators suggested that this finding should be interpreted with appropriate context.


MASSACHUSETTS GENERAL HOSPITAL

A machine profusion process helps supercool human liver without freezing the tissue.

"It should be considered that the livers in this study were initially rejected for transplantation," they wrote, "and the confidence intervals of the lactate concentration at the end of reperfusion largely overlap with time-matched values reported by others during [normothermic machine perfusion] of rejected human livers."

Hepatocellular injury and histology also were evaluated during and after simulated transplantation, respectively, with favorable results. Although sites of preexisting hepatic injury were aggravated by the process, and rates of apoptosis increased, the investigators considered these changes clinically insignificant.

"The use of human livers makes this study clinically relevant and promotes the translation of subzero organ preservation to the clinic," the investigators concluded. "However, long-term survival experiments of transplanted supercooled livers in swine or an alternative large animal model will be needed before clinical translation."

The study was funded by the National Institutes of Health and the Department of Defense. Dr. de Vries and four other coauthors have provisional patent applications related to the study, and one coauthor disclosed a financial relationship with Organ Solutions.

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SOURCE: de Vries RJ et al. Nature Biotechnol. 2019 Sep 9. doi: 10.1038/s41587-019-0223-y.

HCV medications associated with serious liver injury

BY CHRISTOPHER PALMER
MDedge News

The Food and Drug Administration has warned that certain hepatitis C virus medications have led to rare instances of worsening liver function or liver failure.

Many of the affected patients had signs or symptoms of moderate to severe liver impairment (Child-Pugh class B or C), and given that these medications – glecaprevir/pibrentasvir (Mavyret), elbasvir/grazoprevir (Zepatier), and sofosbuvir/velpatasvir/voxilaprevir (Vosevi) – are not indicated for such patients, they should not have been prescribed in the first place, the FDA noted in the drug safety communication. Some cases had other preexisting risk factors, such as liver cancer, alcohol abuse, or illnesses associated with liver problems.

In most cases, impairment or decompensation occurred within the first 4 weeks of starting treatment, and symptoms resolved or new-onset worsening of liver function improved after stopping. These medicines have been widely used and, among patients with no or mild liver impairment, have been shown to be safe and effective.

Health care professionals should continue prescribing these medicines as indicated; they should assess patients at baseline for severity of liver disease and other risk factors and closely monitor patients for signs and symptoms of worsening liver function. Patients should be aware that the risk of injury is rare; if they develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools, they should talk with their health care professional but should continue taking the medications until instructed to stop.

The full communication is available on the FDA website.

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Lowering portal pressure boosts cirrhosis outcomes

BY HEIDI SPLETE
MDedge News

Use of nonselective beta-blockers to reduce portal pressure in cirrhosis improved outcomes in adults with or without ascites, based on data from a meta-analysis of more than 1,000 patients.

Previous research has suggested that nonselective beta-blockers (NSBBs) might have a negative effect on patients with refractory ascites, but the effect on patients with and without ascites has not been assessed, wrote Laura Turco, MD, of the University of Modena and Reggio Emilia, Emilia-Romagna, Italy, and colleagues.

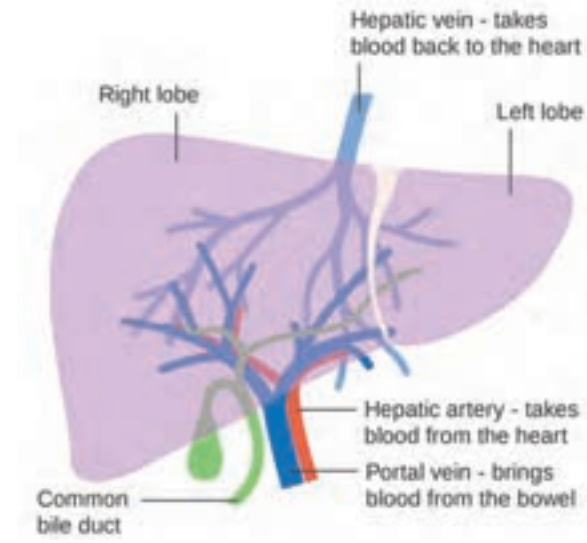
In a study published in Clinical Gastroenterology and Hepatology, the researchers analyzed 1,113 cirrhosis patients including 452 with ascites. Overall, 968 patients had received treatment with NSBBs. Response to pressure reduction was defined as a decrease of more than 20% from baseline or a decrease to less than 12 mm Hg.

A total of 329 of the 661 patients without ascites (50%) met the definition of responders. These responders had significantly lower odds than did nonresponders of a combination of clinical events including ascites, variceal hemorrhage, or encephalopathy (odds ratio, 0.35) and also had significantly lower odds than nonresponders of liver transplantation or death (OR, 0.50).

A total of 188 of the 452 patients with ascites were responders (42%). These responders had significantly lower odds than did nonresponders (OR, 0.27) of variceal hemorrhage, refractory ascites, spontaneous bacterial peritonitis, or hepatorenal syndrome. The responders also had significantly lower odds of liver transplantation or death (OR, 0.47).

The results are important in light of concerns about the impact of NSBBs on renal function and mortality in cirrhosis patients with ascites, the researchers said.

The study findings were limited by several factors, including the use of retrospective data from prospective studies, and the incomplete collection of data on the variables of comorbidities, hepatocellular carcinoma, and other predictive scores; alcohol use or abstinence was a potential confounder as well, the researchers noted.



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However, "By showing that reductions in portal pressure induced by NSBB-based pharmacologic therapy improve outcomes and decrease mortality, our study supports the use of NSBB in all clinical settings (primary or secondary prophylaxis) and in both patients with or without ascites," they concluded. The study was supported by sources including the University of Modena and Reggio Emilia, Yale Liver Center, National Institutes of Health, and Instituto de Salud Carlos III, and was cofunded by the European Union. The researchers had no conflicts to disclose.

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SOURCE: Turco L et al. Clin Gastroenterol Hepatol. 2019 Jun 5. doi: 10.1016/j.cgh.2019.05.050.

USPSTF issues draft recommendation for HCV

BY LUCAS FRANKI
MDedge News

The U.S. Preventive Services Task Force has issued a draft recommendation statement for screening for hepatitis C virus (HCV) infection in adolescents and adults, and now suggests that all adults aged 18-79 years receive screening.

This proposal represents an update and expansion of its current recommendation for screening for HCV infection. The draft recommendation incorporates new evidence and would replace the recommendation made in 2013, which calls for screening in persons at high risk for infection and one-time screening in adults born between 1945 and 1965 (Grade B).

"Today, more people are infected with hepatitis C than there were a decade ago, but there are now better treatments available. The evidence now shows more people can benefit from screening; therefore, we are recommending to screen all adults ages 18-79 for hepatitis C," task force chair Douglas K. Owens, MD, MS, said in a bulletin issued by the USPSTF.

To update the previous recommendation, the USPSTF conducted a systematic review that included a total of 97 studies. No direct evidence was found regarding the benefits of HCV screening versus no screening or repeat versus one-time screening, and no new studies analyzed the psychological and social consequences of HCV screening.

Evidence concerning direct-acting antiviral (DAA) treatment was more compelling given that 49 trials found DAA therapy to be associated with pooled sustained virologic response (SVR) rates between 95.5% and 98.9% across genotypes. The rate of serious adverse events caused by DAA treatment was 1.9%, and the discontinuation of treatment

Continued on page 35

AGA Resource
Help educate your patients about hepatitis C, their risks and treatment options using AGA patient education, which can be found in the GI Patient Center at https://www.gastro.org/practice-guidance/gi-patient-center/topic/hepatitis-c-hcv.

DDSEP 9
Digestive Diseases Self-Education Program

Quick quiz answers

Q1. Correct Answer: B

Rationale
In patients 70 years or older with a history of gastrointestinal bleeding and on chronic NSAIDs, the use of a PPI can reduce the risk of recurrent bleeding. In the setting of an acute bleeding episode, aspirin should resume within 7 days of adequate hemostasis. However, there are no advantages of enteric coated or buffered aspirin in reducing the risk of recurrent bleeding.

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2. Laine L, Jensen D. Management of patients with ulcer bleeding. Am J Gastroenterol. 2012;107:345-60.

Q2. Correct Answer: C

Rationale
Vitamin B_{12} absorption requires intrinsic factor to bind B_{12} to facilitate absorption in the terminal ileum. Any interruption of terminal ileal absorptive capacity can thus lead to vitamin B_{12} deficiency (e.g., Crohn's disease, ileal resection). Intrinsic factor is produced by parietal cells, so any condition that leads to decreased parietal cell mass or function can lead to vitamin B_{12} deficiency (e.g,. atrophic gastritis). In order for intrinsic factor to bind vitamin B_{12}, B_{12} must first be released from binding with the R-protein, which occurs via pancreatic protease breakdown of the R-protein. Patients with chronic pancreatitis are not able to break down the R-protein as efficiently, and thus can develop vitamin B_{12} deficiency.

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Three factors predict 6-month mortality in patients with DILI

BY DOUG BRUNK
MDedge News

Medical comorbidity burden is significantly associated with 6-month and overall mortality in individuals with suspected drug-induced liver injury (DILI).

Those are key findings from a study which set out to investigate the association between comorbidity burden and outcomes of patients with DILI and to develop a model to calculate risk of death within 6 months.

"Drug-induced liver injury is an important cause of liver-related morbidity and mortality that is likely under-recognized," investigators led by Marwan S. Ghabril, MD, AGAF, of the division of gastroenterology and hepatology at Indiana University, Indianapolis, wrote in a study published in Gastroenterology. "Its diagnosis depends on high index of suspicion, compatible temporal relationship, and thorough exclusion of competing etiologies. DILI by an implicated drug commonly occurs in patients with one or several comorbid conditions such as hypertension, diabetes mellitus, cardiovascular disease, renal disease, and malignancy. However, the impact of comorbidity burden on mortality in patients with suspected DILI has not been previously investigated."

For the current analysis and model development, the researchers drew from 306 patients enrolled in the multicenter Drug-Induced Liver Injury Network Prospective Study at Indiana University between 2003 and 2017. To validate their model, they used data from 247 patients who were enrolled in the same study at the University of North Carolina (validation cohort). The primary outcome of interest was mortality within 6 months of onset of liver injury.

Dr. Ghabril and colleagues found that 6-month mortality was 8.5% in the discovery cohort and 4.5% in the validation cohort. "The most common class of implicated agent was antimicrobials with no significant differences between groups," they wrote. "However, herbal and dietary supplements were predominantly implicated in patients with none to mild comorbidity, while cardiovascular agents were predominantly implicated in patients with significant comorbidity."

Among patients in the discovery cohort, the presence of significant comorbidities, defined as a Charlson Comorbidity Index score greater than 2, was independently associated with 6-month mortality (odds ratio, 5.22), as was MELD score (OR, 1.11) and serum level of albumin at presentation (OR, 0.39). When the researchers created a morbidity risk model based on those three clinical variables, it performed well, identifying patients who died within 6 months with a C statistic value of 0.89 in the discovery cohort and 0.91 in the validation cohort. This spurred the development of a web-based risk calculator, which clinicians can access at http://gihep.com/calculators/hepatology/dili-cam/.

The study was funded by grants from the National Institute of Diabetes and Digestive and Kidney Diseases. Dr. Ghabril reported having no financial disclosures, but two coauthors reported having numerous financial ties to industry.

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SOURCE: Ghabril M et al. Gastroenterology. 2019 Jul 11. doi: 10/1053/j.gastro.2019.07.006.

Continued from page 32

because of adverse events was 0.4%. In seven trials involving adolescents, SVR rates after antiviral treatment were similar to those in adults.

Achieving an SVR after DAA treatment was associated with a decreased risk in those treated of all-cause mortality (hazard ratio, 0.40; 95% confidence interval, 0.28-0.56), liver mortality (HR, 0.11; 95% CI, 0.04-0.27), cirrhosis (HR, 0.36; 95% CI, 0.33-0.40), and hepatocellular carcinoma (HR, 0.29; 95% CI, 0.23-0.38), compared with those who did not respond.

Because of the evidence collected, the USPSTF issued a B recommendation for HCV screening in adults and recommended screening for all people aged 18-79 years in the draft recommendation statement. "Clinicians may want to consider screening in adolescents younger than age 18 years and in adults older than age 79 years who are at high risk [for HCV]," the proposal says.

The draft recommendation statement and evidence review is available at www.uspreventiveservicestaskforce.org.

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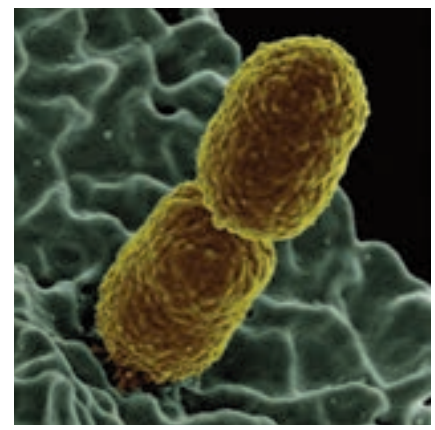
Increased levels of a bacterial strain may be a contributing cause of NAFLD

BY STEVE CIMINO
MDedge News

A new study involving both human patients and mice has confirmed a long-believed association between nonalcoholic fatty liver disease (NAFLD) and an alteration in the gut microbiome that produces high levels of alcohol.

The study was initiated after the treatment of a rare case: a patient who presented with severe nonalcoholic steatohepatitis (NASH) plus auto-brewery syndrome. The patient had a very high blood alcohol concentration but an alcohol-free, high-carbohydrate diet. It was determined that strains of high alcohol-producing *Klebsiella pneumoniae* (HiAlc Kpn) rather than a fungal infection were the catalyst for the high blood alcohol level. As such, Jing Yuan of the Capital Institute of Pediatrics in Beijing and coauthors attempted to "connect these commensal HiAlc Kpn to the pathogenesis of hepatic damage" through this study, which was published in Cell Metabolism.


NIAID

Klebsiella pneumoniae interacting with a human neutrophil.

The researchers began by examining 43 patients with NAFLD and 48 healthy controls. Among the patients with NAFLD, 11 had nonalcoholic fatty liver and 32 had NASH. Specifically, they analyzed the presence and effects of HiAlc Kpn, determining that the abundance of *Klebsiella pneumoniae* was slightly higher in the feces of NAFLD patients, compared with healthy patients, but that their alcohol-producing ability in NAFLD patients was significantly stronger. Of the patients with NAFLD, 61% carried HiAlc and medium alcohol–producing Kpn, compared with 6.25% of the controls.

Another phase of their study involved feeding specific pathogen-free mice either HiAlc Kpn, ethanol, or yeast extract peptone dextrose medium (pair-fed) for 4, 6, and 8 weeks. The mice that were fed HiAlc Kpn or ethanol showed clear microsteatosis and macrosteatosis in their livers at 4 and 8 weeks, compared with the pair-fed mice. In addition, the HiAlc-Kpn-fed and ethanol-fed mice had increased levels of aspartate transaminase and alanine transaminase in their serum and increased levels of triglycerides and thiobarbituric acid reactive substances in their livers. The results overall indicated that the HiAlc-Kpn-fed mice had developed hepatic steatosis.

An additional phase included the intestinal flora from a NASH patient with a specific Kpn strain being fed to germ-free mice. At the same time, two types of intestinal flora from mice with NAFLD were transplanted into healthy mice: one induced by two other specific Kpn strains and one in which those strains had been selectively eliminated. The results saw obvious steatosis in the mice who received the flora from either mice with NAFLD induced by Kpn or the NASH patient at 4 weeks and 8 weeks, respectively. The mice who received the flora win which Kpn had been eliminated saw no fat-related changes in the liver. "These results further suggest that HiAlc Kpn might be one of the major causes of NAFLD development," the researchers wrote.

The authors acknowledged the study's limitations, chiefly including the lack of a clinical cohort of individuals with auto-brewery syndrome but without NAFLD that could be used as a control.

The study was funded by grants from the National Natural Science Foundation for Key Programs of China, the National Natural Science Foundation of China, Megaprojects of Science and Technology Research of China, and CAMS Innovation Fund for Medical Sciences. The authors reported no conflicts of interest.

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SOURCE: Yuan J et al. Cell Metab. 2019 Sep 19. doi: 10.1016/j.cmet.2019.08.018.

Risk in IBD increased

VTE *from page 1*

admissions, 1,160 led to a VTE readmission within 90 days. Readmitted patients had a relatively equal proportion of ulcerative colitis (n = 522) and Crohn's disease (n = 638).

More than 90% of VTE readmissions occurred within 60 days of discharge; the risk was highest over the first 10 days and then decreased in each ensuing 10-day period until a slight increase at the 81- to 90-day period. All patients over age 30 had higher rates of readmission than those of patients under age 18, with the highest risk in patients between the ages of 66 and 80 years (risk ratio, 4.04; 95% confidence interval, 2.54-6.44; *P* less than .01). Women were at lower risk (RR, 0.82; 95% CI, 0.73-0.92; *P* less than .01). Higher risks of readmission were also associated with being on Medicare (RR, 1.39; 95% CI, 1.23-1.58; *P* less than .01) compared with being on private insurance and being cared for at a large hospital (RR, 1.26; 95% CI, 1.04-1.52; *P* = .02) compared with a small hospital.

The highest risk of VTE readmission was associated with a prior history of VTE (RR, 2.89; 95% CI, 2.40-3.48; *P* less than .01), having two or more comorbidities (RR, 2.57; 95% CI, 2.11-3.12; *P* less than .01), and having a *Clostridioides difficile* infection as of index admission (RR, 1.90; 95% CI, 1.51-2.38; *P* less than .01). In addition, increased risk was associated with being discharged to a nursing or care facility (RR, 1.85; 95% CI, 1.56-2.20; *P* less than .01) or home with health services (RR, 2.05; 95% CI, 1.78-2.38; *P* less than .01) compared with a routine discharge.

In their multivariable analysis, similar factors such as a history of VTE (adjusted RR, 2.41; 95% CI, 1.99-2.90; *P* less than .01), two or more comorbidities (aRR 1.78; 95% CI, 1.44-2.20; *P* less than .01) and *C. difficile* infection (aRR, 1.47; 95% CI, 1.17-1.85; *P* less than .01) continued to be associated with higher risk of VTE readmission.

Though they emphasized that the use of NRD data offered the impressive ability to "review over 15 million discharges across the U.S. annually," Dr. Faye and coauthors acknowledged that their study did have limitations. These included the inability to verify via chart review the study's outcomes and covariates. In addition, they were unable to assess potential contributing risk factors such as medication use, use of VTE prophylaxis during hospitalization, disease severity, and family history. Finally, though unlikely, they admitted the possibility that patients could be counted more than once if they were readmitted with a VTE each year of the study.

The authors reported being supported by grants from the National Institutes of Health and various pharmaceutical companies, as well as receiving honoraria and serving as consultants.

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SOURCE: Faye AS et al. Clin Gastroenterol Hepatol. 2019 Jul 20. doi: 10.1016/j.cgh.2019.07.028.

Patient subset has genetic module

Crohn's *from page 1*

lished antibody panels based on prior knowledge preclude the identification of novel pathogenic cell populations in the diseased intestine," they wrote.

Analysis of gene expression revealed significant cellular differences in the immune and stromal cells from inflamed compared to uninflamed ileum tissues. Researchers identified a group of cell subtypes that were highly correlated across inflamed ileums, and which included activated dendritic cells, activated fibroblasts, highly activated T cells, IgG plasma cells, inflammatory macrophages, inflammatory mononuclear phagocytes, and atypical chemokine receptor 1^{+}-activated endothelial cells.

This so-called GIMATS module was present in only five of the patients, but it was independent of pathology severity, disease duration, and systemic markers of inflammation. The authors suggested that the module was associated with a positive feedback loop that increased the clustering of inflammatory mononuclear phagocytes in inflamed tissues.

"Taken together, our results identified a unique cellular organization in inflamed tissues of a subset

Continued on following page

Many options, few new answers

Celiac *from page 1*

out medical supervision, but these strategies raise concerns about accuracy and efficacy, said Benjamin Lebwohl, MD, AGAF, director of clinical research at the Celiac Disease Center at Columbia University in New York.

Potential treatments on the horizon

Dr. Lebwohl

The gluten-free diet is the only treatment proven effective for celiac disease, but it can be expensive or unpalatable for some patients. The diet also entails risks of bowel irregularity and weight gain. "The gluten-free diet remains an inadequate treatment for many people with celiac disease," said Dr. Lebwohl.

Tennyson et al. found that 66% of patients with biopsy-proven celiac disease are interested in nondietary therapy (Therap Adv Gastroenterol. 2013;6[5]:358-64). Such patients are more likely to be male and older than 50 years.

Latiglutenase, a gluten enzyme derived from bacteria and cereal, is among the pharmacotherapies being investigated as a treatment for nonresponsive celiac disease. It reduces or eliminates the toxicity of gluten. In a recent phase 2b trial, however, the treatment did not achieve the primary outcome measure of histologic improvement (Gastroenterology. 2017;152[4]:787-98). Compared with placebo, the drug was not associated with significant improvements in histologic and symptom scores.

Another drug in development is the tight-junction modulator larazotide acetate. Studies of zonula occludens toxin and its mammalian analogue zonulin led to the development of larazotide acetate. Leffler et al. found that a 0.5-mg dose of the drug reduced symptoms of nonresponsive celiac disease in patients who were following a gluten-free diet, compared with patients treated with the diet alone (Gastroenterology. 2015;148[7]:1311-9). Innovate Pharmaceuticals plans to study the drug in phase 3 trials, said Dr. Lebwohl.

ImmunosanT has studied Nexvax2, which promotes gluten peptide desensitization. A phase 2 study examined the drug's efficacy in reducing symptoms during a masked food challenge. The company discontinued this study when an interim analysis showed that the drug provided no more protection from gluten exposure than placebo. Nexvax2 was safe and well tolerated, and the study revealed no new safety signals.

In addition to newly developed therapies, researchers are studying whether drugs marketed for other indications could be effective treatments for celiac disease. For example, budesonide, a treatment for asthma and chronic obstructive pulmonary disease, is being investigated for nonresponsive celiac disease and refractory celiac disease. Other research is examining whether budesonide could provide effective protection after inadvertent gluten exposure. Systemic steroids, immunosuppressants such as azathioprine, chemotherapeutics such as cladribine, and mesalamine, which is a treatment for inflammatory bowel disease, also are under investigation.

But several questions related to drug development for celiac disease remain unanswered. For example, whether researchers should choose clinical or histologic endpoints for their trials is a subject of debate. "Probably, we're going to be looking for two endpoints," said Dr. Lebwohl. No consensus has been established about whether trials should include patients for whom diagnosis is based on a test other than a biopsy. Also, the effect of nondietary therapy on adherence to the gluten-free diet remains to be clarified.

Self-management of celiac disease

"We're in a new era" of self-monitoring and direct-to-consumer advertising aimed at patients with celiac disease, said Dr. Lebwohl. Products and services that enable patients to diagnose and manage themselves independently are broadly available. For example, 23andMe provides at-home testing for HLA-DQ2.5 and HLA-DQ8, which could support a diagnosis of celiac disease. The service does not, however, test for HLA-DQ2.2, which is present in about 5% of patients with celiac disease. This testing consequently has high negative-predictive value, but poor positive-predictive value, said Dr. Lebwohl.

Similarly, ImAware provides blood tests that patients can take at home and send to the company for results. The tests look for antibodies such as tissue transglutaminase immunoglobulin A/immunoglobulin G and deamidated gliadin peptide IgA/IgG. The company advises patients to share their results with a health care professional.

Furthermore, portable devices such as Nima are marketed as gluten detectors. One study of the device included 804 users from all 50 states. The device found gluten in 32% of all restaurant food tested advertised as gluten-free. The interpretation of these results should take into account the fact that the device may detect gluten levels lower than 20 ppm, which generally are safe for patients with celiac disease. Furthermore, the data were uploaded voluntarily by users, and thus are not a random sample (Am J Gastroenterol. 2019;114[5]:792-7). The device cannot detect certain forms of gluten such as barley malt. Because of limitations like these, the Nima device has "vocal critics," said Dr. Lebwohl.

A profusion of books that offer dietary advice for patients with celiac disease also has become available. Data from Google Trends indicate that the popularity of the gluten-free diet spread from small pockets of the country in 2006 to most of the states in 2015.

Yet this "do-it-yourself" approach to celiac disease raises several concerns, said Dr. Lebwohl. Patients are at risk of interpreting their test results incorrectly, for example. Failing to consult a dietitian or physician, each of whom could have expertise in the field, entails risks as well. "Knowledgeable and empathetic care-giving is more important than ever," Dr. Lebwohl concluded.

Dr. Lebwohl is on the medical advisory board of Innovate Biopharmaceuticals, a consultant for Takeda, and an unpaid adviser for the Nima Sensor.

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of patients, thus revealing different pathogenic responses between patients despite similar pathological severity and systemic inflammatory markers," the authors wrote.

The authors then looked for GIMATS expression in a larger cohort of 441 patients with ileal Crohn's disease – including children aged over 2 years but excluding individuals with mutations that are associated with development of anti-TNF–resistant lesions early in life.

Given that 20%-30% of patients with ileal Crohn's disease never respond to anti-TNF therapy, and require surgical intervention for uncontrolled bowel disease, the authors examined whether the GIMATs module might affect patient response to anti-TNF therapy.

They found that enrichment of this module was evident in the early stages of the disease, before the use of biologics therapy, and there were significant differences between treatment responders and nonresponders in their GIMATS module score at baseline. The authors said this suggested TNF blockade might not be enough to affect the inflammatory response associated with the GIMATS module.

"It is interesting that TNF was produced mainly by T cells in patients with low GIMATS module scores, while it was produced both by T cells and inflammatory [mononuclear phagocytes] in patients with a high module scores," they wrote. "By providing a comprehensive network of the cellular and molecular basis for resistance to anti-TNF blockade, our study thus opens novel opportunities for therapeutic discoveries tailored for combination with anti-TNF antibody blockade."

They also found that the GIMATS score did not correlate with disease activity in pediatric patients at diagnosis.

"As was observed in the discovery cohort, patients with high or low GIMATS module score had similar markers of systemic inflammation, indicating that the GIMATS score conveys information regarding response to biologic therapy that is not provided by standard [Crohn's disease] biomarkers," they wrote.

The study was partly supported by an author grant from Boehringer Ingelheim. Three authors also declared advisory board positions, consultancies, and research funding from the pharmaceutical industry, including Boehringer Ingelheim. No other conflicts of interest were declared.

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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

How does diet affect the risk of IBD?

BY ERIK GREB
MDedge News

CHICAGO – Evidence suggests that diet may cause incident inflammatory bowel disease (IBD) and induce associated symptoms, according to a lecture delivered at the 2019 James W. Freston Conference: Food at the Intersection of Gut Health and Disease, sponsored by the American Gastroenterological Association.

Although the literature is highly consistent, it contains discordant findings, and many questions remain unanswered. "We need more rigorous studies, and particularly more interventions, to truly understand the role diet may play in patients with IBD," said Ashwin N. Ananthakrishnan, MD, MPH, associate professor of medicine at Massachusetts General Hospital in Boston.

Food can cause symptoms in IBD

Many patients with IBD are convinced that their diet caused their disease. A relevant point for physicians to consider is that these patients are at least as likely as is the general population to have intolerance or sensitivity to food components such as lactose and gluten. In a prospective questionnaire of 400 consecutive patients with IBD in the United Kingdom, 48% expressed the belief that diet could initiate IBD, and 57% said that diet could trigger a flare-up. In addition, 60% of respondents reported worsening of symptoms after eating certain foods, and about two-thirds deprived themselves of their favorite foods to prevent relapses (Inflamm Bowel Dis. 2016;22[1]:164-70). A French study found similar results. "Clearly there's something there," said Dr. Ananthakrishnan. Patients' beliefs about the relationship between food and their symptoms are not simply misconceptions, he added.

A Canadian study published in 2016 found that almost one-third of patients with IBD avoid many food groups. "But there is significant heterogeneity in the foods that are avoided, and sometimes we mistake this heterogeneity for a lack of association between diet and symptoms in IBD," said Dr. Ananthakrishnan. A larger number of patients avoid certain foods during periods of active disease, which suggests that food exacerbates their symptoms, he added. The same study showed that patients with IBD have more restrictive diets than do community controls. Patients eat fewer fruits and vegetables and generally consume less iron-rich food and less protein-rich food than healthy controls. GI intolerance, rather than professional advice, is the most common reason that patients with IBD restrict their diets (JPEN J Parenter Enteral Nutr. 2016;40[3]:405-11).

A cross-sectional survey of 130 patients with IBD and 70 controls yielded similar results. Among patients, GI symptoms that resulted from consuming foods were not related to disease activity, disease location, or prior surgery. Patients with IBD tended to have greater frequency of GI intolerance to foods than did controls (Scand J Gastroenterol. 1997;32[6]:569-71).

Diet may cause intestinal inflammation

International research has recorded increases in the consumption of sugar and fat (particularly saturated fat) and concomitant decreases in fiber consumption during the past several decades. The incidence of IBD has increased in parallel with these dietary changes with a remarkably similar trajectory, said Dr. Ananthakrishnan. The correlation between dietary changes and IBD incidence "holds true even more strikingly in countries that are now experiencing Westernization," he added. These countries have undergone more rapid dietary changes, and their IBD incidence has doubled or tripled. The transition to "less traditional diets" appears to promote intestinal inflammation, said Dr. Ananthakrishnan.


Dr. Ananthakrishnan

An analysis of data from the European Prospective Investigation into Cancer (EPIC) study found an association between high consumption of sugar and soft drinks, together with low consumption of vegetables, and risk of ulcerative colitis (Inflamm Bowel Dis. 2016;22[2]:345-54). A subsequent analysis of data from two prospective Swedish cohorts, however, found no association between consumption of sugary beverages and risk of Crohn's disease or ulcerative colitis (Clin Gastroenterol Hepatol. 2019;17[1]:123-9).

Although the data on sugar are mixed, data on the association between other macronutrient groups and risk of IBD are more consistent. When Dr. Ananthakrishnan and colleagues examined data from the Nurses' Health Study, they found that the highest quintile of dietary fiber intake was associated with a 40% reduction in risk of Crohn's disease, compared with the lowest quintile. The observed reduction of risk seemed to be greatest for fiber derived from fruits. Fiber from cereals, whole grains, or legumes, however, did not affect risk of Crohn's disease (Gastroenterology. 2013;145[5]:970-7).

A separate analysis of the Nurses' Health Study suggested that high intake of n-3 polyunsaturated fatty acids (PUFAs) and low intake of n-6 PUFAs was associated with a 31% reduction in risk of ulcerative colitis and a 15% reduction in the risk of Crohn's disease. These data were consistent with a previous analysis of EPIC data that found that high intake of n-6 PUFAs was associated with increased risk of ulcerative colitis (Gut. 2009;58[12]:1606-11). Other analyses indicate that genetic polymorphisms likely modify the association between PUFAs and risk of ulcerative colitis, said Dr. Ananthakrishnan. "There may be an additional layer of complexity beyond just measuring your dietary intake."

In addition to macronutrients, micronutrients can modify a patient's risk of ulcerative colitis or Crohn's disease. When Dr. Ananthakrishnan and colleagues examined the Nurses' Health Study, they found an inverse association between vitamin D intake and risk of Crohn's disease (Gastroenterology. 2012;142[3]:482-9). In a separate study, they found that a zinc intake greater than 16 mg/day was associated with reduced risk of Crohn's disease (Int J Epidemiol. 2015;44[6]:1995-2005).

Patients aged older than 40 years and patients of European ancestry tend to be overrepresented in cohort studies, which reduces the generalizability of their conclusions, said Dr. Ananthakrishnan. Furthermore, cohort studies have not produced consistent findings regarding the relationship between various dietary components and risk of IBD. Nevertheless, the data suggest that dietary patterns may be associated with incident Crohn's disease or ulcerative colitis.

An influence of diet on IBD risk is plausible

One mechanism through which diet may exercise a causal influence on the risk of IBD is by affecting the microbiome. In 2011, investigators studied 98 healthy volunteers who answered questionnaires about their diet. The researchers also used 16s rDNA sequencing to characterize the population's stool samples. A diet high in animal protein, amino acids, and saturated fats was associated with large populations of *Bacteroides*. A diet low in fat and in animal protein, but high in carbohydrates and simple sugars was associated with large populations of *Prevotella*. When the investigators conducted a controlled-feeding study of 10 patients, microbiome composition changed within 1 day of initiating a high-fat-and-low-fiber or a low-fat-and-high-fiber diet (Science. 2011;334[6052]:105-8). A more recent study showed that the diversity of the microbiome increased with the adoption of an animal-based diet (Nature. 2014;505[7484]:559-63).

Diet also may exert a causal influence on IBD risk by altering the intestinal barrier. In an experimental model, 5-mg/mL concentrations of fiber from plantain and broccoli significantly reduced the translocation of *Escherichia coli* through a human intestinal epithelial barrier (Gut. 2010;59[10]:1331-9). Increased fiber intake may thus result in reduced intestinal inflammation, said Dr. Ananthakrishnan.

Observational and experimental evidence thus support an effect of diet on the risk of IBD, and experimental evidence indicates that this effect is biologically plausible. Nevertheless, "there are many missing links," and further study will clarify the role of diet in IBD incidence, said Dr. Ananthakrishnan.

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AGA Resource

AGA offers education for your patients about IBD, including lifestyle and nutrition management, in the AGA GI Patient Center at https://www.gastro.org/practice-guidance/gi-patient-center/topic/inflammatory-bowel-disease-ibd.

T cells and IL-2 drive acute celiac symptoms

BY WILL PASS
MDedge News

CD4+ T-cell reactivation and interleukin (IL)–2 release are responsible for acute gastrointestinal symptoms when patients with celiac disease are exposed to gluten, according to investigators.

Although T cells have been well studied in previous celiac disease research, clinical symptoms after acute gluten exposure have never been linked with specific cytokine changes, reported lead author Gautam Goel, PhD, of Massachusetts General Hospital in Boston, and colleagues.

"If treated [celiac disease] patients, i.e., those following a strict [gluten-free diet], are exposed to gluten-containing food, they typically suffer from gastrointestinal reactions occurring 1 to 2 hours after the gluten exposure," the investigators wrote in Science Advances. "There is currently no explanation for the acute gluten-induced symptoms seen in treated [celiac disease] patients."

The current study was prompted by two phase 1 trials involving the therapeutic vaccine Nexvax2, which uses peptide fragments of gluten proteins to desensitize celiac patients to gluten, the investigators explained. During those trials, intradermal injections of Nexvax2 above a certain dose threshold led to gastrointestinal symptoms within 2-5 hours, but not injection-site reactions, which would have been indicative of a cutaneous response to recall antigen.

"Our observations from these phase 1 studies led us to hypothesize that cytokine release occurs following natural gluten exposure and could be used to implicate which arms of the immune system drive early symptoms."

Of the 28 patients in the two trials, all underwent intradermal testing, while 19 also participated in an oral gluten challenge. Following intradermal injection of gluten peptides, patients exhibited gastrointestinal symptoms, along with coordinated elevations of least 15 plasma cytokines; most significantly IL-2, MCP-1, IL-8, IL-10, MIP-1beta, IP-10, and eotaxin. The first cytokines to respond to injection were IL-2 and IL-8, rising within 2 hours, prior to symptoms. At 4 hours, when symptoms were present, peak IL-2 elevations were most dramatic, with a 272-fold elevation, followed by IL-8 (11-fold) and IL-10 (1.2-fold).

"IL-2 is both the earliest and most sensitive marker for the coordinated cytokine release that was almost universal in HLA-DQ2.5 + [celiac disease] patients administered gluten peptides," the investigators wrote.

Similar to intradermal testing, oral challenge with gluten caused IL-2, IL-8, and IL-10 to elevate within 2 hours, and peak within 4-6 hours. Again, IL-2 was most sensitive, with a 15-fold increase at 4 hours. This increase in IL-2 correlated with IL-8 and IL-10 elevations, although IL-2 increases were at least six times greater than the other two cytokines.

"Together, the serum cytokine profile following gluten ingestion is less prominent but qualitatively similar and over a corresponding time course to that after injecting gluten peptides, which is consistent with activated CD4+ T cells being the driver of cytokine release in both scenarios," the investigators wrote.

Further testing showed that, after gluten challenge, plasma levels of IL-2, IL-8, and IL-10 negatively correlated with duodenal villous height-to-crypt depth ratios. In addition, high levels of IL-2 correlated with severe nausea and vomiting, adding to the evidence that celiac symptoms

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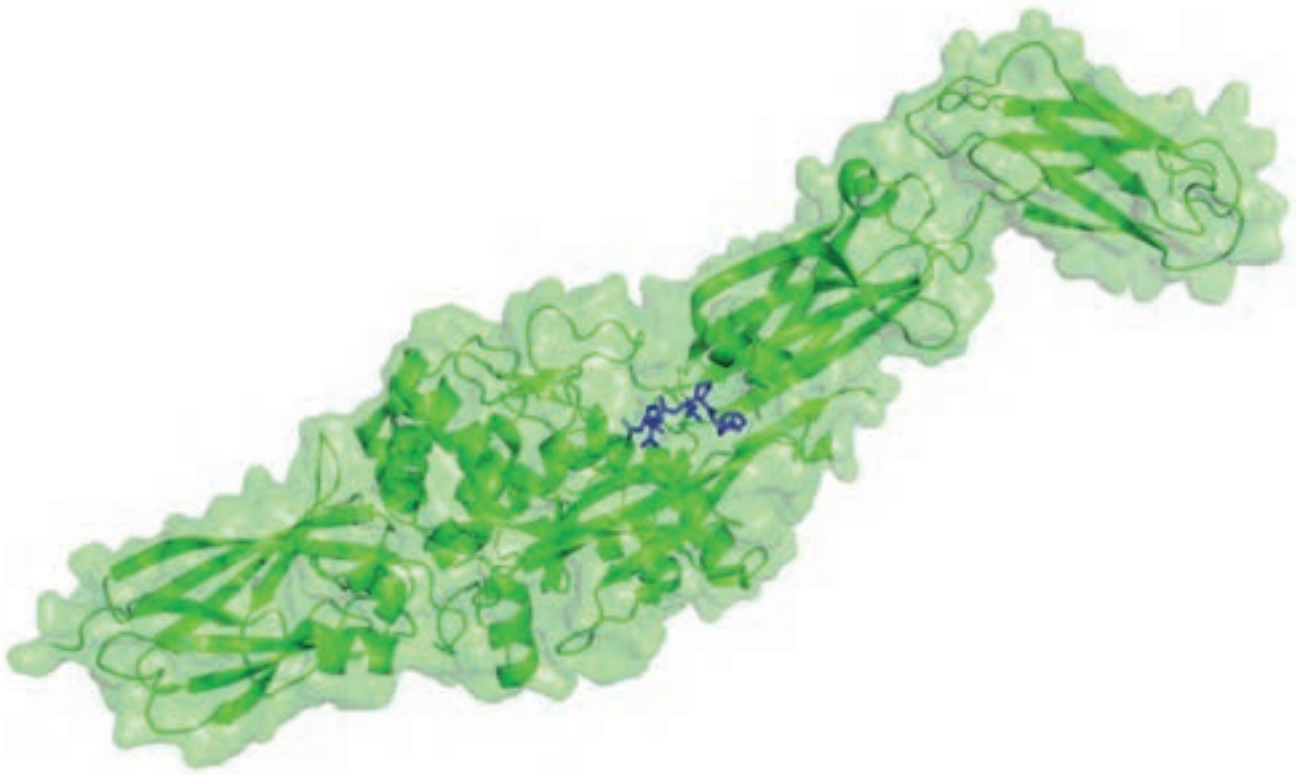

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Tissue transglutaminase 2 (TG2) enzyme bound to a gluten peptide mimic: The protein is shown in green (PDB: 2q3z). The peptide mimic is shown in blue stick form (made in pymol).

FDA approves tenapanor for IBS with constipation

BY CHRISTOPHER PALMER
MDedge News

The Food and Drug Administration has approved tenapanor (Ibsrela) for adults with irritable bowel syndrome with constipation (IBS-C), according to a release from the drug's developer, Ardelyx. The approval is based on a pair of phase 3, randomized, double-blind, placebo-controlled trials in patients meeting the Rome III criteria for IBS-C. Both trials had identical 12-week treatment phases, while trial 1 had a 14-week continuation phase, and trial 2 included a 4-week withdrawal period. The primary endpoint was proportion of responders in the 12-week treatment period; this was defined as a 30% reduction in abdominal pain score and an increase of at least one complete spontaneous bowel movement on average weekly for at least 6 of the first 12 treatment weeks, compared with placebo. Both trials met this endpoint, with trial 1 showing a 37% response rate with treatment versus 24% with placebo, and trial 2 showing rates of 27% and 19%, respectively. Improvements were seen as early as week 1 and were maintained through the end of treatment.

The most common treatment-related adverse event was diarrhea, with severe diarrhea reported in 2.5% of treated patients versus 0.2% of placebo patients. Discontinuation rates were low. Tenapanor is contraindicated in IBS-C patients younger than 6 years because of concerns about dehydration, and use should be avoided in patients aged 6-12 years. Safety and efficacy has not been established in patients younger than 18 years. Tenapanor is also contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

The full prescribing information can be found on the FDA website.

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were linked with specific cytokine elevations.

"The link between immune activation and symptoms was further strengthened by showing that postdose symptoms and cytokine release were both lessened after three weekly doses and absent after 16 twice-weekly injections of gluten peptides," the investigators wrote. "These findings are consistent with the difference in severity of symptoms after gluten ingestion compared to gluten peptide injection being related to potency of the antigen challenge and T-cell activation measured by circulating IL-2 concentration at 4 hours."

Even though IL-2 elevations appeared to drive celiac symptoms, the source of IL-2 was initially unknown. "Activated T cells are the primary source of IL-2, but [dendritic cells] can also secrete IL-2 following ligation of specific pathogen recognition receptors; mast cells also secrete IL-2 following exposure to IL-33 or IL-9," the investigators explained. Still, CD4+ T cells are known to be key players in celiac disease, and the timing and magnitude of IL-2 release made T cells the most likely candidates. To test this hypothesis, the investigators collected blood from patients 6 days after gluten food challenge and incubated these samples for 24 hours with gluten peptides. Results of this test suggested that gluten-specific CD4+ T cells were the most likely source of IL-2.

The connection between particular cytokines and gastrointestinal symptoms is now supported with evidence; however, the investigators pointed out that a relationship between cytokines and other symptoms of celiac disease remains to be seen. "Whether cytokines elevated in blood after injecting gluten peptides or ingesting gluten have any direct extraintestinal effects is unclear," the investigators wrote. "Fatigue, headache, and 'brain fog' are the commonly reported extraintestinal symptoms in [celiac disease] patients. However, symptoms being focused on the upper gastrointestinal tract suggest that cytokines increased in blood have clinical and immunological effects that selectively affect the tissue from which they originate."

The study was supported by the University of Chicago Celiac Disease Center and the University of Oslo KG Jebsen Coeliac Disease Research Centre. The investigators reported additional relationships with several government and nonprofit organizations. Multiple investigators are employees of ImmusanT, which is developing Nexvax2.

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NDMA found in samples of ranitidine, FDA says

BY DOUG BRUNK
MDedge News

According to the Food and Drug Administration, Zantac and other ranitidine medicines contain low levels of a nitrosamine impurity known as N-nitrosodimethylamine (NDMA), which is classified as a probable human carcinogen.

"NDMA is a known environmental contaminant and found in water and foods, including meats, dairy products, and vegetables," Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research, said in a prepared statement issued on Sept. 13, 2019. "The FDA has been investigating NDMA and other nitrosamine impurities in blood pressure and heart failure medicines called Angiotensin II Receptor Blockers (ARBs) since last year. In the case of ARBs, the FDA has recommended numerous recalls as it discovered unacceptable levels of nitrosamines."

Dr. Woodcock said that the agency is working with industry partners to determine whether the low levels of NDMA in ranitidine pose a risk to patients, and it plans to post that information when it becomes available. For now, "patients should be able to trust that their medicines are as safe as they can be and that the benefits of taking them outweigh any risk to their health," she said. "Although NDMA may cause harm in large amounts, the levels the FDA is finding in ranitidine from preliminary tests barely exceed amounts you might expect to find in common foods."

Dr. Woodcock

AGA Resource
Visit the AGA GI Patient Center for education to share with your patients about GERD, including symptoms, testing, lifestyle modifications, and drug treatments at https://www.gastro.org/practice-guidance/gi-patient-center/topic/gastroesophageal-reflux-disease-gerd.

Dr. Woodcock emphasized that the FDA is not suggesting that individuals stop taking ranitidine at this time. "However, patients taking prescription ranitidine who wish to discontinue use should talk to their health care professional about other treatment options," she said. "People taking OTC ranitidine could consider using other OTC medicines approved for their condition."

She advised consumers and health care professionals to report any adverse reactions with ranitidine to the FDA's MedWatch program.

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After a 10-year streak, the number of uninsured rose

BY PHIL GALEWITZ, KAISER HEALTH NEWS

For the first time in a decade, the number of Americans without health insurance has risen – by about 2 million people in 2018 – according to the annual U.S. Census Bureau report released Sept. 10, 2019.

The Census found that 8.5% of the U.S. population went without medical insurance for all of 2018, up from 7.9% in 2017. By contrast, in 2013, before the Affordable Care Act took full effect, 13.3% were uninsured. It was the first year-to-year increase since 2008-2009, Census officials said, adding that most of the drop in health coverage was related to a 0.7% decline in Medicaid participants. The number of people with private insurance remained steady and there was a 0.4% increase in those on Medicare.

Many of those losing coverage were noncitizens, a possible fallout from the Trump administration's tough immigration policies and rhetoric. About 574,000 noncitizens lost coverage in 2018, a drop of about 2.3%, the report found.

"Uninsured noncitizens account for almost a third of the increase in uninsured, which may reflect the administration's more aggressive stance on immigration," said Joseph Antos, a health economist at the American Enterprise Institute.

The increase in the number of uninsured people in 2018 was remarkable because uninsured rates typically fall or hold steady when unemployment rates drop. The U.S. unemployment rate fell slightly from about 4.3% in 2017 to 4% in 2018.

The uninsured rate continued to vary by poverty status and whether a state expanded its Medicaid program under Obamacare. Texas (17.7%), Oklahoma (14.2%), Georgia (13.7%), and Florida (13%) had the highest uninsured rates in 2018, according to the report. None of those states have expanded Medicaid under Obamacare.

The percentage of uninsured children aged under 19 years increased by 0.6 percentage points from 2017 to 2018, to 5.5%.

"The Census data are clear – the uninsured rate for kids is up sharply and it's due to a loss of public coverage – mostly Medicaid," Joan Alker, executive director of Georgetown University Center for Children and Families, said in a statement.

"These children are not getting private coverage as the Trump administration has suggested but rather becoming uninsured," she said. "This serious erosion of children's health coverage is due in large part to the Trump administration's actions that have made health care harder to access and have deterred families from enrolling their children."

The share of Americans without medical insurance fell steadily since 2014 but then leveled off in 2017, the year Mr. Trump became president.

Health care advocates have complained that efforts by the Trump administration and Congress are jeopardizing insurance enrollment. They point to cuts in outreach programs that aim to tell consumers about their health care options under Obamacare and the elimination of the ACA's tax penalty for people who don't have health coverage.

Ms. Alker complained that the administration's policies are causing

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ABIM: Self-paced MOC pathway under development

BY ALICIA GALLEGOS

MDedge News

Physician groups are praising a new option by the American Board of Internal Medicine (ABIM) that will offer doctors a self-paced pathway for maintenance of certification (MOC) in place of the traditional long-form assessment route.

The new longitudinal assessment option, announced in late August, would enable physicians to acquire and demonstrate ongoing knowledge through shorter evaluations of specific content. The option, currently under development, also would provide doctors with immediate feedback about their answers and share links to educational material to address knowledge gaps, according to an announcement. While details are still being fleshed out, a summary of the longitudinal assessment concept by the American Board of Medical Specialties explains that the approach draws on the principles of adult learning and modern technology "to promote learning, retention, and transfer of information."

Dr. Baron

Developing a longitudinal assessment option is part of ABIM's ongoing evolution, Marianne M. Green, MD, chair for ABIM's board of directors, and ABIM President Richard J. Baron, MD, wrote in a joint letter to internists posted on ABIM's blog.

"We recognize that some physicians may prefer a more continuous process that easily integrates into their lives and allows them to engage seamlessly at their preferred pace, while being able to access the resources they use in practice," the doctors wrote.

"Until recently, AGA [American Gastroenterological Association], along with AASLD [American Association for the Study of Liver Diseases], ACG [American College of Gastroenterology], and ASGE [American Society for Gastrointestinal Endoscopy] had been working on a new recertification pathway for GI. That effort has been temporarily suspended as ABIM pursues a pathway that will be available to all internal medicine specialties," said Hashem El Serag, MD, MPH, AGAF, AGA president. "AGA appreciates that ABIM's new longitudinal pathway appears to conform to the principles that the GI societies have espoused. We will monitor the development of the pathway as it moves toward implementation continuing to advocate for the needs of gastroenterologists."

These GI societies are guided by these core principles in their campaign to reform MOC:

- MOC needs to be simpler, less intrusive, and less expensive.
- We continue to support alternatives to the high-stakes, every-10-year recertification exam.
- We do not support single-source or time-limited assessments, as they do not represent the current realities of medicine in the digital age.
- We support the concept that, for the many diplomates who specialize within certain areas of gastroenterology and hepatology, MOC should not include high-stakes assessments of areas in which the diplomate may not practice.
- We support the principles of lifelong learning, as evidenced by ongoing CME activities, rather than lifelong testing.

Douglas DeLong, MD, chair of the American College of Physician's (ACP) board of regents said the option is a positive, first step that will support lifelong learning. He noted the new option is in line with recommendations released in 2019 by the American Board of Medical Specialties' Continuing Board Certification: Vision for the Future Commission, which included ACP concerns.

"It's pretty clear that some of the principles of adult learning – frequent information with quick feedback, repetition of material, and identifying gaps in knowledge – is really how people most effectively learn," Dr. DeLong said in an interview. "Just cramming for an examination every decade hasn't ever really been shown to affect long-term retention of knowledge or even patient care outcomes."

Alan Lichtin, MD, chair of the MOC working group for the American Society of Hematology (ASH), said the self-paced pathway is a much-needed option, particularly the immediate feedback on test questions.

"For years, ASH has been advocating that ABIM move from the traditional sit-down testing to an alternative form of 'formative' assessment that has been adapted by other specialty boards," Dr. Lichtin said in an interview. Anesthesiology and pediatrics have novel testing methods that fit into physicians' schedules without being so disruptive and anxiety provoking. There is instantaneous feedback about whether the answers are correct or not. It is not useful to study hard for a time-intensive, comprehensive test only to get a summary of what was missed a long time after the test. By that point, the exam material is no longer fresh in one's mind and therefore the feedback is no longer useful."

The new pathway is still under development, and ABIM has not said when the option might be launched. In the meantime, the current MOC program and its traditional exam will remain in effect. The ABIM is requesting feedback and comments from physicians about the option. Dr. Baron wrote that more information about the change will be forthcoming in the months ahead.

The ABIM announcement comes on the heels of several ongoing legal challenges levied at the board by a group of internists over its MOC process.

A lawsuit, filed Dec. 6, 2018, in Pennsylvania district court and later amended in 2019, claims that ABIM is charging inflated monopoly prices for maintaining certification, that the organization is forcing physicians to purchase MOC, and that ABIM is inducing employers and others to require ABIM certification. The four plaintiff-physicians are asking a judge to find ABIM in violation of federal antitrust law and to bar the board from continuing its MOC process. The suit is filed as a class action on behalf of all internists and subspecialists required by ABIM to purchase MOC to maintain their ABIM certifications.

Continued on page 52

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the loss of children's coverage. "In a period of continued economic and job growth, we shouldn't be going backwards on health coverage," said Judy Solomon, a senior fellow for the Center on Budget and Policy Priorities, a left-leaning think tank. "This backsliding almost certainly reflects, at least in part, Trump administration policies to weaken public health coverage."

She attributed the drop to the Trump administration making it harder for families to enroll for coverage in Medicaid by curtailing outreach efforts, allowing states to ask for more paperwork and proposing a so-called public charge rule that would make it harder for legal immigrants to get permanent resident status if they have received certain kinds of public assistance – including Medicaid.

Tom Miller, a resident fellow at the American Enterprise Institute, a conservative think tank, said the drop in Medicaid coverage "is a positive."

"When the economy grows Medicaid eventually drops," he said.

One reason for the drop in health coverage is that middle-income families can't afford the rising cost of insurance in the individual market, particularly if they don't qualify for government subsidies, he added.

"On balance, this is some short-term noise," he said of the uptick in the uninsured rate. "I would put more stake in it if happens for several years."

Chris Pope, a senior fellow with the conservative Manhattan Institute, also said he considered the change "fairly small" and likely caused by increasing wages "pushing people above the income eligibility cutoff in Medicaid expansion states."

But he suggested that next year would be a better indicator of how changes in the ACA are playing out. "I expect that the mandate repeal will make next year's increase in the uninsured more significant."

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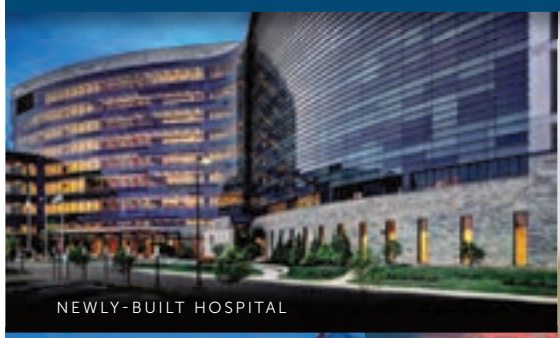

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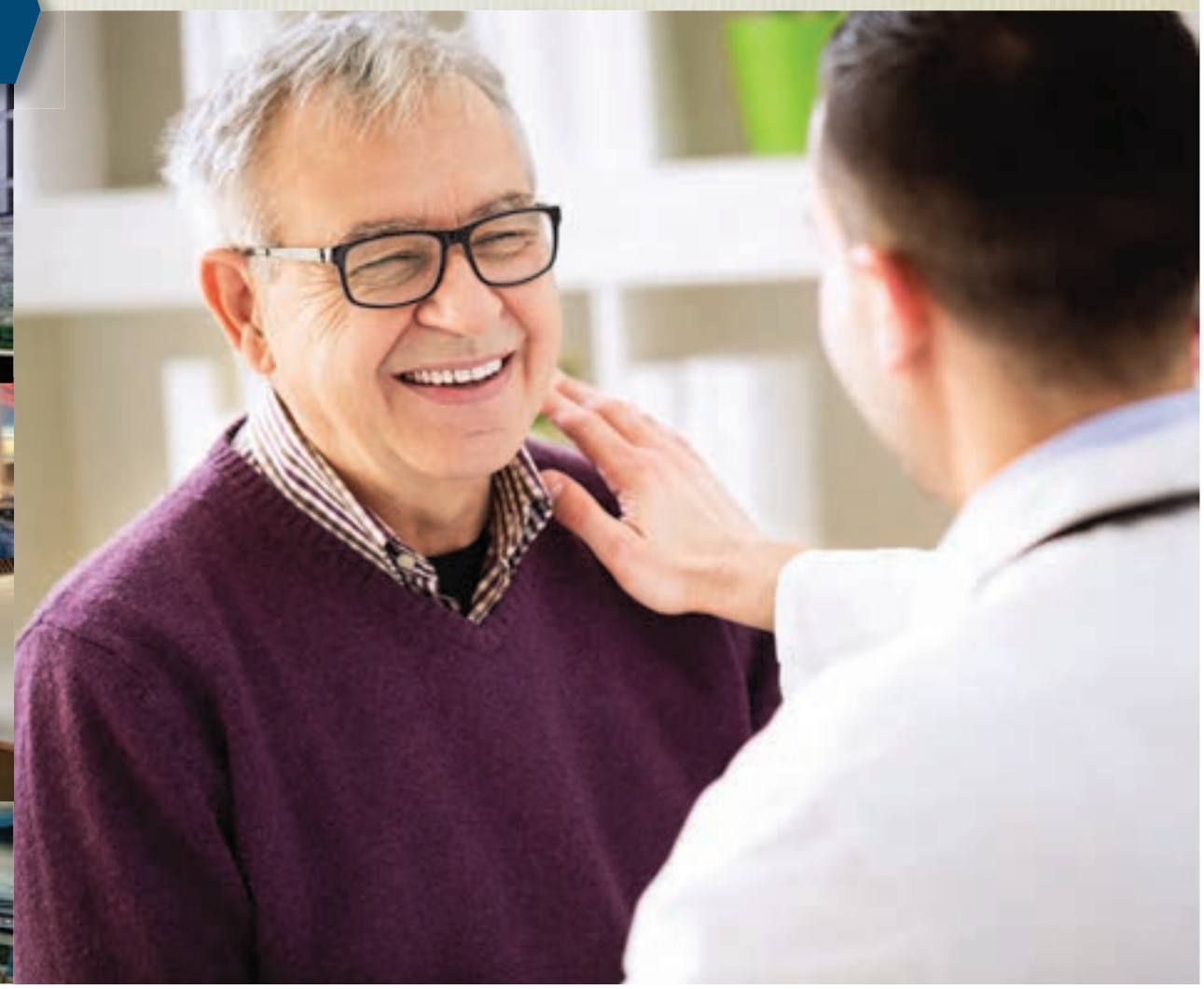

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States pass record number of laws to reel in drug prices

BY STEVEN FINDLAY, KAISER HEALTH NEWS

Whether Congress will act this year to address the affordability of prescription drugs – a high priority among voters – remains uncertain. But states aren't waiting.

So far this year, 33 states have enacted a record 51 laws to address drug prices, affordability, and access. That tops the previous record of 45 laws enacted in 28 states set just last year, according to the National Academy for State Health Policy, a nonprofit advocacy group that develops model legislation and promotes such laws.

Among the new measures are those that authorize importing prescription drugs, screen for excessive price increases by drug companies, and establish oversight boards to set the prices states will pay for drugs.

"Legislative activity in this area is escalating," said Trish Riley, NASHP's executive director. "This year, some states moved to launch programs that directly impact what they and consumers pay for high-cost drugs."

And more laws could be coming before year's end. Of the handful of states still in legislative session – including California, Massachusetts, Michigan, New Jersey, Ohio, and Pennsylvania – debate continues on dozens of prescription drug bills. In New Jersey alone, some 20 proposed laws are under consideration.

"Both Democrat and Republican leaders have shown a willingness to pursue strong measures that help consumers but also protect state taxpayer dollars," said Hemi Tewarson, director of the National Governors Association's health programs.

Ms. Riley, Ms. Tewarson, and others note, however, that states can go only so far in addressing rising drug prices, and that federal legislation would be necessary to have a major effect on the way the marketplace works.

Federal lawmakers are keeping a close eye on the state initiatives, Ms. Tewarson said, to gauge where legislative compromise may lie – even as Congress debates more than a dozen bills that target drug costs.

The pharmaceutical industry has

Continued on following page

Continued from page 49

Physicians in three other lawsuits are also suing medical boards over their respective MOC processes. In February 2019, a radiologist issued a legal challenge against the American Board of Radiology over its MOC regulations. Also in February, two emergency physicians and an anesthesiologist filed a lawsuit against the American Board of Medical Specialties, the American Board of Emergency Medicine, and the American Board of Anesthesiology over MOC requirements. A month later, two psychiatrists issued a legal challenge against the American Board of Psychiatry and Neurology over its MOC process.

Attorneys for all three boards in the ABIM, American Board of Psychiatry and Neurology, and American Board of Radiology cases are seeking to dismiss the complaints. Judges have not yet ruled on the motions. In addition, a motion to consolidate all the cases was denied by the court.

A GoFundMe campaign launched by the Practicing Physicians of America to pay for plaintiffs' costs associated with the class-action lawsuits has now garnered more than $300,000.

agallegos@mdedge.com

Continued from previous page

opposed most – though not all – state bills, said Priscilla VanderVeer, a spokeswoman for the Pharmaceutical Research and Manufacturers of America, the industry's main trade group.

"We agree that what consumers now pay for drugs out-of-pocket is a serious problem," said Ms. VanderVeer. "Many states have passed bills that look good on paper but that we don't believe will save consumers money."

Limiting gag rules for pharmacists

At least 16 states have enacted 20 laws governing the behavior of pharmacy benefit managers. The so-called PBMs serve as middlemen among drugmakers, insurance companies, and pharmacies, largely with pharmaceutical industry support.

Those laws add to the 28 passed in 2018. Most of the new laws ban "gag clauses" that some PBMs impose on pharmacists. The clauses, written into pharmacy contracts, stop pharmacists from discussing with customers whether a drug's cash price would be lower than its out-of-pocket cost under insurance.

With widespread public outrage over gag clauses pushing states to act, federal lawmakers got the message. In October, Congress passed a federal law banning such clauses in PBM-pharmacy contracts nationwide and under the Medicare Part D prescription drug benefit. The Senate passed it 98-2. Even so, many of this year's PBM laws contain additional gag clause limitations that go beyond the 2018 federal law.

Importing cheaper drugs

Four states – Colorado, Florida, Maine, and Vermont – this year have enacted measures to establish programs to import cheaper prescription drugs from Canada and, in Florida's case, potentially other countries. Six other states are considering such legislation.

Medicines in Canada and other countries are less expensive because those nations negotiate directly with drugmakers to set prices.

"This is an area where states once feared to tread," said Jane Horvath, a consultant who has advised Maryland and Oregon, among other states, on prescription drug policy. "Now both Republicans and Democrats view it as a way to infuse more price competition into the marketplace."

Hurdles remain, however. A 2003 law allows states to import cheaper drugs from Canada but only if the federal Health & Human Services Department approves a state's plan and certifies its safety. Between 2004 and 2009, the federal government halted nascent drug import efforts in five states.

Even so, momentum for importation has built in recent years in states and Congress as drug prices have continued to rise. And the Trump administration this summer threw its support behind the idea.

Florida Gov. Ron DeSantis, a Republican and close ally of President Trump, signed his state's measure into law on June 11, claiming he did so after Trump personally promised him the White House would back the initiative.

On July 31, HHS announced an "action plan" to "lay the foundation for safe importation of certain prescription drugs." The plan includes a process to authorize state initiatives. It also requires formal regulatory review, including establishing Food and Drug Administration safety criteria. That process could take up to 2 years.

Two big problems remain: In the weeks since the announcement, the Canadian government has opposed any plan that would rely solely on Canada as a source of imported drugs. The pharmaceutical industry also opposes the plan.

Creating drug affordability boards

Maine and Maryland enacted laws this year that establish state agencies to review the costs of drugs and take action against those whose price increases exceed a certain threshold.

Maryland's law establishes a five-member board to review the list prices and costs of drugs purchased by the state and Maryland's county and local governments. The board will probe drugs that increase in price by $3,000 or more per year and new medicines that enter the market costing $30,000 or more per year or over the course of treatment.

If approved by future legislation, upper payment limits on drugs with excessive price increases or annual costs would take effect in January 2022.

"My constituents have signaled loud and clear that bringing drug prices down is one of their top priorities," said state Sen. Katherine Klausmeier, a Democrat representing Baltimore, who sponsored the legislation.

Maine's law also establishes a five-member board. Beginning in 2021, the board will set annual spending targets for drugs purchased by the state and local governments.

Increasing price transparency

This year, four states – Colorado, Oregon, Texas, and Washington – became the latest to enact laws requiring drug companies to provide information to states and consumers on the list prices of drugs and planned price increases.

The majority of states now have such transparency laws, and most post the data on public websites. The details vary, but all states with such laws seek to identify drugs with price increases above 10% or more a year, and drugs with price increases above set dollar values.

Oregon's new law, for example, requires manufacturers to notify the state 60 days in advance of any planned increase of 10% or more in the price of brand-name drugs, and any 25% or greater increase in the price of generic drugs.

"That 60-days' notice was very important to us," said Rep. Andrea Salinas, chair of the Oregon House's health committee, who represents Lake Oswego. "It gives doctors and patients advance notice and a chance to adjust and consider what to do."

Kaiser Health News is a nonprofit national health policy news service. It is an editorially independent program of the Henry J. Kaiser Family Foundation that is not affiliated with Kaiser Permanente.

AGA Resource

AGA advocates that drug affordability should be focused on decreasing out-of-pocket expenses for patients, maintaining reasonable incentives for innovation, increasing cost transparency, promoting shared decision making, and boosting competition. Learn more about our drug affordability principles at https://www.gastro.org/advocacy-and-policy/issues-and-news/top-issues/drug-affordability-principles.

Private equity and independent gastroenterology practices – what do I need to know?

BY MARC SONENSHINE, MD, MBA

A few years ago, private equity (PE) firms began to focus on independent gastroenterology practices as a target for investment. The first PE investment transaction closed in March of 2016, and now an additional three such partnerships have occurred. Investment firms believe gastroenterology is ripe for investment and subsequent consolidation for the following reasons:

- Gastroenterology is a highly fragmented specialty with many small and mid-sized groups that could be rolled up into larger practice entities that create favorable scalability.
- There are multiple revenue streams through ancillary services that can be packaged into a comprehensive, high-quality gastroenterology practice that has high value for patients and that are delivered outside of a hospital environment.
- There is a growing need for gastroenterology care with increasing demand for chronic GI disease management (fatty liver disease, inflammatory bowel disease, and obesity management, for example) and increasing demand for colon cancer screening.
- The current financial environment is favorable for investment and other sectors of the health care market are rapidly consolidating.

A PE transaction is not appropriate for every practice nor every physician. Further, not every physician group will be desirable for a PE firm. Nonetheless, the current business climate in the GI sector is generally favorable for accepting the PE capital model.

The following are 10 common questions dealing with a PE transaction:

1. What does a PE deal mean for the independent gastroenterologist? A PE transaction and the resulting formation of a managed services organization (MSO) will be a liquidity event for all current owners in the acquired practice. Financial benefits are typically substantial, especially when considering the funds can then be invested by the individual physician and often the money paid can be taxed as capital gains rather than ordinary income. In exchange for the pay-out, the physician group relinquishes managerial control of nonclinical decisions through a managed services agreement (MSA) with the MSO. The MSO is typically formed by the partnership between the practice and the PE firm and provides all nonclinical services to the physician group.

2. What autonomy will be left after signing a PE deal/MSA? Autonomy after the deal closes is determined largely by terms written into the contract prior to the closing and will differ among the various PE firms. There will be conditions important to the MSO and some important to the practice that can be codified in the contract. These conditions are spelled out in an employment agreement with the continuing physician group. Both the PE group and physicians will want to ensure that practice culture is not negatively impacted through an acquisition. Physicians must feel that they retain complete autonomy when it comes to clinical decisions, and the PE group must avoid interfering in the patient-doctor relationship. The PE group wants to improve nonclinical management of the practice, without interfering with the actual care of a patient. Physicians may influence nonclinical managerial decisions, but providers must understand that all nonclinical managerial decisions ultimately will be made by the MSO and PE firm.

3. What makes a good PE partnership? The asset that a PE firm is purchasing and hoping to grow is the revenue from a medical practice that they hope to improve by increasing profitability (through enhanced efficiency), expanding ancillary services and through multiple additional acquisitions to gain scale and size. Ensuring both sides are respected and aligned in decisions helps move the organization forward. A good partnership will build and bridge three types of capital – financial, experiential, and educational. Various factors must be considered; however, most important is mutual respect and admiration between the MSO and the physicians. Managerial styles will vary, but, a shared vision of the future will lead to success.

Both the PE group and physicians will want to ensure that practice culture is not negatively impacted through an acquisition. Physicians must feel that they retain complete autonomy when it comes to clinical decisions, and the PE group must avoid interfering in the patient-doctor relationship.

4. What changes are ahead with a PE deal? A PE firm and the MSO that it controls will put its management team in place to optimize revenue and contain expenses. The PE firm will look to combine practices where synergies exist and growth potential is strategically beneficial. For example, one practice might bring a pathology lab, the other geographic coverage, and the third an infusion center. Larger scale will usually improve negotiating influence with payers and hospitals as well as buying power for operational necessities. The MSO will roll out best practice protocols throughout the group, both back-office as well as patient-facing services. Finally, all PE groups will transition accounting to accrual from cash based as well as work with outside auditors and consultants due to the MSO's bank covenants.

5. What is a platform company? A variation on the PE-based MSO is the formation of a "platform company." This structure typically comes from a more sophisticated, mature practice that already has substantial business structures and managerial team members in place. This type of company can provide services not just to the founding practice, but to others that are "added on" as the organization grows. The investment hold period by the PE firm is typically 4-6 years, and thus, adding expertise to existing processes is usually more efficient and effective than starting from the ground up. Platform companies are typically paid a higher multiple than a company or practice that is "added on" to an existing platform, especially since these owners are taking the greatest risk by being the initial investor.

6. What does the idiom "second bite of the apple" mean? A portion of each owner's proceeds from the initial sale ("first bite of the apple") of the practice is typically converted into stock of the MSO in a tax-favorable method. The PE firm will maintain the largest shareholder position in the MSO (often majority), while the physicians and management team will be minority shareholders in the MSO. The proportion of proceeds rolled into stock depends on negotiations and ranges anywhere from 20% to 50% of the proceeds. The "second bite" is when the PE firm sells the stock of the MSO to the next investor. At the time of that transaction, all shareholders have a liquidity event and often another portion of the proceeds are rolled for the "next bite of the apple." Specific terms of the shares are defined during negotiations, specifically the vesting terms, voting rights associated, and the value of each share.

7. Why would one practice receive a higher multiple compared to another practice? Each practice will have a different intrinsic value to the MSO and PE firm. The range of multiples on the purchased earnings before interest, depreciation, taxes, and amortization (EBIDTA) will depend on the timing of the transaction in the lifecycle of the investment as well as market forces. The number, age, and productivity of a practice's providers, the ability to add certain ancillary services (i.e., revenue sources), the quality of contracts and associated payer mix, and the location of a practice are often the critical elements which the PE firm evaluates in the determination of a group's value. The investment strategy will not be successful if exorbitant multiples are used for every practice. Strategically, a group with multiple providers in a desirable location with limited ancillary services early in the lifecycle will likely receive a higher multiple than a smaller group.

8. What outside professional assistance is needed to consummate a PE deal? Some groups may depend on an investment banker or health care mergers and acquisitions consultant to assist in the process or even seek out a partnership. Larger, more complicated groups with various existing relationships and competing forces often require such professional assistance. However, other smaller groups being approached by the MSO/PE firm as a "bolt-on" acquisition might not require a professional banker as the terms of joining may be more uniform to create a cohesive group of providers upon closing. All transactions, however, will require experienced health care transaction attorneys to ensure compliance with the myriad regulations. Some may engage a tax law attorney or accountant to ensure terms of the transaction are favorable. The PE firm will almost certainly require a quality of earnings evaluation by an outside, third-party financial auditor. One can probably assume close to 5% of proceeds may go

to various professionals assisting in the process of the deal.

9. What are the common governance structures in PE transactions for physician provider service organizations? Like most businesses, a group of individuals typically form a board of directors which work in a decision making capacity and provide advice to the management team of the MSO. The board of directors usually includes successful leaders from other industries or business which bring specific talents, connections, and experiences, as well as individuals from the PE group and management team. Often, the platform practice will have a representative physician sit on the MSO board to ensure the medical provider perspective is prominent. The board of directors typically approves acquisitions and entry into new MSAs with additional practices, sets quarterly or yearly strategic goals, approves the budget and management team compensation structure, and ultimately works on an exit strategy for the PE firm. Finally, pros and cons exist to having a physician as the CEO of the MSO; regardless, the CEO must be a strong leader with a vision and solid ability to communicate, as the PE sponsor and board of directors will have certain expectations, just as the independent gastroenterologist becoming a part of a new entity will have significant insecurities and hesitancies which must be appreciated and reassured.

10. In 3-5 years, what opportunities will a gastroenterologist leaving fellowship face as far as the GI landscape? Beyond the typical hospital-based employment opportunities or academic positions, consolidation of groups from PE acquisitions will likely have led to regional and maybe even national companies competing amongst themselves for talent. Likely, one or two of the currently backed PE companies will have a new investor (i.e., initial exit completed/"second bite"). Each group will try to provide a differing value-based proposition beyond just the location a provider will be practicing. Fellows entering a practice already owned by a PE firm (or if a sale is pending) must clearly understand the legal, financial, and governance implications of these structures. This type of business structure is much different than one would encounter when hired by a physician-owned practice. It is not yet clear how a PE exit (4-6 years after acquisition) will play out for physicians not part of the original practice.

Dr. Sonenshine is a member of Atlanta Gastroenterology Associates. He has no conflicts of interest.

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